UNRAVELLING THE MALE ASPECT OF REPRODUCTIVE RHEUMATOLOGY

Evaluating the effect of immune-mediated diseases and its treatment on male sexual and reproductive health

Proefschrift

Luis Fernando Perez

Layout & Printing: Ridderprint | www.ridderprint.nl
Paper: 100 gsm Recycled
Cover art generated using an artificial intelligence tool (Adobe Firefly), prompt provided by Luis Fernando Perez.

Unravelling the Male Aspect of Reproductive Rheumatology

Evaluating the effect of immune-mediated diseases and its treatment on male sexual and reproductive health

Het ontrafelen van het mannelijke aspect van reproductieve reumatologie
Het evalueren van het effect van immuungemedieerde ziekten en de behandeling daarvan op de seksuele en reproductieve gezondheid van mannen

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. A.L. Bredenoord

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

dinsdag 25 juni 2024 om 15.30 uur

door

Luis Fernando Perez
geboren te Laredo, Texas, Verenigde Staten.

Erasmus University Rotterdam

Promotiecommissie:

Promotoren:	Prof.dr. R.J.E.M. Dolhain Prof.dr. J.M.W. Hazes
Overige leden:	Prof.dr. J.S.E. Laven Prof.dr. I.E. Van Der Horst-Bruinsma Prof.dr. J.L. Boormans

Table of contents

PART I

General Introduction

CHAPTER 1

Introduction to male reproductive rheumatology

The year is 2018, and a 36-year-old man diagnosed with rheumatoid arthritis visits his rheumatologist for a routine follow-up visit. Usually, he comes alone but this time he came accompanied by his partner. The rheumatologist concluded that the arthritis was under control and that the current medication was effective. While the rheumatologist was busy ordering new labs and updating the patients' digital dossier, he noticed that the couple was discussing something, and asked them; "is there anything else you want to discuss?"

Without hesitation, the patient shares with his rheumatologist that they have an active desire to have children and that they would like to discuss some questions;

1. *What is the effect of my disease on my fertility? Can my partner get pregnant? Is it safe?*
2. *Is my current medication safe for men who want to conceive?*
3. *Regarding my medication, are there any known risks for my partner? For the baby?*
4. *Should I stop taking my medication?*
5. *What is the risk of my children "inheriting" my disease?*

The rheumatologist was caught by surprise and had no clear answer for the patient and his partner but promised to come back to them with proper answers. Although these questions are becoming more and more common across Rheumatology outpatient clinics, after doing some research and talking with other colleagues, the rheumatologist was not able to find clear answers to these questions.

Immune-mediated inflammatory diseases

Immune-mediated inflammatory diseases (IMIDs) compromise a common but clinically diverse group of conditions that result from abnormal activity of the immune system and often share common underlying pathogenic features. Although usually classified based on their primary targeted organ (i.e. inflammatory arthritis (IA) – joints, psoriasis - skin), inflammatory responses secondary to IMIDs can compromise almost every organ and system in the human body and lead to acute or chronic inflammatory damage (1).

The most prevalent forms of IA are rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and spondyloarthritis (SpA). These diseases are characterized by their chronicity and by their tendency to affect young people and progress throughout adulthood. They predominantly affect the joints but several extra-articular manifestations such as cardiovascular and respiratory diseases have also been described (2).

Rheumatologists are thoroughly trained to identify these articular and extra-articular manifestations and to intervene, with the objective of avoiding chronic damage.

Nonetheless, our knowledge regarding the impact of IMIDs and its associated pharmacological treatment on the male reproductive system has been for many years a neglected topic. This has resulted in limited awareness of the potential impact of IMIDs on the male reproductive system. As the old saying goes “the eyes can’t see what the mind doesn’t know”.

The male reproductive system

The male reproductive system includes a group of internal (e.g. prostate) and external organs (e.g. testicles, penis) that are responsible for several physiological and reproductive functions; production, maintenance and transport of sperm and semen, to discharge sperm within the female reproductive tract and the production and secretion of male sex hormones responsible for maintaining the system (3).

The entire system is dependent on the coordinated action of hormones that further regulate other cells and organs. Follicle-stimulating hormone (FSH) is produced in the pituitary gland and is responsible for the function and maturation of the testicular Sertoli cells, which in turn are essential for sperm production. Furthermore, Sertoli cells produce inhibin B, which is considered a marker of Sertoli cell function and spermatogenesis. Luteinizing hormone (LH) also secreted in the pituitary gland is responsible for testosterone production by the Leydig cells located in the testicles. Lastly, testosterone is essential for the development of the secondary male sex characteristics and is involved in every step of the male sexual response and is responsible for supporting spermatogenesis.

Reproductive Rheumatology, learning from the female perspective

The idea that IMIDs could impair reproductive health is not new. During the last two decades, our knowledge of how several IMIDs can affect the –female- reproductive system has expanded considerably. At present, we now know that diseases such as IA and their associated pharmacological treatment have a significant influence on many aspects of female reproductive health. Female patients diagnosed with IA have more fertility problems, fewer children and worse pregnancy outcomes than the general population (4-6). It has also been documented that female patients diagnosed with IA benefit from receiving multidisciplinary specialized care before, during and after pregnancy (7). Remarkably, this generated knowledge even led to the formation of a new recognized field in Rheumatology termed “Reproductive Rheumatology” (8).

Guidelines on how to approach reproductive health in patients diagnosed with IMIDs have been published (9, 10), however these guidelines mainly focus on women and

systemic lupus erythematosus. Furthermore, modern treatment strategies for pregnant women diagnosed with an IMID have been successfully applied in the clinic resulting in better maternal and neonatal outcomes (7). A major weakness of the modern Reproductive Rheumatology is that, compared to the information available for women, the impact of IMID and its associated pharmacological therapy on male reproductive health has not been comprehensively evaluated.

Explaining the gender gap in Reproductive Rheumatology

Two major misconceptions could explain this gender gap in Reproductive Rheumatology. First, because IMIDs tend to be more prevalent in women, IMIDs have been long considered "female diseases". Second, the historical belief that male contributions to pregnancy are not relevant. Therefore, before moving forward, it is important to debunk these misconceptions.

First, IMIDs also affect men of all ages. It has been estimated that IMIDs affect around 3-8% of the population, of whom 22% are men (11, 12). It is also well known that specific IMIDs that are more prevalent in men (such as SpA or psoriasis) are more likely to manifest before the age of 50 years. Altogether, this leads to an astonishing number of young men (175 million worldwide) who could potentially receive the diagnosis of an IMID before or during their reproductive years.

Second, male contributions to pregnancy are not just relevant but fundamental for a healthy pregnancy. Recent studies have demonstrated that healthy men are more likely to improve a couple's ability to conceive and have a healthy, uncomplicated pregnancy (13). Furthermore, most men, just like women, aspire to become a parent (14, 15). Their involvement in other important aspects of reproduction such as family planning and fatherhood has also increased considerably (13).

Sexual and reproductive health

According to the World Health Organization (WHO), sexual and reproductive health is defined as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity, in all matters relating to sexuality, the reproductive system and to its functions and processes. Reproductive health, therefore, implies that people are able to have a satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when and how often to do so" (16).

This comprehensive definition developed by WHO is expansive. It includes medical or biological aspects such as erectile dysfunction but also several non-biological aspects.

Of these non-biological aspects, “sexual wellbeing” has been recently identified as a relevant component of sexual health. Sexual wellbeing has been defined as ““the cognitive and emotional evaluation of an individual’s sexuality” (17). It includes seven core domains: sexual safety and security, sexual respect, sexual self-esteem, resilience in relation to past sexual experiences, forgiveness of past sexual events, self-determination in one’s sex life, and comfort with one’s sexuality (18).

Noteworthy, sexual health and sexual wellbeing (and not only fertility/pregnancy issues) are considered to be highly relevant aspects of quality of life. This applies to both women and men of all ages and sexual preferences (19). Accordingly, Reproductive Rheumatology should broaden its scope by including men of all ages and sexual preferences and focus on all components of male sexual and reproductive health.

Can IMIDs impact male sexual and reproductive health?

Based on physiological concepts and limited scientific evidence it was speculated that the diagnosis of an IMID and its associated pharmacological treatment could interfere with all the aforementioned components of sexual and reproductive health. The capability to reproduce and the freedom to do so are directly impacted by the diagnosis of an IMID as patients are frequently advised to delay pregnancy because of high disease activity or exposure to a drug with an unknown reproductive toxicity profile (20). Furthermore, pain and fatigue have been described as important contributors to impaired sexual health (physical) (21). Depression and anxiety, frequently present in patients diagnosed with an IMID (22), are mental health diseases that have been associated with male sexual dysfunction/erectile dysfunction and relationship problems (mental and social) (23). Lastly, IMIDs such as RA have been associated with having a significant social impact and lower quality of life (social well-being) (24).

The first reports of a negative impact of medication on male fertility came in in 1979, when A.J. Levi and colleagues, reported that sulphasalazine, a commonly used immunosuppressive drug for the treatment of diverse IMIDs, was found to be associated with oligospermia (low sperm count or more specifically, fewer than 15 million sperm in 1 milliliter of semen) and infertility (inability to conceive after 1 year of unprotected intercourse) in 4 young men diagnosed with ulcerative colitis (25). They also stated that “the effect of sulphasalazine on spermatogenesis in patients on maintenance treatment clearly requires further investigation”. This statement can be considered one of the first signs that male reproductive health could be impaired in men diagnosed with IMIDs. Unfortunately, for decades, research on this topic mainly focused on the potential effect

of a few immunosuppressive drugs on semen quality. Most of the evidence on this topic is scattered throughout the literature and based on low quality small case series or cross-sectional studies. Interestingly, the potential influence of disease activity was never considered.

While in the field of Rheumatology, this topic remained neglected by the scientific community, researchers from other fields such as Andrology and Urology, provided us with more clues that suggested that “chronic diseases” and inflammation might be associated with male infertility (26).

Evaluating male sexual and reproductive health

Historically, guidelines and recommendations on the evaluation of male sexual and reproductive health have been presented separately.

Sexual health

Sexual health has been defined as a state of physical, emotional, mental and social wellbeing in relation to sexuality. Despite the fact that sexual health is not merely the absence of disease, dysfunction or infirmity, the impact of inflammatory arthritis (IA) on male sexual health has mainly been studied focusing on the physical component of sexual health; erectile function.

Guidelines and recommendations on how to screen, diagnose and treat erectile dysfunction are available (27-29). Noteworthy, the diagnostic criteria and therapeutic options described in these guidelines are based on studies performed with men from the general population and are not necessarily representative for men diagnosed with IA. Furthermore, other relevant aspects of sexual health such as sexual wellbeing are not included in these guidelines.

Therefore, in order to be able to appropriately counsel and advice men with sexual health problems due to IA, we first need to identify and understand the full impact of IA. Herewith, the outcome of interest should not only focus on the physical component but also on the emotional, mental and social components of sexual health.

Reproductive health

Reproductive health implies that people have the capacity to reproduce and the freedom to decide if, when and how often to do so (30). The WHO defines infertility as the inability to conceive after at least 12 months of regular, unprotected sexual intercourse

(31). It is estimated that 8-12% of couples are infertile. Noteworthy, "the male factor infertility" is responsible for around 50% of the causes of infertility worldwide (32).

Guidelines on how to evaluate male infertility have been published (33, 34). Shortly, reproductive history and at least one conventional semen analysis are recommended for the initial evaluation. Conventional semen analysis remains at the center of male fertility evaluation but it is widely known that semen analysis has limited accuracy for determining the male fertility potential or predicting reproductive success (32). Furthermore, evaluating the male reproductive endocrine axis is only recommended in men with oligospermia (sperm concentration below 10×10^6/mL), impaired erectilefunction or if endocrinopathy is suspected.

An important marker of male fertility was recently developed. The sperm DNA fragmentation index (sDFI) reflects the integrity and damage to the sperm DNA and provides a more comprehensive assessment of fertility status compared to conventional semen analysis. Although it is still only used for research purposes, high sDFI has now been associated with male infertility and a higher risk of miscarriages (35).

Evaluating male sexual and reproductive health in Rheumatology, easier said than done

Sexual and reproductive health are important contributors to our patients quality of life. The majority of health care professionals acknowledge the importance of discussing this topic with their patients' but also acknowledge communication problems, lack of knowledge on the topic and simply lack of confidence and interest on the topic (33). Therefore, it is of the uttermost importance to properly understand how IA and other IMIDs impact male sexual health and to have insight into the needs of the patients in this regard. Furthermore, because of the many communication barriers commonly associated with this topic, it is also important to evaluate how rheumatologists perceive this topic. Ultimately, understanding both sides will allow us to better design strategies that will allow health care professionals and patients to approach this problem more efficiently.

Why (and how) is it important to evaluate the impact of IMIDs and pharmacological treatment on male sexual and reproductive health?

Altogether, it can concluded that these clues indicate that not only testicular toxicity associated with exposure to certain immunosuppressive drugs but also other factors related to the disease itself could result in an impaired male sexual and reproductive

health. First, it is important to critically review the available scientific evidence on the topic and summarize it by means of conducting systematic reviews on the topic. By doing do, an up-to-date review of all the relevant literature will become available to the scientific community. Second, it is evident that original research on this topic is urgently needed.

Conducting original research on the impact of IMIDs and pharmacological treatment on male sexual and reproductive health is a major scientific challenge. As stated before, sexual and reproductive health is a broad topic with several outcomes of interest. Evaluating these outcomes requires a meticulous scientific approach.

Consequently, it can be concluded that unraveling the importance of the male aspect of Reproductive Rheumatology requires original research using different study designs. These studies range from large epidemiological studies that evaluate the impact of IA on markers of male sexual and reproductive health, to clinical and translational studies that evaluate the testicular toxicity profile of immunosuppressive drugs to qualitative and quantitative studies with the potential to describe the subjective feelings and ideas behind the impact of IA on male sexual health.

AIMS OF THIS THESIS

The aim of this thesis is to evaluate the impact of IMIDs and its associated pharmacological treatment on several outcomes of male sexual and reproductive health.

REFERENCES

1. Schett G, McInnes IB, Neurath MF. Reframing Immune-Mediated Inflammatory Diseases through Signature Cytokine Hubs. New England Journal of Medicine. 2021;385(7):628-39.
2. Figus FA, Piga M, Azzolin I, McConnell R, Iagnocco A. Rheumatoid arthritis: Extra-articular manifestations and comorbidities. Autoimmunity Reviews. 2021;20(4):102776.
3. Gurung P, Yetiskul E, Jialal I. Physiology, Male Reproductive System. 2023.
4. Brouwer J, Dolhain R, Hazes JMW, Visser JA, Laven JSE. Reduced Ovarian Function in Female Rheumatoid Arthritis Patients Trying to Conceive. ACR Open Rheumatol. 2019;1(5):327-35.
5. Brouwer J, Dolhain RJEM, Hazes JMW, Erler NS, Visser JA, Laven JSE. Decline of ovarian function in patients with rheumatoid arthritis: serum anti-Müllerian hormone levels in a longitudinal cohort. RMD Open. 2020;6(3):e001307.
6. Brouwer J, Fleurbaaij R, Hazes JMW, Dolhain R, Laven JSE. Subfertility in Women With Rheumatoid Arthritis and the Outcome of Fertility Assessments. Arthritis Care Res (Hoboken). 2017;69(8):1142-9.
7. Smeele HT, Röder E, Wintjes HM, Kranenburg-van Koppen LJ, Hazes JM, Dolhain RJ. Modern treatment approach results in low disease activity in 90% of pregnant rheumatoid arthritis patients: the PreCARA study. Ann Rheum Dis. 2021;80(7):859-64.
8. Sammaritano LR, Chakravarty EF. Reproductive Rheumatology: Meeting Today's Challenges. Rheum Dis Clin North Am. 2017;43(2):xiii-xiv.
9. Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. Arthritis Care Res (Hoboken). 2020;72(4):461-88.
10. Götestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Annals of the Rheumatic Diseases. 2016;75(5):795.
11. Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. Rheumatology (Oxford). 2014;53(4):650-7.
12. El-Gabalawy H, Guenther LC, Bernstein CN. Epidemiology of Immune-Mediated Inflammatory Diseases: Incidence, Prevalence, Natural History, and Comorbidities. The Journal of Rheumatology. 2010;85:2.
13. Kotelchuck M, Lu M. Father's Role in Preconception Health. Matern Child Health J. 2017;21(11):2025-39.
14. Genesoni L, Tallandini MA. Men's psychological transition to fatherhood: an analysis of the literature, 1989-2008. Birth. 2009;36(4):305-18.
15. Eisenberg ML, Barratt CLR, De Jonge CJ. Don't forget the father. Fertility and Sterility. 2022;117(5):936-7.
16. Glasier A, Gülmezoglu AM, Schmid GP, Moreno CG, Van Look PF. Sexual and reproductive health: a matter of life and death. Lancet. 2006;368(9547):1595-607.
17. Öberg K, Fugl-Meyer KS, Fugl-Meyer AR. On sexual well-being in sexually abused Swedish women: Epidemiological aspects. Sexual and Relationship Therapy. 2002;17(4):329-41.
18. Mitchell KR, Lewis R, O'Sullivan LF, Fortenberry JD. What is sexual wellbeing and why does it matter for public health? Lancet Public Health. 2021;6(8):e608-e13.
19. Flynn KE, Lin L, Bruner DW, Cyranowski JM, Hahn EA, Jeffery DD, et al. Sexual Satisfaction and the Importance of Sexual Health to Quality of Life Throughout the Life Course of U.S. Adults. The journal of sexual medicine. 2016;13(11):1642-50.
20. Stransky O, Hunt N, Richards JS, Talabi MB. Exploring Family Planning, Parenting, and Sexual and Reproductive Health Care Experiences of Men With Rheumatic Diseases. J Rheumatol. 2022;49(3):251-5.

21. Östlund G, Björk M, Valtersson E, Sverker A. Lived Experiences of Sex Life Difficulties in Men and Women with Early RA - The Swedish TIRA Project. Musculoskeletal Care. 2015;13(4):248-57.
22. Baillet A, Gossec L, Carmona L, Wit M, van Eijk-Hustings Y, Bertheussen H, et al. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. Ann Rheum Dis. 2016;75(6):965-73.
23. Liu Q, Zhang Y, Wang J, Li S, Cheng Y, Guo J, et al. Erectile Dysfunction and Depression: A Systematic Review and Meta-Analysis. J Sex Med. 2018;15(8):1073-82.
24. Lapsley HM, March LM, Tribe KL, Cross MJ, Courtenay BG, Brooks PM, et al. Living with rheumatoid arthritis: expenditures, health status, and social impact on patients. Ann Rheum Dis. 2002;61(9):818-21.
25. Levi AJ, Fisher AM, Hughes L, Hendry WF. Male infertility due to sulphasalazine. Lancet. 1979;2(8137):276-8.
26. Choy JT, Eisenberg ML. Male infertility as a window to health. Fertil Steril. 2018;110(5):810-4.
27. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol. 1994;151(1):54-61.
28. Rosen RC, Cappelleri JC, Gendrano N. The International Index of Erectile Function (IIEF): a state-of-the-science review. International Journal of Impotence Research. 2002;14(4):226-44.
29. Wespes E, Amar E, Hatzichristou D, Montorsi F, Pryor J, Vardi Y. Guidelines on Erectile Dysfunction. European Urology. 2002;41(1):1-5.
30. Glasier A, Gülmezoglu AM, Schmid GP, Moreno CG, Van Look PFA. Sexual and reproductive health: a matter of life and death. The Lancet. 2006;368(9547):1595-607.
31. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al. The International Glossary on Infertility and Fertility Care, 2017. Fertil Steril. 2017;108(3):393-406.
32. Agarwal A, Baskaran S, Parekh N, Cho C-L, Henkel R, Vij S, et al. Male infertility. The Lancet. 2021;397(10271):319-33.
33. Kelder I, Sneijder P, Klarenbeek A, Laan E. Communication practices in conversations about sexual health in medical healthcare settings: A systematic review. Patient Education and Counseling. 2022;105(4):858-68.
34. Salonia A, Bettocchi C, Boeri L, Capogrosso P, Carvalho J, Cilesiz NC, et al. European Association of Urology Guidelines on Sexual and Reproductive Health-2021 Update: Male Sexual Dysfunction. Eur Urol. 2021;80(3):333-57.
35. Agarwal A, Majzoub A, Esteves SC, Ko E, Ramasamy R, Zini A. Clinical utility of sperm DNA fragmentation testing: practice recommendations based on clinical scenarios. Transl Androl Urol. 2016;5(6):935-50.

PART II

Impact of immune-mediated inflammatory diseases on male sexual and reproductive health

CHAPTER 2

Sexual function and reproduction can be impaired in men with rheumatic diseases: a systematic review

Published

Perez-Garcia LF, Te Winkel B, Carrizales JP, Bramer W, Vorstenbosch S, van Puijenbroek E, Hazes JMW, Dolhain RJEM.

Semin Arthritis Rheum. 2020 Jun;50(3):557-573.

ABSTRACT

Background

Information about the possible effect of rheumatic diseases on male sexual function and reproduction (sexual health) is scarce and difficult to summarize. Factors known to impair sexual health, such as inflammation, medication use and hypogonadism can be present in a significant proportion of male patients with rheumatic diseases.

Objectives

The objective of our study was to systematically review the literature for the influence of paternal rheumatic disease on sexual health, such as sexual function, reproductive hormones, male fertility, pregnancy and offspring outcomes.

Methods

English language articles identified through Embase, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Google Scholar and the Clinical trial registries of Europe and the USA published until February 2019. Literature was synthesized in narrative form and in summary tables. Outcomes were categorized as: sexual function, reproductive hormones, fertility and pregnancy and offspring outcomes. Results are presented per category and per disease.

Results

9735 articles were identified with our search strategy. After removal of duplicates, excluding articles by screening titles and abstracts and assessing eligibility by reading 289 fulltext articles, 87 articles fulfilled the eligibility criteria. All included studies enrolled patients diagnosed with a rheumatic disease and had results at least on one of the outcome categories. Sexual function was the most common category, followed by reproductive hormones, fertility and pregnancy and offspring outcomes. Sexual function is impaired in a high proportion of patients with rheumatic diseases. This was statistically significant in most of the studies where a control group was available. Clinically relevant abnormalities in reproductive hormones were mainly identified in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) and a positive correlation with disease activity were reported. Semen quality in men with rheumatic diseases can be impaired in patients with SLE, SpA, sarcoidosis, BD and MWS. Sperm count and motility were the most common semen quality parameters affected. No negative effect of paternal RA and vasculitis on pregnancy outcomes were reported in 3 studies. No studies reporting the effect of paternal disease on offspring outcomes were identified.

Conclusion

This systematic review suggests that sexual health is impaired in men with rheumatic diseases. The degree and extent of sexual health impairment vary per disease. More research is needed to fully understand the link between rheumatic diseases and impaired male sexual health. Meanwhile, rheumatologists should be aware of this association and discuss it with their patients.

INTRODUCTORY CLINICAL CASE

A 38-year-old man, was recently diagnosed with rheumatoid arthritis (RA). During the first follow up appointment he informs his rheumatologist, that he and his wife wish to conceive in the near future. For this reason, they want information about whether RA can affect sexuality and pregnancy outcomes. During the discussion it becomes apparent that the patient is having problems regarding his sexual function; sexual intercourse causes pain and sometimes getting an erection is difficult. He is worried that his RA could interfere with his sexual health and more importantly, his desire to become a father. The rheumatologist discusses treatment strategies that are known to be safe in men with a wish to conceive and promises to come back to him with more information about RA related sexual health outcomes. Thereafter, the rheumatologist discusses with some of his colleagues several questions:

1. Can rheumatic diseases affect male sexual function, reproductive hormones, fertility and pregnancy outcomes? Can disease activity impair male sexual health?
2. Which sexual health problems are common in male patients with rheumatic diseases?
3. In male patients with rheumatic disease, what is the importance of good paternal health for positive pregnancy and offspring outcomes?

INTRODUCTION

This case described above represents a frequent clinical scenario for rheumatologists around the world. For many years rheumatic diseases have been considered as diseases of women though it is estimated that the overall lifetime risk for developing a rheumatic disease for men is 1 in 20 (1). Especially in studies on reproductive rheumatology, there is a clear gender bias that has resulted in significant scientific knowledge focused only on the female perspective. Reducing this knowledge gap is important because sexual health and reproduction are as important for men as it is for women.

Sexual health, the state of physical, mental and social well-being in relation to sexuality, has been recognized as an important factor than can have positive or negative effects in an individual's quality of life and the World Health Organization (WHO) states that sexual health problems require specific action for their identification, prevention and treatment. Men diagnosed with rheumatic diseases have specific needs and thus require a health strategy of their own (2, 3). Nonetheless, information regarding this topic is scarce and scattered.

In addition to this, the WHO also considers the need to make informed and responsible choices about reproduction as one of their main sexual health concerns (4). Human

reproduction is a biological process that requires the correct structure and function of several organs and systems in men and women. For men, an adequate testicular function that results in healthy spermatozoa can be considered as one of the most important steps in male reproduction, but many other factors contribute to the success of a spermatozoon fertilizing an ovum, from a delicate balance among hormones secreted in the hypophysis and the testicles (*reproductive hormones*) to spermatogenesis and proper conditions for storage of the mature spermatozoa (*fertility*) to intercourse and ejaculation (*sexual function*).

All of these organs and physiologic processes can be impaired by inflammation secondary to rheumatic diseases and could have detrimental effects on both reproductive function and pregnancy outcomes (5-7). In addition, other well-known factors have detrimental effects on sexual health like chronic pain and fatigue, as well as psychological factors, such as depression and anxiety, all of them highly prevalent in patients with rheumatic diseases. Rheumatologists taking care of men with rheumatic diseases must consider this to adjust treatment accordingly. Improving men's preconception health might result in improved pregnancy outcomes by enhancing men's biologic and genetic contributions to the pregnancy conception (*pregnancy and offspring outcomes*) (8).

Information regarding the effect of rheumatic diseases on male sexual health is needed to improve the way rheumatologists counsel and treat male patients with rheumatic diseases.

The objective of our study was to systematically review the literature for the influence of paternal rheumatic disease on sexual health, such as sexual function, reproductive hormones, male fertility, pregnancy outcome and on their offspring health outcome. This systematic review (SR) will answer the following questions:

- What is the influence of rheumatic diseases on male **sexual function**?
- What is the influence of rheumatic diseases on male **fertility** and **reproductive hormones**?
- What is the influence of paternal rheumatic diseases on **pregnancy and offspring outcomes**?

METHODS

Protocol and registration

This SR is part of a larger SR that included other immune-mediated diseases (IMD) from Gastroenterology and Dermatology. The complete protocol was registered in PROSPERO and is available in https://www.crd.york.ac.uk/prospero/display_record.

php?RecordID=99845. The protocol and this SR were written according to the PRISMA-P statement (9-10).

Search

A search strategy was developed by an experienced medical librarian (WMB) using a structured methodology (9, 10). The searches combined keywords regarding male sexual function and fertility, pregnancy outcomes and offspring's health with a list of IMDs (which included Rheumatic diseases). Our full electronic search strategy is provided in supplement 1.

Information sources

A systematic literature search was performed in the bibliographic databases: Embase (via Elsevier embase.com), MEDLINE via Ovid, Cochrane Central Register of Trials (CENTRAL) and Web of Science Core Collection. Additionally, Google Scholar and the Clinical trial registries of Europe and the USA were searched. We also contacted authors for further information and included references from the primary search publications, in case these were missed in our search. The databases were searched from inception until February 2019.

Eligibility criteria

The literature search was limited to the English language and human subjects. Case-control studies, cohort studies, cross-sectional studies, case reports and case series were included. Conference abstracts from before April 2016 were excluded if more recent conference abstracts were found we contacted the authors and searched for published data. Publications without original data, such as reviews, were excluded.

In the case of studies reporting pregnancy and offspring outcomes, publications were included if the diagnosis of the IMD took place before conception. In case of studies just reporting fertility parameters (i.e. semen analysis, sexual dysfunction) we included publications were the diagnosis of a rheumatic disease was taken into consideration. No restrictions were made in regard to the comparison groups. The outcome data should include at least one of the following outcomes; sexual function, reproductive hormones, fertility, pregnancy or offspring outcomes.

Study selection

All articles were imported into EndNote X9. After removal of duplicates with the method described by Bramer (11), two reviewers (LP and JC) independently and blindly screened titles, abstracts and full-text of the records for eligibility. Disagreements were resolved

by consensus with the help of a third reviewer; RD, for sexual function, reproductive hormones and fertility outcomes and BW for pregnancy outcomes.

Data collection process

Two reviewers (LP and JC) extracted relevant information for each studied outcome from the included articles.

Risk of bias in individual studies

The methodological quality of the studies was assessed with the Newcastle Ottawa Scale (NOS), developed for case-control and cohort studies (12). Case series were graded conform the cohort studies (without controls). In the case of cross-sectional studies, an adapted scale was used (13). Using this method, points were awarded to each publication, related to the selection of the study group, the comparability of the study groups and the ascertainment of the outcomes. The score ranges from 0-9, with scores >5 representing good-quality studies. The results are presented in Tables 2-5. Quality assessment was done by LP and JC for the sexual function, reproductive hormones and fertility data, and the pregnancy and child outcome data by BW.

Synthesis of results

Sexual health outcomes were classified in 4 categories:

1. **Sexual function** (sexual dysfunction, premature ejaculation, erectile dysfunction).
2. **Reproductive hormones** (testosterone, LH, FHS, inhibin).
3. **Fertility** (sperm quality, testicular volume, time to pregnancy, number of children).
4. **Pregnancy and offspring outcomes** (congenital malformations, premature birth, impact on offspring).

Additional analysis

Due to the diversity of the methods used to report outcomes of interest in this SR performing a meta-analysis was not possible.

RESULTS

Study selection

A total of 9735 references were identified (4505 from Embase, 3524 from Medline-Ovid, 1666 from Web of Science and 40 from Cochrane central) and imported into EndNote X9. After removing 2851 duplicates, 6884 articles were eligible for title and abstract

screening. 6597 articles were excluded during this phase and 287 articles were eligible for full-text reading. 202 articles were excluded after full-text reading (see flowchart in figure 1) and 87 articles fulfilled the criteria for rheumatic diseases.

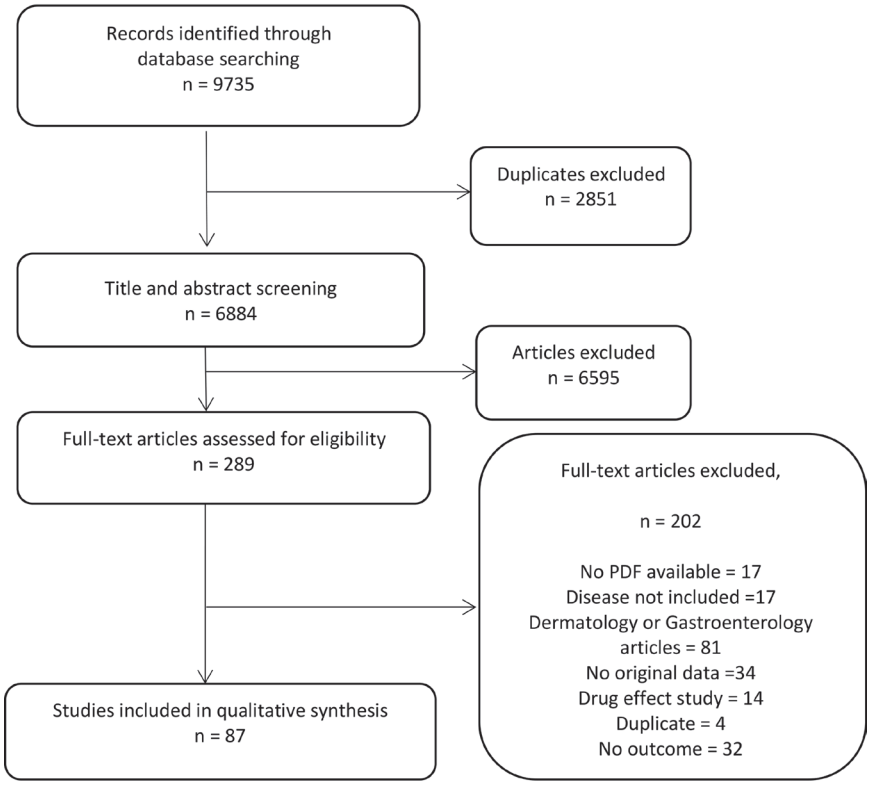


Figure 1. Flowchart of study selection

Summary of findings per disease.

Results are presented per disease and divided into 4 categories (*sexual function, reproductive hormones, fertility outcomes and pregnancy and offspring outcomes*) (See Table 1).

- **Rheumatoid arthritis**

- **Sexual function**

Sexual function in RA was studied in 8 articles that included 282 patients with a mean age of 41.07 years. Three studies were in European populations, 3 in Africa, 1 in North America and 1 in Asia. Three articles assessed Sexual Dysfunction (SD) by interview, the International Index of Erectile Function (IIEF) was used in 3 articles, the Questionnaire for Screening Sexual Dysfunctions (QSD) in 1 article, and ICD-9 diagnosis code in 1 article.

Table 1. Number of articles included per disease

Disease	Number of articles included	Sexual function	Reproductive hormones	Fertility	Pregnancy outcome
Rheumatoid arthritis	11	8	3	0	2
Systemic Lupus Erythematosus	10	4	5	8	0
Ankylosing Spondylitis	24	17	2	7	0
Systemic Sclerosis	7	7	0	1	0
Behçet Syndrome	9	5	0	4	1
Sarcoidosis	16	0	1	15	0
Antiphospholipid syndrome	4	2	0	3	0
Vasculitis	3	0	2	0	1
Auto-inflammatory syndromes	4	0	2	1	1

The prevalence of SD was significantly higher in men with RA than in healthy controls in all the included studies (range, 33-62% vs 11-40%, respectively), this was associated with disease activity and other disease-related factors, such as fatigue and pain.

Elst et al reported that 32 male patients with RA (mean age 46.2 ±7 years) and a diminished functional capacity had lesser sexual motivation and that 9 (27%) of patients wanted advice from experts for their sexual problems (14). SD was common in 32 RA patients (mean age 55 years), particularly impotence (defined as the inability to obtain an erection firm enough for vaginal penetration, or the inability to sustain the erection until completion of intercourse) was significantly more prevalent in RA patients than in age-matched controls (62% vs 40%, $p<0.05$) (15).

SD was reported in 49 out of 91 (53.8%) RA male patients (mean age 51.4 ±9.4 years) in an Egyptian multicenter study. Using the IIEF, a statistically significant correlation between SD and several factors that are usually present in RA patients was reported. These factors were; pain, cardiovascular disease, age, disease activity, fatigue, tender joint count and psychological status. Interestingly, the number of intramuscular steroid injections, but not the oral intake of prednisone, was correlated with more SD (16).

Using the IIEF questionnaire in a case-control study, Gaber et al assessed the prevalence of SD in 29 RA male patients (mean age 45.2 ± 12.1 years). A mean DAS28 score of 3.5 (standard deviation 1.45), suggestive of moderate disease activity was reported. Overall, SD was reported in 14 (48.3%) of patients vs 12 (33.3%) in controls (p=0.2). All SD parameters were significantly higher in RA patients compared to controls and multivariate regression analysis revealed that severe RA (DAS28 >5.1) was associated with a higher risk of SD (OR 2.7, 95% CI 1.09-6.05) (17).

In a multicenter study from the Netherlands, van Berlo et al included 76 male patients with RA (mean age 57.6 [standard deviation 10.6] years, mean DAS28 3.5 [standard deviation 1.45]) and found that RA patients differed significantly from 54 controls (mean age 54.9 [standard deviation 9.4]) regarding the frequency of sexual activities and libido (lower in RA than in controls, $p<0.05$). Physical functioning ($p<0.01$) and, to a lesser extent, disease duration and activity ($p<0.05$) significantly correlated with various sexual problems. Patients and controls did not differ regarding sexual satisfaction (18). In a comparable study, Gordon et al reported that among 31 RA patients (mean age 37 years), 10 (33%) admitted periods of erectile dysfunction (ED) and that 15 (50%) experienced decreased libido (19).

In a study comparing 24 male young RA patients (mean age 31.3 ± 7.35 years) and 18 age-matched healthy controls, Nasr et al reported that SD was present in 11 (45.8%) of these patients compared to 2 (11.1%) controls. There were a significant correlation between dehydro-epiandrosterone sulfate (DHEA) levels, total and free testosterone levels and the IIEF score ($p=<0.001$) (20).

In a large population-based study from Taiwan that analyzed the data of 6319 patients diagnosed with ED, an association between ED and prior diagnosis of RA was reported. The OR for prior RA diagnosis among cases with ED was 1.67 (95%, CI 1.36–2.05) that of controls after adjusting for several confounders (21).

- **Reproductive hormones**

Results on reproductive hormones were reported in 3 RA-related studies. In all of these studies, patients with RA were found to have lower total and free testosterone levels than healthy controls.

The androgenic status of 31 male patients with RA (median age 55 years) was investigated by Gordon et al, after correcting for age-related changes to the pituitary-testicular axis, patients with RA still showed significantly lower serum testosterone and significantly greater serum LH and FSH compared to 33 males with Ankylosing Spondylitis (AS) (median age 37 years) and 95 age-matched healthy controls. Serum FSH was significantly higher in RA patients compared to healthy controls (19).

Nasr et al also studied the andrological profile of 24 men with RA (mean age 31.3 ± 7.3 years) and compared them to 18 healthy controls (mean age 30.8 ± 7.4 years). They found that RA patients have statistically significant lower DHEA (71.13 ± 22.71 vs 236.61 ± 105.41 ug/dl, $p<0.001$), total testosterone (1.5 ± 0.6 vs 4.7 ± 1.7 ng/ml, $p<0.001$) and free testosterone levels (32.7 + 14.2 vs 188.0 + 70.5 pg/ml, $p<0.001$) (20).

In one of the few prospective studies identified in this SR, a group of 41 RA male patients (mean age 53 years) were followed from disease onset through 2 years by Tengstrand et al. Early in the disease course, RA patients younger than 50 years had lower mean testosterone than controls (16.2 [standard deviation 3.5] vs 23.3 [standard deviation 7.5] UI/l, p=<0.001). A reduction of disease activity (lower DAS28 score) during the 2-year follow up correlated significantly with an increase in testosterone levels (r^s=-0.46, p=0.006) (22).

- **Fertility**

No studies were included.

- **Pregnancy and offspring outcomes**

Using data from a nationwide Norwegian registry, Wallenius et al reported no increased risk of adverse pregnancy outcomes or preeclampsia in partners of men with inflammatory joint disease, regardless of whether the father had or had not been exposed to Disease-Modifying Anti-Rheumatic Drugs (DMARDs) (23). In a similar study, data from a Danish population-based cohort were presented by Rom et al where paternal RA was not found to be associated with reduced fetal growth or preterm birth among 1086 children exposed to paternal RA compared to non-exposed children (24).

- **Systemic Lupus Erythematosus**

- **Sexual function**

Sexual function in Systemic Lupus Erythematosus (SLE) was reported in 4 studies from Latin America, using the following outcome measures: IIEF in 1 article and interview in 3 articles. These studies included data on 229 patients with a mean age of 31.5 years and 175 healthy controls with a mean age of 28.8 years.

SD prevalence ranged from 12 to 68% in SLE patients compared to 0 to 22% in healthy controls. The association between disease activity and SD was analyzed in 2 studies and no association was reported (25, 26). In a multicenter study from Latin America that included 174 young SLE patients (mean age 36.1 ± 1.0 years) a significantly increased prevalence of ED in men with SLE compared to controls (68% vs 22%, p=0.001) was reported. Among these patients the presence of persistent lymphopenia (≤1000 cells/mcl at three consecutive times, p=0.006) and the use of prednisone (9.3 ± 1.2 vs 5.3 ± 1.2 mg, p=0.026) were recognized as independent risk factors for ED (OR 2.79, CI95% [2.79–5.70], p=0.001 and 2.15, CI95% [1.37–3.37], p=0.001, respectively). Interestingly, only 7% of patients had been questioned about their sexual function in the previous 3 visits to the rheumatologist while 82% of the patients considered it would be appropriate to be asked about it (25).

Using a self-administrated questionnaire Silva et al reported a prevalence of ED of 20% in 25 SLE young patients (mean age 26 years) compared to 0% in 25 healthy controls (mean age 27 years) (p=<0.0001) (26). In 2 similar studies that also included young SLE patients (mean age 27 and 36 years, respectively), the prevalence of SD was found to be significantly higher in SLE patients compared to age-matched controls (12% vs 0% and 30 vs 0%, respectively) (27, 28).

- **Reproductive hormones**

Higher levels of FSH and LH, an indication of hypogonadism, in SLE patients compared to healthy control were a common finding in 5 studies included for this section. Unfortunately, the cause of hypogonadism in these men was not established.

In a study that included 25 young SLE patients (mean age 27 years [15-45]) and 25 age-matched healthy controls, it was shown that SLE patients had higher median FSH (5.8 [2.1–25] vs 3.3 [1–9.9] IU/L, p=0.002) and higher median LH (5.8, CI95% [1.4–15.6] vs 3.7, CI95% [1.8–5.8] IU/L, p=0.008) levels than controls. Low morning total testosterone levels were reported in 6 (24%) SLE patients compared to 0 controls (27). Gonadal function was assessed by Soares et al and they found that SLE patients with severe sperm abnormalities (azoospermia/oligospermia) had significantly higher median FSH level than patients with mild sperm abnormalities (10.9, CI95% [3.9–25] vs 3.3, CI95% [1–17.9] IU/L, p=0.0001) (29).

Testicular cell function was determined by measuring serum inhibin B levels in a study that included 34 SLE patients (age 15-45 years) and it was reported that 8 (23.5%) patients had low serum inhibin B levels. This was associated with higher levels of FSH and LH and with lower sperm concentration, sperm count and motile sperm count (30). In a small study that included 4 patients with juvenile-onset SLE, only one patient with sperm abnormalities had high FSH levels and a slight elevation of LH levels (31).

In a recent study by Tiseo et al that included 28 young SLE patients (mean age 33 years) the median level of LH (6.5, CI95% [1.8–13] vs 3.95, CI95%[1.9–7.9] IU/L, p=0.001) and total testosterone levels (500, CI95% [262–1500] vs 389, CI95% [162–729] ng/dl, p=0.002) were significantly higher in SLE patients compared to 34 age-matched controls(32). A potential limitation of this study was the exclusion of azoospermic SLE patients.

- **Fertility**

Fertility parameters were reported in 9 studies, mainly from Brazil (n=7). These studies included data on 263 SLE patients with a mean age of 30.2 years and 139 healthy controls with a mean age of 30.4 years. Sperm abnormalities, mainly lower median

total sperm count, were a common finding in SLE patients. Infertility and subfertility as measured by the number of children per man, severe sperm abnormalities and the DNA fragmentation index (DFI) was also a relevant finding in 3 studies. Cyclophosphamide (CYC) was used in more than half of patients but could not solely explain these findings.

Soares et al reported a significantly lower testicular volume in 35 SLE patients compared to controls (15 vs 20 ml, p=0.003) and lower median total sperm count (70 x 10^6 vs 172 x 10^6, p=0.002). In addition, all patients had semen abnormalities according to WHO guidelines (29). In contrast, Suehiro et al reported no difference in testicular volume among patients and controls (30).

Farhat et al prospectively investigated the correlation of air pollutants exposure concentrations and semen quality in SLE patients and found that only CYC use and ozone had an association with sperm quality abnormalities. Even in patients not exposed to CYC a detrimental effect of ozone exposure on semen quality of SLE patients was observed (33).

Klinefelter syndrome (KS) may predispose men to develop SLE and primary testicular failure. An increased prevalence of KS in men with SLE was reported in a study that included 212 men with SLE (235 per 10,000 male SLE patients vs 17 per 10,000 in live male births). Interestingly, all SLE patients that were known to be infertile had KS. The authors went further recommending that any male SLE patient whose fertility is questionable should be evaluated for features of KS (34).

Regarding juvenile-onset SLE, a small study that included 4 patients (mean age 19 years) also demonstrated semen quality abnormalities in all of these patients; nonetheless, a medication effect could be responsible for these findings (31).

The integrity of genetic material in the spermatozoon is of essential importance for successful fertilization. The sperm DNA Fragmentation Index (DFI), a novel diagnostic tool used in infertility clinics, measures sperm DNA damage. DFI levels above 25% are strongly associated with infertility. DFI was significantly higher in SLE patients compared to controls (62, CI95% [31-97]% vs 25.5, CI95% [0-100]%, p=<0.001) in a study were conventional sperm parameters were similar in both groups. Interestingly, no correlations were found between DFI with disease activity (SLEDAI-2K and SLICC/ACR-DI) or medication use(32).

Information about the number of children per man diagnosed with SLE was reported in 2 studies. In the study by Silva et al the percentage of partners with gestations was statistically lower in SLE patients compared with 25 age-matched healthy controls (20%

vs 60%, p=0.0086) (26). Soares et al reported that 20% of SLE patients fathered children after disease onset, compared with 80% controls (p=0.0001) (29).

- **Pregnancy and offspring outcomes**

No articles were included.

- **Antiphospholipid Syndrome**

Only 2 studies and 2 case reports of antiphospholipid syndrome (APS) patients were included.

In a small study that included 11 patients with APS (mean age 46.2 years), ED was observed more frequently in APS than in 22 age-matched controls (45.5% vs 4.5%) and previous arterial thrombosis was significantly higher in patients with ED compared to those without ED (100% vs 16.7%, p=0.0152) (35).

ED was significantly higher in 12 APS patients (mean age 37.5 years) than in 20 age-matched controls (25% vs 0%, p=0.044). Median sperm concentration, sperm motility, and normal sperm forms were comparable in APS patients and controls (141.5, CI95% [33–575] vs. 120.06, CI95% [34.5– 329]x10^6/ml, p=0.65; 61.29, CI95% [25–80] vs. 65.42, CI95% [43–82]%, p=0.4; 21.12, CI95% [10–42.5] vs. 23.95, CI95% [10– 45]%, p=0.45, respectively), and none of them had oligo/azoospermia. The median penis circumference was significantly lower in APS patients with ED vs those without ED (8.1, CI95% [6-10] vs 10.2, CI95% [10-11] cm, p=0.007) (36). Testicular thrombosis secondary to APS was described in case reports (37, 38).

- **Spondyloarthropathies**

From the long list of diseases classified as spondyloarthropathies, our SR search strategy only identified articles that reported SD in AS (n=15) and psoriatic arthritis (PsA) (n=1).

- **Sexual function**

A total of 15 studies were included in this section where many different questionnaires were used (IIEF used in 7 articles). In summary, 884 AS patients with a mean age of 37.9 years answered questionnaires or interviews for SD screening. Most of these studies are from Turkey (8), followed by Korea with 2 studies and India, Morocco, Tunes, China and Brazil with 1 study each. It was reported that SD can be a problem for 30-82.5% of male patients with AS (vs 12.5-43% in healthy controls), this was associated with disease activity, disease duration, depression, fatigue and limited joint mobility (39-54).

In a study that included 73 patients with AS, Rostom et al, reported that 70 (95.9%) patients had never been asked before by doctors about sexual activity (40). Interestingly, 3 studies from Turkey reported a lower or similar prevalence of SD in patients and healthy controls (42-44). Specific findings per article can be found in table 2.

- **Reproductive hormones**

Two studies performed an andrological evaluation in men with SpA. Hypogonadism was associated with inflammation in SpA patients in Italian patients (55) while in a Brazilian study the concentration of LH, FSH and testosterone was comparable among AS patients and healthy controls (56).

The Italian study included 10 young patients (mean age 28.7 ± 8.6 years) diagnosed with AS or PsA (n=5/5) and a statistically significant difference in plasma hormone levels between patients and 20 age-matched healthy controls was detected: in patients LH and FSH values were higher (7.2, CI95% [4.5–7.9] and 5.7, CI95% [3.5–12.1] UI/L vs. 3.6, CI95% [3.1–4.2] and 3.4, CI95% [2.6–4.1] UI/L, respectively, both p=<0.01) and testosterone was lower (14.2, CI95% [9.9–18.1] vs. 20.4, CI95% [18.1– 22.5] nmol/L, p=<0.01). After 1 year of treatment with TNF inhibitors normal hormone levels were observed in this group (55).

Testicular Sertoli function was also evaluated in AS using inhibin B. It is considered an important marker of gonadal function and spermatogenesis. Median inhibin B levels were lower in AS patients and controls (68, CI95% [23–265] vs 112.9, CI95% [47.8–231.9] pg/ml, p=0.111). Other hormones, such as FSH and LH were similar in both groups (56).

- **Fertility**

Five studies analyzed the impact of AS on sperm quality and reported inconsistent results. In total, data from 158 SpA patients, mainly diagnosed with AS (mean age 32.9 years) and 231 healthy controls (mean age 33.5 years) were included. This population was more heterogeneous, 3 studies are from Europe, 1 from Latin America and 1 from Asia. No differences in the semen quality between patients and healthy controls were reported in 3 studies, but the presence of varicocele was significantly higher in patients compared to controls in 2 studies and this was associated with semen quality abnormalities. In 2 studies, sperm motility was significantly reduced in SpA patients. This was associated with disease activity and improved after treatment with TNF inhibitors. In addition, an increased rate of infertility was reported in one study.

Table 2. Summary of sexual function results.

Study	Number of cases/controls (mean age in years)	Diagnostic/ Screening tool used	Main findings	Study type and Quality assessment (NOS)
Rheumatoid arthritis				
Elst (14) Netherlands	Cases: 32 (46.2 ± 7) Controls: 236 (NA)	Interview and sexual motivation scale	Impotence was significantly more prevalent in RA patients than in age-matched controls (62% vs 40%, p<0.05) Patients with tender joint count <6 had stronger sexual motivation than those with >6. No statistically significant difference was found between disease activity and lower sexual interaction. 27% of patients wanted advice for their sexual problems	Case-control 2
Blake (15) USA	Cases: 32 (57.2) Controls: 21 (55.1)	Interview and the Azrin Marital Happiness Scale (AMHS).	Impotence prevalence was statistically significant in RA patients compared to controls (62% – 40%). • Associated with older age, DM2, hypertension and methotrexate use. Depression was not associated with impotence.	Case-control 5
El Miedany (16) Egypt	Cases: 91(51.4 +9.4) Controls: NA	IIEF	SD reported by 53.8% of male patients with RA. SD correlated with: • Pain score, cardiovascular disease, age, disease activity, psychological status, fatigue score, number of intramuscular steroid injection, tender joint count. No correlation with DMARDs or oral steroid therapy.	Cohort 2
Gaber (17) Egypt	Cases: 29 (45.2 ± 12.1) Controls: 36 (43.2 ± 9.7)	IIEF	SD present in 48.3% of RA patients (33.3% in controls). SD significantly associated with: • Longer morning stiffness duration. • Higher DAS28 score.	Case-control 3
Van Berlo (18) Netherlands	Cases: 76 (57.6 [SD 10.6]) Controls: 54 (54.9 [SD 9.4])	Questionnaire for screening sexual dysfunctions (QSD)	Statistically significant differences among RA patients and controls: • Feel any desire for sexual contact with their partner (85% vs 96%) • Masturbate (52% vs 79%). • Have sexual daydreams or fantasies (65% vs 89%). Physical functioning, disease duration and activity correlated with various sexual problems. 41% of men had troubles with several joints during sexual activities.	Case-control 6

Table 2. Continued

Study	Number of cases/controls (mean age in years)	Diagnostic/ Screening tool used	Main findings	Study type and Quality assessment (NOS)
Gordon (19) Scotland	Cases: 31 (55) Controls: 95 (NA)	Interview	33% of RA patients admitted periods of impotence and 50% experienced decreased libido.	Case-control 3
Nasr (20) Egypt	Cases: 24 (31.3 ± 7.3) Controls: 18 (30.8 ± 7.4)	IIEF	45.8% of patients with RA were diagnosed with ED compared to 11.1% of controls. • 20.8% of RA patients had moderate ED compared to 0% of controls. No significant correlation found between IIEF and disease activity. Significant correlation found between dehydroepiandrosterone (DHEA) levels, total and free testosterone levels and IIEF score.	Case-control 4
Keller (21) Taiwan	Cases:6310 (NA) Controls: 37860 (NA)	ICD-9 diagnosis	The OR for prior RA among cases with ED was 1.67 (95%, CI 1.36 – 2.05) that of controls after adjusting for several factors.	Cohort 4
Systemic lupus erythematosus				
Merayo-Chalico (25) Mexico	Cases: 174 (36.1 ± 1.0) Controls: 105 (NA)	IIEF	Prevalence of SD in SLE patients was 68% vs 22% in healthy controls (p=0.001). Significant differences were reported among patients with SLE and SD and those without SD: • Presence of persistent lymphopenia (≤1000cells/mcl at three consecutive times, p=0.006). • Higher prednisone dose (9.3 ± 1.2 vs 5.3 ± 1.2 mg, p=0.026). • SLICC damage score (1.25 ± 0.14 vs 0.80 ± 0.16 points, p = 0.042). No difference regarding disease activity (SLEDAI score 4.89 ± 0.54 vs 3.65 ± 0.52, p = 0.16). Only 7% of patients had been questioned about their sexual function. • 82% of patients considered it would be appropriate to be asked about their sexual function	Cross-sectional 4

Table 2. Continued

Study	Number of cases/controls (mean age in years)	Diagnostic/ Screening tool used	Main findings	Study type and Quality assessment (NOS)
Silva (26) Brazil	Cases: 25 (26) Controls: 25 (27)	Interview	SD present in 20% of SLE patients compared to 0% in healthy controls (p=0.0001). The SLEDAI [0 (0-12) vs 0 (0-6), P = 0.295] and SLICC/ACR-DI [0 (0-1) vs 0 (0-3), P = 0.36] medians were similar in SLE patients with SD/ ED in comparison with those with normal function.	Case-control 3
Rabelo-Junior (28) Brazil	Cases: 10 (36.9) Controls: 20 (32.4)	Self-administered non specified questionnaire	SD significantly higher in SLE patients compared to controls (30% vs 0%, p=0.029).	Cross-sectional 5
Vecchi (27) Brazil	Cases: 25 (27) Controls: 25 (27)	Interview	SD present in 12% of SLE patients vs 0% in controls, p=0.0638. None of the patients or controls had ED. Frequency of sexual intercourse was similar among both groups.	Case-control 8
Antiphospholipid syndrome				
Lopes Gallinaro (35) Brazil	Cases: 11 (46.2 ± 9.4) Controls: 22 (42.3 ± 6.0)	IIEF	SD was significantly observed more frequently in APS than controls (45.5% vs 4.5%, p=0.0096). Moderate/severe ED was more common in APS than controls (36.4% vs 0%, p=0.0081). Erectile function and intercourse satisfaction were the areas with the most significant differences among APS patients and controls. Arterial events were significantly higher in APS patients with SD than those without SD (100% vs 16.7%, p=0.0152).	Cross-sectional 4
Rabelo-Junior (36) Brazil	Cases: 12 (37.5) Controls: 20 (32.4)		Erectile dysfunction was significantly higher in APS patients than in controls (25% vs 0%, p=-0.044). 42% of APS patients with previous arterial thrombosis had SD compared with no patients with arterial events (p=0.204).	Cross-sectional 5

Table 2. Continued

Study	Number of cases/controls (mean age in years)	Diagnostic/ Screening tool used	Main findings	Study type and Quality assessment (NOS)
Spondyloarthropathies				
Dhakad (39) India	Cases: 100 (34.42 ± 9.78) Controls: 100 (36.39 ±8.07)	IIEF	SD was more common in AS patients: • Erectile function, orgasmic function, intercourse satisfaction and overall satisfaction were found to be significantly lower in the AS group as compared to controls . ED in 42% of AS patients (vs 18% in controls, p=0.0006) • Associated with higher age, longer AS duration, anxiety, depression and higher BASFI.	Case-control 5
Rostom (40) Morroco	Cases: 110 (38.9 ± 12.5) Controls: NA	Self-administered questionnaire	95.9% had never been asked about sexual activity by their doctors and 41% discussed the impact of AS on sexual activity with their partners. From those sexually active: • 44% were unsatisfied. • 41% reported ED. • 38.4% had orgasmic problems. What is the cause of your sexual problems? • Fatigue (90%). • Pain (69%). • Depression (62.5%).	Cross-sectional 2
Sariyildiz (41) Turkey	Cases: 70 (36.4 ± 7.4) Controls: 60 (35.2 ± 7.7)	IIEF	Patients with AS had significantly lower scores in each of the 5 domains of the IIEF compared to healthy controls (p=<0.05). Negative correlation between BASFI scores and IIEF scores (p=<0.01). • BASFI was independently associated with orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. BASDAI negatively correlated with erectile function, intercourse satisfaction and IEEF total scores (p=<0.05). • BASMI was independently associated with erectile function (p < 0.05)	Cross-sectional 4
Rezvani (42) Turkey	Cases: 39 (38) Controls: 27 (30)	IIEF	Prevalence of ED was higher in healthy controls compared to patients with AS (51.9% vs 43.%, respectively, p=0.512).	Case-control 3

Table 2. Continued

Study	Number of cases/controls (mean age in years)	Diagnostic/ Screening tool used	Main findings	Study type and Quality assessment (NOS)
Tarhan, (43) Turkey	Cases: 50 (38.5 ± 10.3) Controls: 50 (38.7± 7.0)	Interview	Similar prevalence of premature ejaculation in AS patients and healthy controls (32 and 30%, p=0.331).	Case-control 3
Ozkorumak (45) Turkey	Cases: 43 (36.2 ± 8.7) Controls: 43 (36.5± 6.5)	DSM-IV criteria (diagnosis confirmed by psychiatrists) and Glombok-Rust Inventory of Sexual Satisfaction (GRISS)	SD diagnosis established in 41.9% of patients vs 14.6% of controls (p=0.08). GRISS total score modestly correlated with depression and anxiety scores and with disease activity (BASDAI). GRISS scores significantly higher in AS patients than controls. Significant differences in: • Premature ejaculation • Dissatisfaction • Impotence	Cross-sectional 5
Bal (44) Turkey	Cases: 37 (42.8 ± 10.8) Controls: 67 (43.6 ± 5.9)	IIEF	Prevalence of ED similar between patients and controls (35.1% vs 26.9%, p=0.335). The only statistically significant difference was detected in sexual desire (lower in AS patients, p=0.014). No correlation between IIEF scores, AS disease duration and activity parameters was reported.	Cross-sectional 4
Oh (46) Korea	Cases: 22 (37.8) Controls: NA	IIEF	63.6% of AS patients had ED. • Decreased to 45.5% after 3 months of anti-TNF therapy. There were significant improvements in 4 IIEF-5 domains after 3 months of anti TNF therapy (all except orgasmic function).	Cross-sectional 2
Cakar (47) Turkey	Cases: 53 (32.8 ± 12.1) Controls: NA	Interview "According to you, does AS affect you negatively during sexual intercourse?"	50.94% of AS patients admitted as affected with regard to sexual intercourse. Patients with lumbar column and hip involvement and those with higher depression scores were more likely to report sexual intercourse dissatisfaction.	Cross-sectional 3
Dincer (48) Turkey	Cases: 65 (32.98 ± 11) Controls: 45 (30.1 ± 6.2)	Brief Male Sexual Function Inventory (BMSFI)	Patients with AS had significantly lower sexual drive, problem assessment, erection and overall satisfaction scores compared with healthy controls. 20.5% of AS patients were significantly more likely to report that they were not sexual satisfied vs 8.8% of healthy controls (p=<0.05). SD associated with depression and limited joint mobility (BASMI)	Case-control 6

Table 2. Continued

Study	Number of cases/controls (mean age in years)	Diagnostic/ Screening tool used	Main findings	Study type and Quality assessment (NOS)
Pirildar (49) Turkey	Cases: 65 (36 ± 8.1) Controls: 65 (37 ± 5.2)	IIEF	AS patients had significantly lower erectile function, orgasmic function, intercourse and overall satisfaction scores (p=<0.05). 12% with AS had mild or moderate ED (controls not reported). ED was associated with morning stiffness (>4h).	Case-control 4
Shen (51) China	Cases: 78 (40) Controls: NA	Modified Body Image Questionnaire	56.3% of AS patients reported impaired sexual function (vs 29.8% in controls, p<0.001). Disease activity, body image disturbance and physical impairments were linked with impaired sexual functioning.	Cross-sectional 5
Younes (52) Tunisia	Cases: 42 (36 ± 8.1) Controls: NA	Interview	44% AS patients reported sexual problems and 40% reported negative reactions of their spouses to the disease. BASMI >4 was associated with sexual problems.	Cross-sectional 5
Santana (53) Brazil	Cases: 40 (45.8 ± 11.4) Controls: 40 (46 ± 11.1)	IIEF	IIEF total score was lower in AS patients than in controls (22 vs 29 points, P=<0.0001). 82.5% of AS patients had mild to severe ED compared to 12.5% of controls (p=<0.001). Disease activity (BASDAI) was associated with sexual impairment (p=<0.001)	Cross-sectional 3
Gallinaro (54) Brazil	Cases: 28 (43.9) Controls: 28 (38.4)	Interview Sexual activity questionnaire	61.9% of patients reported pain after sexual relationship, spine mobility was reduced in 95.2% of these patients. 85.% of patients reported achieving sexual satisfaction. Correlation with longer disease duration and higher disease activity scores (BASFI, BASDAI)	Cross-sectional 4
Systemic sclerosis				
Hong (68) Canada & USA	Cases: 48(52 ± 1.7) Controls: 55 (53 ± 2.3)* *Controls: RA patients	IIEF	ED prevalence was significantly higher in SSc patients than RA patients (81% vs 48%, p=<0.05). For the majority of these patients, ED symptoms began after disease onset. Raynaud's phenomenon (RP) was associated with ED (Relative risk (RR)=4.0, p=<0.01).	Case-control 3

Table 2. Continued

Study	Number of cases/controls (mean age in years)	Diagnostic/ Screening tool used	Main findings	Study type and Quality assessment (NOS)
Ostojic (62) Serbia	Cases: 5 (38.8) Controls: NA	IIEF	3/5 patients reported that impotence occurred "very early" in their disease (average 4 months after first symptom). Patients with ED had: • Higher skin scores. • More lung fibrosis on chest X-rays. • More restrictive lung disease. 1 patient developed Peyronie's disease (fibrosis of corporal body and penile skin).	Case series 8
Proietti (63) Italy	Cases: 14 (41) Controls: NA	IIEF Duplex ultrasound (US)	Almost all patients were found to have moderate or severe degrees of vasculogenic SD. Erectile function domain score were significantly improved by once-daily tadalafil (13.0 ± 6.8 to 17.0 ± 9.0, $p < 0.05$)	Cohort 2
Rosato (64) Italy	Cases: 20 (49) Controls: NA	IIEF Videocapillaroscopy Doppler US	All patients presented moderate to severe ED (100%). Reduction of arterial flow was present in all SSc patients. Venocclusive dysfunction was evident in 55% patients. A high degree of arteriolar damage was evident. No association with videocapillaroscopy abnormalities.	Cross-sectional 6
Foocharoen (66) European multicenter	Cases: 130 (52.3) Controls: NA	IIEF	81% of SSc patients had variable degrees of ED. • The largest group of all participants (38%) had severe ED. • 90.1% of patients reported that ED began after disease onset. The presence of ED was associated with more severe organ involvement.	Cohort 5
Sanchez (67) France	Cases: 13 (55.9) Controls: NA	IIEF	ED was found in 87.5% of SSc patients (mean IIEF-5 score 21 (mean [SD]: 16.0 [5.3]).	Cross-sectional 6
Aversa (65) Italy	Cases: 15 (47 ± 12.5) Controls: NA	IIEF Doppler US	High incidence of ED (86%, mean IIEF score 13.3), positively correlated with age and disease duration. All of the patients (irrespective of ED status) had a marked reduction of arterial flow with the presence of concomitant mild venoocclusive dysfunction in 66%. Morphology of cavernous arteries at power energy revealed the presence of high degree of arteriolar damage.	Case-series 8

Table 2. Continued

Study	Number of cases/controls (mean age in years)	Diagnostic/ Screening tool used	Main findings	Study type and Quality assessment (NOS)
Behçet Syndrome				
Erdogru (69) Turkey	Cases: 24 (39.1) Controls: NA	Interview	*Patients with Neuro- Behçet. ED was present in 63% of BS patients. 58% of ED were classified as mixed vasculogenic.	Cross-sectional 3
Aksu (70) Turkey	Cases: 2 (45) Controls: NA	Interview	Case report 2 patients with BS and ED caused by severe venous leak detected by penile Doppler US and cavernosography.	Case report
Hiz (71) Turkey	Cases: 42 (33.7 ± 7.2) Controls: 42 (34.5 ± 4.9)	IIEF Beck Depression Inventory (BDI)	IIEF scores were significantly lower in BS patients than controls (20 vs 29, p=0.001). The mean BDI score was found to be significantly higher in the patient group compared to the control group (P < 0.001). The IIEF score was not related to active skin findings, active oral ulcers, active genital ulcers, eye involvement, or medication for BS, but it was related with history of arthritis.	Case control 4
Gul (72) Turkey	Cases: 24 (35.8 ± 8.9) Controls: 24 (37.3 ± 9.8)	GRISS and Arizona Sexual Experience Scale (ASEX)	SD was present in 80% of participants compared to 32% of healthy controls (p=0.0001). SD was significantly more frequent in patients with depression than those without it (93 vs 61%, p=0.001). Significantly higher levels of impotence, premature ejaculation and satisfaction subscale scores in BS patients than in controls.	Case-control 3
Batmaz (73) Turkey	Cases: 72 (35.5 ± 7.8) Controls: 62 (36.5 ± 4.9)	IIEF	Patients with BS scored significantly lower in IIEF scores than healthy controls. Associated with: Age, duration of disease, depression and quality of life. No association was found between IIEF scores and medication use, active oral/genital ulcers, ocular involvement, venous thrombosis and arthritis.	Cross-sectional 2

Table 3. Summary of reproductive hormones.

Study	Number of cases/controls (mean age in years)	Main findings	Study type and Quality assessment (NOS)
Rheumatoid arthritis			
Gordon (19) Scotland	Cases: 31 (55) Controls: 95 (NA)	Patients with RA compared to AS patients and healthy controls showed significantly: • Lower serum testosterone (p=<0.05). • Significantly greater serum LH (p=<0.05). Serum FSH was significantly higher in RA patients compared to controls but not in AS patients. Serum testosterone levels showed significant negative correlations with ESR and RF titers.	Case-control 3
Nasr (20) Egypt	Cases: 24 (31.3 ± 7.3) Controls: 18 (30.8 ± 7.4)	Patients and controls showed statistically significant differences in: • Lower DHEA (mean ± SD: 71.13 ± 22.71 vs 236.61 ± 105.41 ug/dl, p=0.000). • Lower total and free testosterone (mean ± SD: 1.5 ± 0.69 vs 4.72 ± 1.75 ng.ml, p=0.000).	Case-control 4
Tengstrand (22) Sweden	Cases: 40 (53) Controls: 131 (NA)	Compared to controls, patients younger than 50 years had: • Lower testosterone concentrations (16.2 [3.5] vs 23.3 [7.5], [=<0.001). • Lower SHBG concentrations (26 [7] vs 34 [12], p=0.20). • Lower NST concentrations (11.2 [2.5] vs 14.9 [4.5], p=0.004) Patients older than 50 years had on average significantly lower LH levels than controls (4.3 [3.3] vs 6.2 [2.1]. p=0.001). **After 2 year follow-up:** Mean testosterone levels increased in the responder group but were unchanged in the non-responders (17.7 [5.8] vs 13.9 [3.5], p=0.25). Lower disease activity did not affect LH, which remained low during the 2 years follow-up period.	Case-control 6
Systemic lupus erythematosus			
Vecchi (27) Brazil	Cases: 25 (27) Controls: 25 (27)	Median of FSH and LH were significantly higher in SLE patients versus controls (5.8 vs. 3.3 IU/l; 5.8 vs. 3.7 IU/l; respectively, p=0.002). The frequencies of elevated FSH and lower morning total testosterone levels were significantly higher in SLE patients compared with controls (28%vs. 0%; 24% vs. 0%; respectively, p=0.009).	Case-control 8
Soares (29) Brazil	Cases: 35 (28.9 ± 8.8) Controls: 35 (29.1 ± 8.9)	FSH levels were higher in SLE patients with severe sperm abnormalities (3.3 [1-17.9] vs 10.9 [3.9-25] IU/l). Elevated FSH levels were detected in 42.9% of patients who underwent IV CYC therapy compared with 9.5% of those who did not.	Case-control 6

Table 3. Continued

Study	Number of cases/controls (mean age in years)	Main findings	Study type and Quality assessment (NOS)
Suehiro (30) Brazil	Cases: 34 (30) Controls: NA	Eight SLE patients (23.5%) had low serum inhibin B levels (Group 1, median 11.05 pg/ml) and 26 (76.5%) had normal serum levels (Group 2, median 141.05 pg/ml). Elevated FSH levels were detected in 100% of the patients of Group 1 compared with none in the normal serum inhibin B Group.	Cross-sectional 3
Silva (31) Brazil	Cases: 4 (19) Controls: NA	Normal hormone levels in patients (FSH, LH, prolactin, testosterone).	Case-series 7.5
Tiseo (32) Brazil	Cases: 28 (33) Controls: 34 (36.5)	Median of LH (6.5 vs 3.95 IU/L) and total testosterone levels (500 vs 389 ng/dl) were significantly higher in SLE patients compared to controls (p=0.001).	Case-control 6
Spondyloarthropathies			
Ramonda (55) Italy	Cases: 10 (28.7 ± 8.6) Controls: 20 (27.4 ± 4.2)	In AS patients LH and FSH values were higher (7.2 and 5.7 UI/L vs. 3.6 and 3.4 UI/L) and testosterone was lower (14.2 vs. 20.4 nmol/L) (p=0.01).	Case-control 4
Almeida (56) Brazil	Cases: 20 (33) Controls: 24 (28.5)	The median inhibin B levels were comparable in AS patients and controls (68 vs 112.9 pg/mL, p=0.111). The median of FSH levels (3.45 vs. 3.65 IU/L) and the other hormones were also similar in both groups.	Cross-sectional 4

Ramonda et al detected a significant reduction in the percentage of progressive and non-progressive motile sperm in 10 AS patients (mean age 28.7 years) compared to 20 age-matched controls. Importantly, a possible influence of disease activity on semen quality was detected as these abnormalities improved after treatment with TNF inhibitors (55). Micu et al included baseline semen samples for 20 patients (mean age 34.7 years [S.D. 9.2]) with high disease activity (mean BASDAI 7.5 [S.D. 1.1] and mean CRP 2.9 mg/dl [95% CI 2.1, 3.6]). Interestingly, no statistically differences were noticed when comparing samples from active patients and healthy controls (normospermia in 91% vs 71.4%, respectively (57). No differences in sperm quality between AS patients and healthy controls were reported in other studies (56, 58) (See table 4).

In a small study from Villiger et al semen quality of 26 SpA patients with and without TNF inhibitors was compared. Sperm abnormalities were more frequent in patients without TNF-inhibitors (10/11) than in patients with TNF-inhibitors (11/15). Patients without TNF-inhibitors had poorer sperm motility and vitality (p=0.001). No significant correlation between disease activity (BASDAI/C-Reactive protein) and sperm quality was reported (59).

The incidence of varicocele was significantly higher in AS patients than in healthy controls in two studies (40 vs 8%, p=0.027 and 52 vs 20%, p=0.009). This was also associated with sperm abnormalities (58, 60).

In a study by Uzunaslan et al, an increased rate of infertility in men after a diagnosis of AS was reported (9.1% vs 2.9% in healthy controls, p=0.404) and AS patients had fewer children than healthy controls (1.921 vs 2.466, p=0.013) (61).

- **Pregnancy and offspring outcomes**

No articles were included.

- **Systemic sclerosis**

- **Sexual function**

Seven studies that included 24 Systemic Sclerosis (SSc) patients with a mean age of 47.2 years fulfilled the inclusion criteria (6 studies from Europe and 1 from North America). Using the IIEF in 7 studies, the prevalence of SD in men with SSc was very high, ranging from 60% to 100% (healthy controls were not included in these studies). Damage to small blood vessels and fibrosis are responsible for many of the clinical manifestations of SSc. These factors are also important in the pathogenesis of SD and the association between them and the presence of SD in men with SSc has been studied by several groups.

Table 4. Summary of fertility outcomes.

Study	Number of cases/controls (mean age in years)	Main findings	Study type and Quality assessment (NOS)
Systemic lupus erythematosus			
Silva (26) Brazil	Cases: 25 (26) Controls: 25 (27)	Percentage of partner with gestation was statistically lower in SLE patients compared to controls: • 20% vs 60% (p=0.0086) Regarding gonadal function: • 60% of SLE patients vs 0% if controls presented sperm quality abnormalities (p=0.001). • Reduction of testicular volume correlated to semen abnormalities severity (suggestion of severe lesion of the seminiferous tubules).	Case-control 3
Rabelo-Junior (28) Brazil	Cases: 10 (36.9) Controls: 20 (32.4)	Median right testicular volume by US was significantly lower in SLE-APS patients (10.38 (3.9–16.7) vs. 13.4 (8.5–20.6) mL, p=0.03). Median values of sperm concentration and sperm motility were significantly lower in SLE patients: • Sperm concentration (41.1 [0-145] vs 120 [34.5-329] x 10^6/ml, p=0.003). • Sperm motility (47.2 [0-87.5] vs 65.42% [43-82], p=0.047). Median penis circumference was significantly reduced in SLE-APS patients with ED compared to patients without ED (8.17 [8–8.5] vs. 9.14 [7–10.5] cm, p=0.0397).	Cross-sectional 5
Farhat (33) Brazil	Cases: 26 (29.8) Controls: NA	An increase of 23.5 ug/m3 of ozone averaged over the 0-90 day period before collection of sample was associated with a decrease of 30.6 million spermatozoa/ml (95% CI, 2.0-59.3; p=0.040). No effects were observed with other pollutants.	Cross-sectional 3
Vecchi (27) Brazil	Cases: 25 (27) Controls: 25 (27)	The median testicular volume by right and left Prader was significantly lower in SLE compared with controls (15 vs. 20 ml and 15 vs. 20 ml; respectively), p=0.006. Median penis length and circumference were significantly lower in SLE compared with controls (8 vs. 10 cm, p=0.0001). The frequencies of oligo/azoopermia (44 vs. 0%, p=0.0002) and asthenozoospermia (36 vs 0%, p=0.0016) in SLE patients were higher than controls. The median of sperm concentration, total sperm count, total motile sperm count, sperm motility and normal sperm by WHO guidelines were uniformly and significantly lower in SLE patients versus controls.	Case-control 8

Table 4. Continued

Study	Number of cases/controls (mean age in years)	Main findings	Study type and Quality assessment (NOS)
Soares (29) Brazil	Cases: 35 (28.9 ± 8.8) Controls: 35 (29.1 ± 8.9)	The median of the testicular volume in both testes according to Prader orchidometry were significantly lower in SLE patients than in controls (15 ml vs 20 ml at the right testicle [p=0.003] and 15 ml vs 20 ml at the left testicle [p=0.004]). All 35 male SLE patients (100%) had semen abnormalities according to WHO guidelines: • SLE patients had a lower median total sperm count (70 x10^6 vs 172 X 10^6, p=0.002) and a lower median total motile sperm count (32 X10^6 vs 119 X 10^6, p=0.004) compared with controls. Seven SLE patients (20%) fathered children after disease onset, compared with 28 controls (80%), p=0.0001. No significant difference regarding the presence of varicocele among both groups.	Case-control 6
Suehiro (30) Brazil	Cases: 34 (30) Controls: NA	No significant difference in testicular volume in SLE patients with low or normal inhibin B levels. Patients with low inhibin B levels had lower median sperm concentration (2 vs 56.5 10^6/ml, p=0.024), total sperm count (6 vs 133 10^6/ml, p=0.023) and total motile sperm count (3 vs 69.5 10^6/ml, p=0.025) compared with patients with normal inhibin B levels. Inhibin B levels were positively correlated with sperm concentration and total motile sperm count. No significant difference regarding the presence of varicocele among both groups.	Cross-sectional 3
Scofield (34) USA	Cases: 76 (NA) Controls: NA	Klinefelter's syndrome (KS) prevalence of 264 per 10,000 men with SLE (>15 times higher than the general population) "Are you infertile?" • All men subsequently found to have KS answered the question with a response other than "no". • This question was 100% sensitive and 33% specific for identification of KS in men with SLE.	Cohort 4
Silva (31) Brazil	Cases: 4 (19) Controls: NA	Normal testicular volume in 100%. Sperm quality abnormalities in 100%.	Case-series 7.5
Tiseo (32) Brazil	Cases: 28 (33) Controls: 34 (36.5)	The sperm DNA fragmentation index (DFI) was significantly higher in SLE patients compared to controls (62 [31-97] vs 25.5 [0-100]%, p=<0.001) in a study were conventional sperm parameters were similar in both groups. No correlations were evidenced between DFI with multiple variables: age, BMI, disease duration, disease activity, cumulative doses of prednisone, cyclophosphamide, methotrexate, azathioprine or mycophenolate mofetil.	Case-control 6

Table 4. Continued

Study	Number of cases/controls (mean age in years)	Main findings	Study type and Quality assessment (NOS)
Antiphospholipid syndrome			
Rabelo-Junior (36) Brazil	Cases: 12 (37.5) Controls: 20 (32.4)	Sperm quality was comparable in APS patients and controls: • Sperm concentration: 141.5 [33–575] vs. 120.06 [34.5– 329] 10^6/ml, p=0.65. • Sperm motility: 61.29 [25–80] vs. 65.42 [43–82]%, p=0.4. • Normal sperm morphology: 21.12 [10–42.5] vs. 23.95 [10– 45]%, p=0.45.	Cross-sectional 5
Rabelo-Junior (28) Brazil	Cases: 10 (36.9) Controls: 20 (32.4)	Median values of sperm concentration (41.1 vs. 120.06 ×10^6/mL, p=0.003) and sperm motility (47.25 vs. 65.42%, p=0.47) were significantly lower in SLE-APS patients compared to that in controls. The frequency of oligo/azoospermia was significantly higher in SLE-APS patients (40 vs. 0%, p=0.007).	Cross-sectional 5
Spondyloarthropathies			
Ramonda (55) Italy	Cases: 10 (28.7 ± 8.6) Controls: 20 (27.4 ± 4.2)	Semen analysis highlighted a significant reduction in the percentage of progressive and non-progressive motile sperm in patients compared with control subjects (p=<0.05). Two inverse Spearman correlations were detected: • CRP and percentage of sperm with normal morphology (P=0.026; r=-0.0728). • DAS-28 and overall motility (p=.048; r= -0.949). The other sperm parameters and the percentage of sperm aneuploidies in the SpA patients did not show significant differences.	Case-control 4
Nukumizu (58) Brazil	Cases: 20 (33) Controls: 24 (28.5)	AS patients and controls had normal external genitalia. Sperm analysis was comparable in both groups. Varicocele was found in 40% of AS patients compared to 8% of healthy controls and this finding was associated with sperm abnormalities (p=0.175).	Cross-sectional 4
Micu (57) Norway	Cases: 23 (34.7) Controls: 42 (34.8)	Sperm quality in patients with active AS was comparable to sperm quality in healthy controls.	Case-control 4
Villiger (59) Switzerland	Cases: 26 (30) Controls: 102 (35)	Impaired sperm quality was especially found in AS patients without TNF-inhibitors and active disease: Sperm abnormalities were found in 10/11 patients without TNF-inhibitor therapy. • Sperm of these 11 patients had significantly poorer motility (p=0.001) and vitality (p=0.001) compared to 15 patients tested during longstanding TNF-inhibitor therapy.	Cross-sectional 4

Table 4. Continued

Study	Number of cases/controls (mean age in years)	Main findings	Study type and Quality assessment (NOS)
Uzunaslan (61) Turkey	Cases: 79 (38.3) Controls: 43 (42)	Higher infertility rate after diagnosis in AS patients was reported (9.1%) but this was not significant compared to healthy controls (2.9%), p=0.502. AS patients had significantly fewer children when compared with other groups (p=0.013): • AS: 1.9 • BS: 2.3 • Familial Mediterranean Fever (FMF): 2.4 • Healthy controls: 2.4	Case- control 3
Systemic sclerosis			
Hong (68) Canada & USA	Cases: 48(52 ± 1.7) Controls: 55 (53 ± 2.3)* *Controls: RA patients	Patients with SSc had significantly y lower number of biological children than patients with RA (2.0 ± 0.2 vs 2.7 ± 0.2, p=<0.01). Men with RP fewer children than men without RP (2.0 ± 0.2 vs 2.6 ± 0.2, p=<0.02).	Case-control 3
Bechet's syndrome			
Cetinel (74) Turkey	Cases: 104(40) Controls: 31 (29)	The frequency of epididymitis was significantly higher in patients with BS than controls (19.2 vs 0%, p=0.001). The frequency of infertility was higher in patients with BS than controls (9.6 vs 2.3%, p=NA).	Case-control 5
Uzunaslan (61) Turkey	Cases: 162 (39) Controls: 43 (42)	Higher infertility rate after diagnosis in AS patients was reported (BS with major organ involvement 7.95% and BS without major organ involvement 10.2%) but this was not significant compared to healthy controls (2.9%, p=0.502) • 17.7 of male patients with BD was considered to have compromised fertility and among them the most common etiology was varicocele. The average number of children (2.3), miscarriages (0.4) and of children born with congenital abnormalities (4.4) was similar to controls.	Case-control 4
Auger (76) France	Cases: 68 (28) Controls: 1448 (NA)	66.7% of patients with BS were considered normozoospermic. Differences in the sperm concentration, count, motility and morphology were significant when comparing data to healthy controls.	Case-control 5

Table 5. Summary of pregnancy and offspring outcomes.

Study	Patients/ controls	Findings	Quality assessment
Rheumatoid arthritis			
Rom (24) Denmark	NA	Among 1086 born children exposed to paternal RA: • No statistically significant associations were found with indicators of fetal growth, preterm birth compared to the general population.	Cohort 8
Wallenius (23) Norway	NA	Among 2,777 births from 1,796 men with RA: • Relative risks from serious malformation were not different between DMARD exposed and non-exposed group. • Birth weight was not different between groups.	Cohort 6
Bechet syndrome			
Uzunaslan (61) Turkey	Cases: 162 (39) Controls: 43 (42)	The number of infants with congenital anomalies was not increased among patients with BS when compared with other groups.	Case-control 4

In a small case series that included 5 young patients with SSc (mean age 38.8 years) Ostojic et al reported the impact of microvasculopathy and fibrosis on the development of ED in men with SSc. They found that ED was present in 60% of their patients. ED was a frequent early clinical feature of SSc (average 4 months after presenting the first symptom). Although microvascular abnormalities were not associated with ED, fibrotic changes in the lungs were more frequently reported in patients with ED. Interestingly, Peyronie's disease, a fibrotic condition of the penis, developed in one SSc patient (62).

The extent of penile damage was investigated by Proietti et al in 14 patients with diffuse or limited SSc by evaluating cavernous artery flow. They found that almost all patients had moderate or severe degrees of vasculogenic-SD. Both, erectile function and vascular measures of cavernous arteries improved after once-daily tadalafil intake (63).

To investigate the association between vascular damage and ED in SSc patients, Rosato et al enrolled 20 SSc patients (mean age 49 years) and found that all had moderate to severe ED. Together with ultrasound (US) findings, it was concluded that all of them had vasculogenic ED (64).

Aversa et al included 15 patients with SSc in a study that used US to describe the penile vasculature in SSc. A high prevalence of ED (86%, mean IIEF score 13.3) was reported. All patients (irrespective of ED status) had a marked reduction of arterial flow with the presence of concomitant mild venoocclusive dysfunction in 66% of them (65).

In the largest study known to date, a multicenter European cohort, data of 130 SSc patients was collected and a prevalence of ED of 81% (105/130) was reported. 40 (38%)

patients had severe ED (IIEF-5 score <7) (66). Similarly, Sanchez et al and Hong et al reported an ED prevalence of 87.5% and 81%, respectively (67, 68).

- **Fertility**

The number of children per man can be considered as a good proxy of fertility. Hong et al compared this parameter in 48 patients with SSc and 55 patients with RA and they found that patients with SSc had significantly fewer biological children than those with RA [2.0 ± 0.2 (0.4) vs 2.7 ± 0.2 (0.5), respectively, p=<0.01]. Among patients with SSc, and to a lesser extent RA, the presence of Raynaud's phenomenon (RP) was significantly associated with this finding (80% of patients with RP had ED vs 50% of patients without RP, p=<0.01) (68).

- **Reproductive hormones and Pregnancy and offspring outcomes**

No articles were included.

- **Behçet Syndrome**

- **Sexual function**

Sexual function in Behçet's syndrome (BS) was reported in 5 studies from Turkey, using the following outcome measures: IIEF in 2 articles, interview in 2 articles and the Arizona Sexual Experience Scale (ASEX) in 1 study. These studies included data on 164 patients with a mean age of 37.2 years and 128 healthy controls with a mean age of 36.1 years. In this group, the prevalence of SD ranged from 63-80% in BS and 32% in healthy controls.

In a small study of 19 male patients (mean age 39.1 years) diagnosed with Neuro-Behçet, ED was reported in 12 (63%) patients. Mixed vasculogenic impotence was responsible for 63% of ED cases(69). Inspired by these findings, Aksu et al reported 2 cases of ED in patients with BS, they determined that the cause of ED was severe venous leak possibly secondary to disease-related thrombosis (70).

In the first study that used standardized methods (IIEF) to screen for SD in 42 BS patients (mean age 33.7 years), Hiz et al found that the total IIEF score was significantly lower in BS patients compared to 42 age-matched healthy controls (20.6 [standard deviation 4.04] vs 29.21 [standard deviation 0.750] p=<0.001). Scores of 26 or higher were considered as normal sexual function. Lower IIEF scores were associated with higher depression scores. No association between ED and medication use or the presence of oral and genital ulcers was found (71).

The association between ED and depression in patients with BS was further investigated by Gul et al in a study of 24 BS male patients (mean age 35.8 years). They reported that

SD was significantly more prevalent in BS than in controls (80 vs 32%, p=0.001). This was associated with higher depression scores. Male patients with BS were found to have more problems in the following areas: impotence, premature ejaculation and sexual satisfaction (72). Similar findings were reported by Batmaz et al in a group of 72 sexually active male BS patients (mean age 36.5 years) (73).

- **Fertility**

Cetinel et al sent questionnaires to 104 male patients with BS (mean age 31 years) to screen for urologic manifestations and found a significantly high frequency of epididymitis in patients with BS compared to controls (19.2 vs 0%, p=0.001). They also found a higher incidence of infertility and varicocelectomy in BS patients, but the difference was not statistically significant compared to healthy controls (74).

The incidence of varicocele was also increased in BS in a study that included 47 patients with BS (mean age 23.4 ± 3.2 years) and 31 age-matched healthy controls. Scrotal pain or a palpable mass was detected by physical examination in 24 (51.1%) BS patients and in 5 (16%) healthy controls (p=0.002). No sperm analysis was performed in these patients (75).

A large study that included 162 male patients with BS, compared fertility rates among them and patients with other rheumatic diseases (AS, Familiar Mediterranean Fever (FMF)) and healthy controls). Interestingly, a trend for an increased rate of infertility (defined as the inability to conceive after 1 year of unprotected intercourse) after diagnosis was found in all the groups with rheumatic diseases (BS: 9%, FMF: 7.5% and AS 9.1%) but this was not significant compared to the rate seen in healthy controls (2.9%) (p=0.404). With the exemption of AS, the average number of children was similar among groups (61).

In the only identified study that investigated semen quality in BS patients, Auger et al using sperm banking data compared the sperm characteristics of BS patients and healthy fertile men. Moderate alterations in semen quality were observed. Of particular interest, the authors reported that sperm alterations were present even before treatment and this might be related to disease-related factors (76).

- **Reproductive hormones**

No articles were included.

- **Pregnancy and offspring outcomes**

The average number of miscarriages and the percentage of infants born with congenital anomalies were not increased in children fathered by patients with major organ BS when compared with healthy controls (0.429 vs 0.398 and 4.49 vs 4.85%, respectively) (61).

- **Other rheumatic diseases**
- **Sarcoidosis**

In a study that included 30 patients diagnosed with sarcoidosis (mean age 43.6 years), Spruit et al found that sarcoidosis patients were more likely to have lower median free testosterone concentrations than 26 age-matched healthy controls [7.32 (5.48-8.72) vs 9.25 (7.54-9.87) ng/dl, p=0.0062] (77).

Azoospermia, teratozoospermia and oligospermia were frequent findings in case reports of patients with sarcoidosis (78-86). Treatment with corticosteroids improved semen quality in some cases (79, 80, 86, 87). Granulomas were also reported in testicles and epididymis of patients with sarcoidosis (88-92).

- **Vasculitis**

Hypogonadism was reported in 10 out of 19 (52.6%) male patients diagnosed with Granulomatosis with Polyangiitis (GPA) (mean age 58.4 years) compared to 0 out of 38 age-matched controls (p=<0.001). No correlation with clinical factors or current/past medication use was found. Authors concluded that a subclinical involvement of the testes in GPA patients was possible (93).

Androgen deficiency and its association with fatigue were analyzed in a study that included 70 male patients with ANCA-associated vasculitis (mean age 59 years). A high prevalence of androgen deficiency among these patients was reported (47%) and testosterone levels were associated with physical functioning and fatigue (94).

Pregnancy outcomes among partners of male patients with vasculitis were analyzed by Clowse et al. Data from 107 patients were reported, 54 men reported conceiving 157 pregnancies. Pregnancy loss rate was not significantly higher among pregnancies conceived following a diagnosis of vasculitis (n=139) compared to those prior to diagnosis (n=18) (41.2% vs 23%; relative risk 2.34 [CI95% 0.71 – 7.70], p=0.16) (95).

- **Autoinflammatory syndromes**

Azoospermia due to testicular amyloidosis in a patient with FMF, confirmed with a testicular biopsy, was reported (96). Fever was shown to drastically reduce sperm output and this was accompanied by an increase in the percentage of abnormal spermatozoa in a study conducted by French et al (97).

The rate of abortions was comparable in 222 pregnancies among 60 partners of male patients diagnosed with FMF (7%) and 788 pregnancies among 230 healthy women married to healthy men (16%) (98).

A small retrospective study from France reviewed the medical records of all male patients diagnosed with Muckle-Wells syndrome (MWS) and NLRP3 mutations founding that 6 out of 9 patients were unable to conceive a pregnancy despite regular sexual activity during at least 2 years and that sperm quality was abnormal in 88% of the samples obtained. Multiple mechanisms were discussed as possible causes for this association, such as recurrent fever episodes, excessive amounts of IL-1B and IL-18 (99).

- **Autoimmune diseases in general**

Retrospective cohort studies from the United States have reported an increased risk of developing any rheumatic disease in patients diagnosed with hypogonadism and infertility. Among 123,460 males diagnosed with hypogonadism (mean age 46.5 years) and 370,380 age-matched males not diagnosed with hypogonadism multivariable analysis showed that untreated hypogonadism was associated with an increased risk of developing any rheumatic autoimmune diseases (3.2 versus 2.2 %; HR = 1.33, 95 % CI = 1.41, 1.52) (100). Using the same database, Brubaker et al reported a higher risk of developing RA and general immune disorders, like SLE, (HR 1.56, 95% CI 1.19–2.05 and HR 3.11, CI95% 2.00–4.86, respectively) among 33,077 infertile men (mean age 33 years) compared to 77,693 age-matched vasectomized men (101).

DISCUSSION

Summary of evidence

Sexual function

Our study found that male patients with rheumatic diseases have a high prevalence of SD; this was statistically significant in many studies when comparing patients with rheumatic diseases to age-matched healthy controls. In addition, SD seems to occur at a younger age in patients with rheumatic diseases. For comparison, in a multicenter study that included data from 27,839 adult men (aged 20-75 years), the overall self-reported prevalence of SD was 16% and it ranged from 8% in men aged 20-29 years to 37% in men aged 70-75 years (102).

Recently, the EULAR published recommendations on screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases (103). As it is the

case for these comorbidities (i.e. cardiovascular disease, infections and depression), SD can represent an important burden to male patients and contribute to a lower quality of life. Most of these patients remain undiagnosed and uninformed about SD. We encourage rheumatologists to talk about sexual health with their patients. The use of widely available screening tools and early referrals to specialists should be considered in men with rheumatic diseases and SD, especially those trying to conceive. For clinical practice and future research projects in this topic, we recommend the use of validated screening tools (I.E. IIEF for sexual dysfunction).

Rheumatic diseases can affect several organs via factors like systemic inflammation in RA and SLE and fibrosis in SSc. These factors have been shown to be associated with the increased prevalence of SD in men with rheumatic diseases. A link between RA-induced inflammation and cardiovascular disease is already known and has been widely studied. Based on our SR findings, it is plausible that a similar link between RA-induced inflammation and the development of SD exists and that it could be an early sign of endothelial dysfunction. In addition to the classical factors associated with SD such as older age, depression and anxiety, this link could also play an important role in the pathogenesis of SD in men with rheumatic diseases

In conclusion, SD is a common problem in male patients with rheumatic diseases. This association might result from the fact that several key factors contribute to the etiopathogenesis of rheumatic diseases and SD.

Reproductive hormones

A clear effect of rheumatic diseases on the pituitary-testicular axis exists. Hypogonadism and testicular dysfunction was a common finding, especially in patients with RA and SLE and this was associated with disease activity. Especially in patients with SLE, differentiating between primary (Klinefelter Syndrome, drug toxicity) and secondary hypogonadism (inflammation) should be considered in future research projects and in the clinic.

Interestingly, when comparing the androgenic status of men with RA and AS, a rheumatic disease that is more prevalent in men than women, it was found that only RA had a detrimental effect on testicular function. It is possible that based on different inflammatory phenotypes, disease activity in RA and SLE can result in testicular damage via different mechanisms.

Fertility

Infertility affects 10-15% of men in their prime reproductive age and the cornerstone of laboratory evaluation of infertile men is a conventional semen analysis (104). Semen quality in men with rheumatic diseases can be impaired in patients with SLE, SpA, sarcoidosis, BD and MWS. Sperm count and motility were the most common semen quality parameters affected. Systemic inflammation can cause impaired spermatogenesis by mechanisms that have not been described yet.

Varicocele, one of the most common 'reversible' causes of infertility in the general population, can be present in more than half of men with AS and to a lesser extent in BS. Rheumatologists should be aware of this association and actively screen it in every AS/BS patient with a wish to conceive. We also encourage researchers to take this association into account when studying semen quality of male patients with AS (and other rheumatic diseases), since we believe that some of the findings regarding impaired semen quality could be associated with non-identified varicocele and not to the disease itself or as a side effect of therapy.

Unexplained subfertility is a common problem in women with RA (105) but fertility status in men with rheumatic diseases has not been extensively studied. Men with AS, SLE and SSc had a lower number of children than controls in small studies, nevertheless, since many factors that might contribute to these findings such as voluntary childlessness (related or unrelated to the diagnosis of a rheumatic disease) were not reported, larger epidemiological studies that take these factors into account are needed to verify this association.

Since conventional semen analysis can be normal in infertile patients, DFI might be a better marker for infertility in men with SLE and other rheumatic diseases. More studies are needed to make recommendations on the use of DFI in this population.

Pregnancy and offspring outcomes

The information regarding the influence of paternal RA and vasculitis on pregnancy outcomes is based on a few studies. We found no evidence pointing towards a negative effect of paternal RA and vasculitis on pregnancy outcomes. Unfortunately, there is no information about pregnancy outcomes in partners of male patients with other rheumatic diseases and over the impact of paternal disease on offspring's outcomes.

Conclusion

"A systemic disease is one that affects a number of organs and tissues, or affects the body as a whole" (106). The collaboration between multiple organs is needed to achieve full male sexual health and it is now evident that many of these organs can suffer detrimental effects secondary to rheumatic diseases. Rheumatic diseases and male sexual health should not be considered anymore as being unrelated conditions.

Unfortunately, several limitations should be addressed; most of the studies included small numbers of patients and controls. In addition, studies about sexual function and fertility in men with rheumatic diseases suffer from inconsistent methodological quality, definitions of sexual dysfunction varied in several studies, a wide variety of screening questionnaires and/or diagnostic tools were used, relevant comorbidities that can also have a direct effect on sexual function such as depression were not reported in all studies and results might only apply to the specific populations studied.

More and better research is needed to fully understand the effect of rheumatic diseases in male sexual health. Epidemiological, clinical and basic science studies are needed and should be done in such a way that results can be comparable in different populations. For this reason, for future research we strongly advice on the use of standardized methods and definitions. Collaboration between rheumatologists, andrologists and other experts on this topic is encouraged.

We also encourage rheumatologists and other clinicians taking care of men with rheumatic diseases to consider male sexual health in their clinical practice. Timely detection and treatment of SD and fertility problems can have a big impact on the quality of life of patients and avoid the use of expensive medical care. To achieve this, rheumatologists and patients must have the opportunity and the necessary tools to discuss this topic.

We conclude that male sexual and reproductive health is affected by rheumatic diseases, the degree and extent of this is still unknown and varies per disease. More research is needed and rheumatologists should address this topic with their patients.

REFERENCES

1. Crowson CS, Matteson EL, Myasoedova E, Michet CJ, Ernste FC, Warrington KJ, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheum. 2011;63(3):633-9.
2. Flurey C, White A, Rodham K, Kirwan J, Noddings R, Hewlett S. 'Everyone assumes a man to be quite strong': Men, masculinity and rheumatoid arthritis: A case-study approach. Sociol Health Illn. 2018;40(1):115-29.
3. Flurey CA, Hewlett S, Rodham K, White A, Noddings R, Kirwan J. Men, rheumatoid arthritis, psychosocial impact and self-management: A narrative review. J Health Psychol. 2016;21(10):2168-82.
4. Organization WH. Developing sexual health programmes - A framework for action. 2010.
5. Fraczek M, Kurpisz M. Cytokines in the male reproductive tract and their role in infertility disorders. J Reprod Immunol. 2015;108:98-104.
6. Loveland KL, Klein B, Pueschl D, Indumathy S, Bergmann M, Loveland BE, et al. Cytokines in Male Fertility and ReprA
8. Kotelchuck M, Lu M. Father's Role in Preconception Health. Matern Child Health J. 2017;21(11):2025-39.
9. Bramer WM, de Jonge GB, Rethlefsen ML, Mast F, Kleijnen J. A systematic approach to searching: an efficient and complete method to develop literature searches. J Med Libr Assoc. 2018;106(4):531-41.
10. Bramer WM, Rethlefsen ML, Mast F, Kleijnen J. Evaluation of a new method for librarian-mediated literature searches for systematic reviews. Res Synth Methods. 2018;9(4):510-20.
11. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. Journal of the Medical Library Association : JMLA. 2016;104(3):240-3.
12. Wells G SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013.
13. Modesti PA, Reboldi G, Cappuccio FP, Agyemang C, Remuzzi G, Rapi S, et al. Panethnic Differences in Blood Pressure in Europe: A Systematic Review and Meta-Analysis. PLoS One. 2016;11(1):e0147601.
14. Elst P, Sybesma T, van der Stadt RJ, Prins AP, Muller WH, den Butter A. Sexual problems in rheumatoid arthritis and ankylosing spondylitis. Arthritis Rheum. 1984;27(2):217-20.
15. Blake DJ, Maisiak R, Koplan A, Alarcon GS, Brown S. Sexual dysfunction among patients with arthritis. Clin Rheumatol. 1988;7(1):50-60.
16. El Miedany Y, El Gaafary M, El Aroussy N, Youssef S, Ahmed I. Sexual dysfunction in rheumatoid arthritis patients: Arthritis and beyond. Clin Rheumatol. 2012;31(4):601-6.
17. Gaber W, Moghazy A, Niazy M, Salem HK. Risk factors for sexual dysfunction in Egyptian patients with rheumatoid arthritis and its relation to disease activity. Egypt Rheumatol. 2017;39(3):135-8.
18. van Berlo WTM, van de Wiel HBM, Taal E, Rasker JJ, Weijmar Schultz WCM, van Rijswijk MH. Sexual functioning of people with rheumatoid arthritis: A multicenter study. Clin Rheumatol. 2007;26(1):30-8.
19. Gordon D, Beastall GH, Thomson JA, Sturrock RD. Androgenic status and sexual function in males with rheumatoid arthritis and ankylosing spondylitis. Q J Med. 1986;60(231):671-9.
20. Nasr MM, El-Shafey AM. Sexual performance in rheumatoid arthritis patients - An unnoticed problem. Egypt Rheumatol. 2013;35(4):201-5.
21. Keller JJ, Lin HC. A population-based study on the association between rheumatoid arthritis and erectile dysfunction. Ann Rheum Dis. 2012;71(6):1102-3.
22. Tengstrand B, CarlstrÖM K, HafstrÖM I. Gonadal Hormones in Men with Rheumatoid Arthritis — From Onset Through 2 Years. The Journal of Rheumatology. 2009;36(5):887-92.

23. Wallenius M, Lie E, Daltveit AK, Salvesen KA, Skomsvoll JF, Kalstad S, et al. Brief report: No excess risks in offspring with paternal preconception exposure to disease-modifying antirheumatic drugs. Arthritis Rheum. 2015;67(1):296-301.
24. Rom AL, Wu CS, Olsen J, Kjærgaard H, Jawaheer D, Hetland ML, et al. Fetal growth and preterm birth in children exposed to maternal or paternal rheumatoid arthritis: A nationwide cohort study. Arthritis Rheum. 2014;66(12):3265-73.
25. Merayo-Chalico J, Barrera-Vargas A, Morales-Padilla S, Reyna-De La Garza R, Vázquez-Rodríguez R, Sotomayor M, et al. Epidemiologic profile of erectile dysfunction in SLE: A multi-center study in Latin American patients. Ann Rheum Dis. 2017;76:586.
26. da Silva CAA, Bonfá E, Borba EF, Braga AP, Soares PMF, de Moraes AJP, et al. Reproductive health in male systemic lupus erythematosus. Rev Bras Reumatol. 2009;49(3):215-22.
27. Vecchi AP, Borba EF, Bonfá E, Cocuzza M, Pieri P, Kim CA, et al. Penile anthropometry in systemic lupus erythematosus patients. Lupus. 2011;20(5):512-8.
28. Rabelo-Júnior CN, Bonfá E, Carvalho JF, Cocuzza M, Saito O, Abdo CH, et al. Penile alterations with severe sperm abnormalities in antiphospholipid syndrome associated with systemic lupus erythematosus. Clin Rheumatol. 2013;32(1):109-13.
29. Soares PMF, Borba EF, Bonfa E, Hallak J, Corrêa AL, Silva CAA. Gonad evaluation in male systemic lupus erythematosus. Arthritis Rheum. 2007;56(7):2352-61.
30. Suehiro RM, Borba EF, Bonfa E, Okay TS, Cocuzza M, Soares PMF, et al. Testicular Sertoli cell function in male systemic lupus erythematosus. Rheumatology (UK). 2008;47(11):1692-7.
31. Silva CAA, Hallak J, Pasqualotto FF, Barba MF, Saito MI, Kiss MHB. Gonadal function in male adolescents and young males with juvenile onset systemic lupus erythematosus. J Rheumatol. 2002;29(9):2000-5.
32. Tiseo BC, Bonfa E, Borba EF, Munhoz GA, Wood G, Srougi M, et al. Complete urological evaluation including sperm DNA fragmentation in male systemic lupus erythematosus patients. Lupus. 2018:961203318815764.
33. Farhat J, Lima Farhat SC, Ferreira Braga AL, Cocuzza M, Borba EF, Bonfá E, et al. Ozone decreases sperm quality in systemic lupus erythematosus patients. Rev Bras Reumatol. 2016;56(3):212-9.
34. Scofield RH, Bruner GR, Namjou B, Kimberly RP, Ramsey-Goldman R, Petri M, et al. Klinefelter's syndrome (47,XXY) in male systemic lupus erythematosus patients: Support for the notion of a gene-dose effect from the X chromosome. Arthritis Rheum. 2008;58(8):2511-7.
35. Lopes Gallinaro A, Silva CA, Rabelo Junior CN, Correia Caleiro MT, De Carvalho JF. Moderate/severe erectile dysfunction in patients with antiphospholipid syndrome. Lupus. 2012;21(3):319-23.
36. Rabelo-Júnior CN, Freire De Carvalho J, Lopes Gallinaro A, Bonfá E, Cocuzza M, Saito O, et al. Primary antiphospholipid syndrome: Morphofunctional penile abnormalities with normal sperm analysis. Lupus. 2012;21(3):251-6.
37. Uthman I, Salti I, Khamashta M. Endocrinologic manifestations of the antiphospholipid syndrome. Lupus. 2006;15(8):485-9.
38. Walker G, Merry P, Sethia K, Ball RY. A case of testicular lupus. Lupus. 2000;9(5):397-8.
39. Dhakad U, Singh BP, Das SK, Wakhlu A, Kumar P, Srivastava D, et al. Sexual dysfunctions and lower urinary tract symptoms in ankylosing spondylitis. Int J Rheum Dis. 2015;18(8):866-72.
40. Rostom S, Mengat M, Mawani N, Jinane H, Bahiri R, Hajjaj-Hassouni N. Sexual activity in Moroccan men with ankylosing spondylitis. Rheumatol Int. 2013;33(6):1469-74.
41. Sariyildiz MA, Batmaz I, Dilek B, Inanir A, Bez Y, Tahtasiz M, et al. Relationship of the sexual functions with the clinical parameters, radiological scores and the quality of life in male patients with ankylosing spondylitis. Rheumatol Int. 2013;33(3):623-9.

42. Rezvani A, Ök S, Demir SE. Assessment of sexual functions in male patients with ankylosing spondylitis compared with healthy controls. Turk J of Rheumatol. 2012;27(4):233-40.
43. Tarhan F, Tarhan H, Karaoğullarindan U, Can E, Divrik T, Zorlu F. Premature ejaculation in patients with ankylosing spondylitis. Int J Androl. 2012;35(1):74-8.
44. Bal S, Bal K, Turan Y, Deniz G, Gürgan A, Berkit IK, et al. Sexual functions in ankylosing spondylitis. Rheumatol Int. 2010:1-6.
45. Özkorumak E, Karkucak M, Civil F, Tiryaki A, Özden G. Sexual function in male patients with ankylosing spondylitis. Int J Impotence Res. 2011;23(6):262-7.
46. Oh JS, Heo HM, Kim YG, Lee SG, Lee CK, Yoo B. The effect of anti-tumor necrosis factor agents on sexual dysfunction in male patients with ankylosing spondylitis: A pilot study. Int J Impotence Res. 2009;21(6):372-5.
47. Cakar E, Dincer U, Kiralp MZ, Taskaynatan MA, Yasar E, Bayman EO, et al. Sexual problems in male ankylosing spondylitis patients: Relationship with functionality, disease activity, quality of life, and emotional status. Clin Rheumatol. 2007;26(10):1607-13.
48. Dincer U, Cakar E, Kiralp MZ, Dursun H. Assessment of sexual dysfunction in male patients with Ankylosing Spondylitis. Rheumatol Int. 2007;27(6):561-6.
49. Pirildar T, Müezzinoğlu T, Pirildar Ş. Sexual function in ankylosing spondylitis: A study of 65 men. J Urol. 2004;171(4):1598-600.
50. Yim SY, Lee IY, Lee JH, Jun JB, Kim TH, Bae SC, et al. Quality of marital life in Korean patients with spondyloarthropathy. Clin Rheumatol. 2003;22(3):208-12.
51. Shen BY, Zhang AX, Liu JW, Da ZY, Xu XJ, Gu ZF. A primary analysis of sexual problems in Chinese patients with ankylosing spondylitis. Rheumatology International. 2013;33(6):1429-35.
52. Younes M, Jalled A, Aydi Z, Zrour S, Korbaa W, Ben Salah Z, et al. Socioeconomic impact of ankylosing spondylitis in Tunisia. Joint Bone Spine. 2010;77(1):41-6.
53. Santana T, Skare T, Delboni VS, Simione J, Campos APB, Nisihara R. Erectile dysfunction in ankylosing spondylitis patients. Int Braz J Urol. 2017;43(4):730-5.
54. Gallinaro AL, Akagawa LL, Otuzi MH, Sampaio-Barros PD, Goncalves CR. Sexual activity in ankylosing spondylitis. Rev Bras Reumatol. 2012;52(6):887-91.
55. Ramonda R, Foresta C, Ortolan A, Bertoldo A, Oliviero F, Lorenzin M, et al. Influence of tumor necrosis factor alpha inhibitors on testicular function and semen in spondyloarthritis patients. [Erratum appears in Fertil Steril. 2014 May;101(5):1058]. Fertil Steril. 2014;101(2):359-65.
56. Almeida BP, Saad CGS, Souza FHC, Moraes JCB, Nukumizu LA, Viana VST, et al. Testicular Sertoli cell function in ankylosing spondylitis. Clin Rheumatol. 2013;32(7):1075-9.
57. Micu MC, Micu R, Surd S, Gîrlovanu M, Bolboac' SD, Ostensen M. TNF-α inhibitors do not impair sperm quality in males with ankylosing spondylitis after short-term or long-term treatment. Rheumatology. 2014;53(7):1250-5.
58. Nukumizu LA, Saad CG, Ostensen M, Almeida BP, Cocuzza M, Gonçalves C, et al. Gonadal function in male patients with ankylosing spondylitis. Scand J Rheumatol. 2012;41(6):476-81.
59. Villiger PM, Caliezi G, Cottin V, Förger F, Senn A, Østensen M. Effects of TNF antagonists on sperm characteristics in patients with spondyloarthritis. Ann Rheum Dis. 2010;69(10):1842-4.
60. Ozgocmen S, Kocakoc E, Kiris A, Ardicoglu A, Ardicoglu O. Incidence of varicoceles in patients with ankylosing spondylitis evaluated by physical examination and color duplex sonography. Urology. 2002;59(6):919-22.
61. Uzunaslan D, Saygin C, Hatemi G, Tascilar K, Yazici H. No appreciable decrease in fertility in Behçet's syndrome. Rheumatology. 2014;53(5):828-33.
62. Ostojic P, Damjanov N. The impact of depression, microvasculopathy, and fibrosis on development of erectile dysfunction in men with systemic sclerosis. Clin Rheumatol. 2007;26(10):1671-4.

63. Proietti M, Aversa A, Letizia C, Rossi C, Menghi G, Bruzziches R, et al. Erectile dysfunction in systemic sclerosis: Effects of longterm inhibition of phosphodiesterase type-5 on erectile function and plasma endothelin-1 levels. J Rheumatol. 2007;34(8):1712-7.
64. Rosato E, Aversa A, Molinaro I, Pisarri S, Spera G, Salsano F. Erectile dysfunction of sclerodermic patients correlates with digital vascular damage. Eur J Intern Med. 2011;22(3):318-21.
65. Aversa A, Proietti M, Bruzziches R, Salsano F, Spera G. The penile vasculature in systemic sclerosis: A duplex ultrasound study. J Sex Med. 2006;3(3):554-8.
66. Foocharoen C, Tyndall A, Hachulla E, Rosato E, Allanore Y, Farge-Bancel D, et al. Erectile dysfunction is frequent in systemic sclerosis and associated with severe disease: a study of the EULAR Scleroderma Trial and Research group. Arthritis Res Ther. 2012;14(1):R37.
67. Sanchez K, Denys P, Giuliano F, Palazzo C, Berezne A, Abid H, et al. Systemic sclerosis: Sexual dysfunction and lower urinary tract symptoms in 73 patients. Presse Medicale. 2016;45(4):E79-E89.
68. Hong P, Pope JE, Ouimet JM, Rullan E, Seibold JR. Erectile Dysfunction Associated with Scleroderma: A Case-Control Study of Men with Scleroderma and Rheumatoid Arthritis. J Rheumatol. 2004;31(3):508-13.
69. Erdogru T, Kocak T, Serdaroglu P, Kadioglu A, Tellaloglu S. Evaluation and therapeutic approaches of voiding and erectile dysfunction in neurological Behcet's syndrome. J Urol. 1999;162(1):147-53.
70. Aksu K, Keser G, Gunaydin G, Ozbek SS, Colakoglu Z, Gumusdis G, et al. Erectile dysfunction in Behcet's disease without neurological involvement: two case reports. Rheumatology (Oxford). 2000;39(12):1429-31.
71. Hiz O, Ediz L, Gülcü E, Tekeoglu I. Effects of behçet's disease on sexual function and psychological status of male patients. J Sex Med. 2011;8(5):1426-33.
72. Gül IG, Kartalci Ş, Cumurcu BE, Karincaoğlu Y, Yoloğlu S, Karlidağ R. I Behçet's disease with or without depression. J Eur Acad Dermatol Venereol. 2013;27(10):1244-51.
73. Yıldız M, Batmaz Í, Sula B, Uçmak D, Sarıyıldız MA, Dağgülli M, et al. Sexual Dysfunction in Male Patients With Behçet's Disease. Acta Reumatol Port. 2016;41(1):56-61.
74. Cetinel B, Obek C, Solok V, Yaycioglu O, Yazici H. Urologic screening for men with Behcet's syndrome. Urology. 1998;52(5):863-5.
75. Yilmaz O, Yilmaz S, Kisacik B, Aydogdu M, Bozkurt Y, Erdem H, et al. Varicocele and epididymitis in Behcet disease. J Ultrasound Med. 2011;30(7):909-13.
76. Auger J, Sermondade N, Eustache F. Semen quality of 4480 young cancer and systemic disease patients: baseline data and clinical considerations. Basic clin androl. 2016;26:3.
77. Spruit MA, Thomeer MJ, Gosselink R, Wuyts WA, Van Herck E, Bouillon R, et al. Hypogonadism in male outpatients with sarcoidosis. Respiratory Medicine. 2007;101(12):2502-10.
78. Babst C, Piller A, Boesch J, Schmid HP. Testicular sarcoidosis. Urol Case Rep. 2018;17:109-10.
79. Canguven O, Balaban M, Selimoglu A, Albayrak S. Corticosteroid therapy improves the outcome of semen analysis in an oligozoospermic patient with epididymal sarcoidosis. Korean J Urol. 2013;54(8):558-60.
80. Kovac JR, Flood D, Brendan Mullen J, Fischer MA. Diagnosis and treatment of azoospermia resulting from testicular sarcoidosis. J Androl. 2012;33(2):162-6.
81. Paknejad O, Sadighi Gilani MA, Khoshchehreh M. Testicular masses in a man with a plausible sarcoidosis. Indian J Urol. 2011;27(2):269-71.
82. Hassan A, El-Mogy S, Zalata K, Mostafa T. Bilateral epididymal sarcoidosis. Fertil Steril. 2009;91(5):1957.e1-.e4.
83. Takiguchi Y, Matsuno D, Kurosu K, Okada O, Tatsumi K, Ohta S, et al. Impaired spermatogenesis by testicular sarcoidosis. Respirology. 2008;13(7):1082-4.
84. Rees DA, Dodds AL, Rathbone N, Davies JS, Scanlon MF. Azoospermia in testicular sarcoidosis is an indication for corticosteroid therapy. Fertil Steril. 2004;82(6):1672-4.

85. Svetec DA, Waguespack RL, Sabanegh Jr ES. Intermittent azoospermia associated with epididymal sarcoidosis. Fertil Steril. 1998;70(4):777-9.
86. Thomas K, Keeping I, Haddad NG. An unusual case of sarcoidosis associated with poor sperm function. J Obstet Gynaecol. 2001;21(3):322-3.
87. Boura P, Tselios K, Skendros P, Kountouras J. Antiphospholipid syndrome in Greece: Clinical and immunological study and review of the literature. Angiology. 2004;55(4):421-30.
88. Wong JA, Grantmyre J. Sarcoid of the testis. Can J Urol. 2006;13(4):3201-3.
89. Datta SN, Freeman A, Amerasinghe CN, Rosenbaum TP. A case of scrotal sarcoidosis that mimicked tuberculosis. Nat Clin Pract Urol. 2007;4(4):227-30.
90. Kodama K, Hasegawa T, Egawa M, Tomosugi N, Mukai A, Namiki M. Bilateral epididymal sarcoidosis presenting without radiographic evidence of intrathoracic lesion: Review of sarcoidosis involving the male reproductive tract. Int J Urol. 2004;11(5):345-8.
91. Smyth LG, Long RM, Lennon G. A case of epididymal sarcoidosis. Can Urol Assoc J. 2011;5(5):E90-1.
92. Vasu TS, Lai RS, Amzuta IG, Nasr MR, Lenox RJ. Sarcoidosis presenting as intrascrotal mass: Case report and review. Southern Medical Journal. 2006;99(9):995-7.
93. Richter JG, Becker A, Specker C, Schneider M. Hypogonadism in Wegener's granulomatosis. Scand J Rheumatol. 2008;37(5):365-9.
94. Tuin J, Sanders JS, Buhl BM, van Beek AP, Stegeman CA. Androgen deficiency in male patients diagnosed with ANCA-associated vasculitis: a cause of fatigue and reduced health-related quality of life? Arthritis Res Ther. 2013;15(5):R117.
95. Clowse ME, Richeson RL, Pieper C, Merkel PA, Vasculitis Clinical Research C. Pregnancy outcomes among patients with vasculitis. Arthritis Care Res (Hoboken). 2013;65(8):1370-4.
96. Haimov-Kochman R, Prus D, Ben-Chetrit E. Azoospermia due to testicular amyloidosis in a patient with familial Mediterranean fever. Hum Reprod. 2001;16(6):1218-20.
97. French DJ, Leeb CS, Jecht EW. Reduction in sperm output by febrile attacks of Familial Mediterranean Fever: a case report. FERTIL STERIL. 1973;24(6):490-3.
98. Ben-Chetrit E, Berkun Y, Ben-Chetrit E, Ben-Chetrit A. The outcome of pregnancy in the wives of men with familial mediterranean fever treated with colchicine. Semin Arthritis Rheum. 2004;34(2):549-52.
99. Tran TA, Koné-Paut I, Marie I, Ninet J, Cuisset L, Meinzer U. Muckle-Wells Syndrome and Male Hypofertility: A Case Series. Semin Arthritis Rheum. 2012;42(3):327-31.
100. Baillargeon J, Al Snih S, Raji MA, Urban RJ, Sharma G, Sheffield-Moore M, et al. Hypogonadism and the risk of rheumatic autoimmune disease. Clin Rheumatol. 2016;35(12):2983-7.
101. Brubaker WD, Li S, Baker LC, Eisenberg ML. Increased risk of autoimmune disorders in infertile men: analysis of US claims data. Andrology. 2018;6(1):94-8.
102. Rosen RC, Fisher WA, Eardley I, Niederberger C, Nadel A, Sand M, et al. The multinational Men's Attitudes to Life Events and Sexuality (MALES) study: I. Prevalence of erectile dysfunction and related health concerns in the general population. Curr Med Res Opin. 2004;20(5):607-17.
103. Baillet A, Gossec L, Carmona L, Wit Md, van Eijk-Hustings Y, Bertheussen H, et al. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. Annals of the Rheumatic Diseases. 2016;75(6):965-73.
104. Esteves SC. Novel concepts in male factor infertility: clinical and laboratory perspectives. Journal of assisted reproduction and genetics. 2016;33(10):1319-35.
105. Brouwer J, Fleurbaaij R, Hazes JMW, Dolhain R, Laven JSE. Subfertility in Women With Rheumatoid Arthritis and the Outcome of Fertility Assessments. Arthritis Care Res (Hoboken). 2017;69(8):1142-9.
106. Kinder JM, Stelzer IA, Arck PC, Way SS. Immunological implications of pregnancy-induced microchimerism. Nat Rev Immunol. 2017;17(8):483-94.

Supplement 1. Search strategy

embase.com 4505

('autoimmune disease'/de OR 'autoimmune skin disease'/de OR 'autoimmune liver disease'/de OR 'autoimmunity'/de OR 'autoantibody'/de OR 'autoinflammatory disease'/de OR 'Rheumatoid Arthritis'/exp OR arthritis/de OR 'ankylosing spondylitis'/de OR 'spondyloarthropathy'/exp OR 'systemic sclerosis'/exp OR 'systemic lupus erythematosus'/exp OR 'mixed connective tissue disease'/exp OR 'Sjoegren syndrome'/exp OR 'antiphospholipid syndrome'/de OR 'vasculitis'/exp OR 'rheumatic polymyalgia'/de OR 'aortic arch syndrome'/de OR 'Wegener granulomatosis'/de OR 'Churg Strauss syndrome'/exp OR 'Goodpasture syndrome'/de OR 'giant cell arteritis'/de OR 'polyarteritis nodosa'/de OR 'cryoglobulinemic vasculitis'/de OR ('cryoglobulinemia'/de AND 'vasculitis'/de) OR 'anaphylactoid purpura'/de OR 'mucocutaneous lymph node syndrome'/de OR 'Behcet disease'/de OR 'dermatomyositis'/de OR 'familial Mediterranean fever'/de OR ('mevalonate kinase deficiency'/de AND ('recurrent fever'/de OR 'hereditary periodic fever'/de)) OR 'tumor necrosis factor receptor associated periodic syndrome'/de OR 'CINCA syndrome'/de OR 'systemic juvenile idiopathic arthritis'/de OR 'familial cold autoinflammatory syndrome'/de OR 'Muckle Wells syndrome'/de OR 'psoriasis'/exp OR 'atopic dermatitis'/de OR 'suppurative hidradenitis'/de OR 'pemphigus'/de OR 'bullous pemphigoid'/de OR 'dermatitis herpetiformis'/de OR 'linear iga bullous dermatosis'/de OR 'chronic urticaria'/de OR 'leukocytoclastic vasculitis'/de OR 'lichen planus'/de OR 'skin lupus erythematosus'/exp OR 'skin sarcoidosis'/de OR 'morphea'/de OR 'alopecia areata'/de OR 'pyoderma gangrenosum'/de OR 'acute febrile neutrophilic dermatosis'/de OR 'acne conglobata'/de OR 'acne fulminans'/de OR 'acne vulgaris'/de OR 'neurodermatitis'/de OR 'erythema nodosum'/de OR 'inflammatory bowel disease'/exp OR 'autoimmune hepatitis'/de OR 'primary biliary cirrhosis'/de OR 'primary sclerosing cholangitis'/de OR 'systemic sclerosis'/de OR 'liver transplantation'/de OR 'kidney transplantation'/de OR 'graft recipient'/de OR 'lupus erythematosus nephritis'/de OR 'glomerulonephritis'/exp OR 'interstitial nephritis'/de OR 'sarcoidosis'/de OR 'minimal change glomerulonephritis'/de OR 'cryoglobulinemia'/de OR 'immunoglobulin A nephropathy'/de OR (Autoinflammat* OR auto-inflammat* OR autoimmun* OR auto-immun* OR autoantibod* OR auto-antibod* OR ((Rheumatoid OR Idiopath* OR Undifferentiat* OR Psoria* OR enteropa*) NEAR/3Arthritis) OR (Ankylos* NEAR/3 Spondyl*) OR spondyloarthropath* OR (Reactive NEAR/3 arthropath*)

OR (systemic NEAR/3 (sclero* OR lupus)) OR (mixed NEAR/3 connective NEAR/3 disease*) OR Sjoegren* OR Sjogren* OR antiphospholipid* OR vasculitis OR (rheuma* NEAR/3 polymyalg*) OR (aortic-arch NEAR/3 syndrome*) OR (Takayasu NEAR/3 arterit*) OR (Granulomatosis NEAR/3 (Wegener OR polyangiitis)) OR (microscop* NEAR/3 polyangiit*) OR (Churg NEAR/3 Strauss) OR (Eosinophilic NEAR/3 granulomatosis NEAR/3 polyangii*) OR Goodpasture OR anti-GBM OR ((giant-cell* OR cranial*) NEAR/3 arterit*) OR ((polyarteritis OR poliarteritis OR arteritis OR periarteri* OR panarteritis) NEAR/3 (nodosa OR nodular)) OR kussmaul OR (cryoglobulin* NEAR/3 vasculit*) OR ((anaphylact* OR allergic) NEAR/3 (purpura* OR diathesis)) OR (Henoch NEAR/3 (Schonlein OR Schoenlein)) OR ((IgA OR 'immunoglobulin A') NEAR/3 vasculitis) OR (mucocutan* NEAR/3 (lymph-node* OR lymphadenopat*)) OR Kawasaki OR Behcet* OR dermatomyosit* OR Dermatopolymyos* OR dermatomucomyosit* OR poikilodermatomyosit* OR (hepp NEAR/3 unverrricht) OR ((famil* OR inherit*) NEAR/3 (Hibernian OR Mediterran* OR period*) NEAR/3 fever*) OR (paroxysma* NEAR/3 polyserosit*) OR ((period* OR recurr*) NEAR/3 polyserosit*) OR ((Periodic* OR recurr*) NEAR/3 Fever NEAR/6 Mevalona* NEAR/3 Deficien*) OR ((TNF* OR 'tumor necrosis factor') NEAR/3 Receptor NEAR/6 Periodic*) OR CINCA OR (Cryopyrin NEAR/3 Periodic*) OR (chronic* NEAR/3 infantil* NEAR/3 neurolog* NEAR/3 cutan* NEAR/3 articul*) OR still*-disease* OR (systemic* NEAR/3 juvenil* NEAR/3 idiopath* NEAR/3 arthrit*) OR (famil* NEAR/3 cold NEAR/3 urticar*) OR (Muckle NEAR/3 Wells) OR (urticar* NEAR/3 deaf* NEAR/3 amyloidos*) OR (NLRP12 NEAR/3 Periodic NEAR/3 Fever) OR psoria* OR ((atopic* OR infant*) NEAR/3 (dermatit* OR eczem*)) OR ((atopic*) NEAR/3 disease*) OR (neurodermatitis NEAR/3 (constitutional* OR dissemina*)) OR (suppurat* NEAR/3 hidradenit*) OR pemphigus* OR (bullous* NEAR/3 pemphigoid*) OR (dermatit* NEAR/3 herpetiform*) OR duhrig OR duehrig OR hidroa OR hydroa OR (linear NEAR/3 (iga OR 'immunoglobulin A') NEAR/3 dermatos*) OR (chronic* NEAR/3 urticar*) OR ((leukocytoclast* OR hypersensitiv* OR allerg*) NEAR/3 vasculit*) OR (allergic* NEAR/3 arteriolit*) OR (lichen NEAR/3 (planus OR ruber)) OR ((skin OR cutane* OR cutis) NEAR/3 (lupus OR sarcoidos*)) OR morphea OR (circumscri* NEAR/3 scleroder*) OR (alopec* NEAR/3 areat*) OR (pyoderm* NEAR/3 (gangre* OR ulcer*)) OR (dermatit* NEAR/3 ulcer*) OR (acute NEAR/3 (febrile OR fever) NEAR/3 neutroph* NEAR/3 dermato*) OR (sweet* NEAR/3 syndrom*) OR (Acne NEAR/3 (vulgar* OR juvenil* OR conglobat* OR fulminan*)) OR (perifolliculi* NEAR/3 conglumerat*) OR (Rosacea* NEAR/3 papulopustul*)

OR neurodermatit* OR (Prurigo NEAR/3 nodula*) OR (erythem* NEAR/3 (nodos* OR contusifor*)) OR (inflammat* NEAR/3 bowel*) OR IBD OR Crohn OR (Ulcer* NEAR/3 colit*) OR (primar* NEAR/3 (biliar* OR scleros*) NEAR/3 (cirrhosis* OR cholangit*)) OR ((liver* OR hepatic OR kidney* OR renal* OR organ*) NEAR/3 (transplant*)) OR ((lupus OR lupoid) NEAR/3 (nephr* OR glomerulonephr* OR kidney* OR erythem*)) OR glomerulonephrit* OR (anti-glomerular NEAR/3 basement NEAR/3 membrane) OR (glomerul* NEAR/3 (nephr* OR kidney*)) OR ((interstitial* OR tubulointerstitial*) NEAR/3 nephrit*) OR sarcoidos* OR (besnier NEAR/3 boeck) OR schaumann* OR (lymphogranulom* NEAR/3 benign*) OR (minimal-change NEAR/3 (disease)) OR (Membran* NEAR/3 nephropa*) OR (dense NEAR/3 deposit* NEAR/3 disease*) OR cryoglobulin* OR cryoimmunoglobulin* OR (('immunoglobulin A' OR iga) NEAR/3 nephropat*) OR (Acute NEAR/3 anterior NEAR/3 uveitis)):ab,ti) AND ('male fertility'/exp OR 'male infertility'/exp OR 'sperm quality'/exp OR 'spermatozoon count'/de OR 'spermatozoon motility'/de OR 'spermatozoon'/exp OR spermatogenesis/exp OR sperm/exp OR 'semen analysis'/de OR (((male OR man OR men) NEAR/6 (fertil* OR infertil* OR subfertil* OR reproducti* OR steril*)) OR aspermi* OR asthenospermi* OR azoospermi* OR oligospermi* OR ejaculat* OR ((sperm* OR semen OR seminal) NEAR/6 (count* OR motility OR abnormal* OR qualit* OR morpholog* OR dna OR characteristic* OR function* OR activit* OR damage OR analy*)) OR spermatoz* OR spermatogen* OR aspermatogen*):ab,ti OR (('paternal exposure'/exp OR 'father'/exp OR (paternal OR father* OR ((male OR men OR man OR paternal*) NEAR/6 (exposure OR drug OR medication OR patient*))):ab,ti) AND ('pregnancy outcome'/exp OR 'sexual dysfunction'/exp OR 'newborn disease'/exp OR 'congenital disorder'/exp OR 'pregnancy disorder'/exp OR 'labor complication'/exp OR 'placenta'/exp OR 'reproduction'/de OR Childbirth/exp OR Conception/exp OR 'prenatal development'/exp OR 'progeny'/exp OR infertility/de OR 'induced abortion'/de OR (((pregnan* OR obstetr* OR labor OR labour) NEAR/3 (outcome* OR disorder* OR complication*)) OR (sexual* NEAR/3 dysfunction*) OR (Erect* NEAR/3 Dysfunct*) OR (impoten* NEAR/3 vascul*) OR dyspareun* OR (Prematur* NEAR/3 ejaculat*) OR placenta* OR ((newborn* OR neonat* OR fetus OR fetal OR foetus OR foetal) NEAR/3 (health* OR disease OR death)) OR 'birth weight' OR birthweight OR lbw OR vlbw OR elbw OR (small NEAR/3 (date OR gestation*)) OR congenital* OR preeclamp* OR eclamp* OR miscarriag* OR abort* OR reproduct* OR Childbirth* OR Conception* OR progeny OR offspring OR (prenatal* NEAR/3 develop*)):ab,ti))) NOT ([animals]/lim NOT [humans]/lim) NOT (([Conference Abstract]/lim AND [1800-2016]/py) OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim NOT ([animals]/lim NOT [humans]/lim)

Medline ovid 3524

(Autoimmune Diseases/ OR Autoimmunity/ OR Autoantibodies/ OR Hereditary Autoinflammatory Diseases/ OR Arthritis, Rheumatoid/ OR Arthritis/ OR Spondylitis, Ankylosing/ OR Spondylarthropathies/ OR Scleroderma, Systemic/ OR Lupus Erythematosus, Systemic/ OR Mixed Connective Tissue Disease/ OR Sjogren's Syndrome/ OR Antiphospholipid Syndrome/ OR Vasculitis/ OR Aortic Arch Syndromes/ OR Granulomatosis with Polyangiitis/ OR Churg-Strauss Syndromeleukocy/ OR Anti-Glomerular Basement Membrane Disease/ OR Giant Cell Arteritis/ OR Polyarteritis Nodosa/ OR (Cryoglobulinemia/ AND Vasculitis/) OR Purpura, Schoenlein-Henoch/ OR Mucocutaneous Lymph Node Syndrome/ OR Behcet Syndrome/ OR Dermatomyositis/ OR Familial Mediterranean Fever/ OR (Mevalonate Kinase Deficiency/ AND (Relapsing Fever/)) OR Cryopyrin-Associated Periodic Syndromes/ OR Arthritis, Juvenile/ OR Cryopyrin-Associated Periodic Syndromes/ OR exp Psoriasis/ OR Dermatitis, Atopic/ OR Hidradenitis Suppurativa/ OR Pemphigus/ OR Pemphigoid, Bullous/ OR Dermatitis Herpetiformis/ OR Linear IgA Bullous Dermatosis/ OR Vasculitis, Leukocytoclastic, Cutaneous/ OR Lichen Planus/ OR Scleroderma, Localized/ OR Alopecia Areata/ OR Pyoderma Gangrenosum/ OR Sweet Syndrome/ OR Acne Conglobata/ OR Acne Vulgaris/ OR Neurodermatitis/ OR Erythema Nodosum/ OR exp Inflammatory Bowel Diseases/ OR Hepatitis, Autoimmune/ OR Liver Cirrhosis, Biliary/ OR Cholangitis, Sclerosing/ OR Scleroderma, Systemic/ OR Liver Transplantation/ OR Kidney Transplantation/ OR Lupus Nephritis/ OR exp Glomerulonephritis/ OR Nephritis, Interstitial/ OR Sarcoidosis/ OR Cryoglobulinemia/ OR immunoglobulin A nephropathy/ OR (Autoinflammat* OR auto-inflammat* OR autoimmun* OR auto-immun* OR ((Rheumatoid OR Idiopath* OR Undifferentiat* OR Psoria* OR enteropa*) ADJ3 Arthritis) OR (Ankylos* ADJ3 Spondyl*) OR spondyloarthropath* OR (Reactive ADJ3 arthropath*) OR (systemic ADJ3 (sclero* OR lupus)) OR (mixed ADJ3 connective ADJ3 disease*) OR Sjoegren* OR Sjogren* OR antiphospholipid* OR vasculitis OR (rheuma* ADJ3 polymyalg*) OR (aortic-arch ADJ3 syndrome*) OR (Takayasu ADJ3 arterit*) OR (Granulomatosis ADJ3 (Wegener OR polyangiitis)) OR (microscop* ADJ3 polyangiit*) OR (Churg ADJ3 Strauss) OR (Eosinophilic ADJ3 granulomatosis ADJ3 polyangii*) OR Goodpasture OR anti-GBM OR ((giant-cell* OR cranial*) ADJ3 arterit*) OR ((polyarteritis OR poliarteritis OR arteritis OR periarteri* OR panarteritis) ADJ3 (nodosa OR nodular)) OR kussmaul OR (cryoglobulin* ADJ3 vasculit*) OR ((anaphylact* OR allergic) ADJ3 (purpura* OR diathesis)) OR (Henoch ADJ3 (Schonlein OR Schoenlein)) OR ((IgA OR immunoglobulin A) ADJ3 vasculitis) OR (mucocutan* ADJ3 (lymph-node* OR lymphadenopat*))

OR Kawasaki OR Behcet* OR dermatomyosit* OR Dermatopolymyos* OR dermatomucomyosit* OR poikilodermatomyosit* OR (hepp ADJ3 unverrricht) OR ((famil* OR inherit*) ADJ3 (Hibernian OR Mediterran* OR period*) ADJ3 fever*) OR (paroxysma* ADJ3 polyserosit*) OR ((period* OR recurr*) ADJ3 polyserosit*) OR ((Periodic* OR recurr*) ADJ3 Fever ADJ6 Mevalona* ADJ3 Deficien*) OR ((TNF* OR tumor necrosis factor) ADJ3 Receptor ADJ6 Periodic*) OR CINCA OR (Cryopyrin ADJ3 Periodic*) OR (chronic* ADJ3 infantil* ADJ3 neurolog* ADJ3 cutan* ADJ3 articul*) OR still*-disease* OR (systemic* ADJ3 juvenil* ADJ3 idiopath* ADJ3 arthrit*) OR (famil* ADJ3 cold ADJ3 urticar*) OR (Muckle ADJ3 Wells) OR (urticar* ADJ3 deaf* ADJ3 amyloidos*) OR (NLRP12 ADJ3 Periodic ADJ3 Fever) OR psoria* OR ((atopic* OR infant*) ADJ3 (dermatit* OR eczem*)) OR ((atopic*) ADJ3 disease*) OR (neurodermatitis ADJ3 (constitutional* OR dissemina*)) OR (suppurat* ADJ3 hidradenit*) OR pemphigus* OR (bullous* ADJ3 pemphigoid*) OR (dermatit* ADJ3 herpetiform*) OR duhrig OR duehrig OR hidroa OR hydroa OR (linear ADJ3 (iga OR immunoglobulin A) ADJ3 dermatos*) OR (chronic* ADJ3 urticar*) OR ((leukocytoclast* OR hypersensitiv* OR allerg*) ADJ3 vasculit*) OR (allergic* ADJ3 arteriolit*) OR (lichen ADJ3 (planus OR ruber)) OR ((skin OR cutane* OR cutis) ADJ3 (lupus OR sarcoidos*)) OR morphea OR (circumscri* ADJ3 scleroder*) OR (alopec* ADJ3 areat*) OR (pyoderm* ADJ3 (gangre* OR ulcer*)) OR (dermatit* ADJ3 ulcer*) OR (acute ADJ3 (febrile OR fever) ADJ3 neutroph* ADJ3 dermato*) OR (sweet* ADJ3 syndrom*) OR (Acne ADJ3 (vulgar* OR juvenil* OR conglobat* OR fulminan*)) OR (perifolliculi* ADJ3 conglumerat*) OR (Rosacea* ADJ3 papulopustul*) OR neurodermatit* OR (Prurigo ADJ3 nodula*) OR (erythem* ADJ3 (nodos* OR contusifor*)) OR (inflammat* ADJ3 bowel*) OR IBD OR Crohn OR (Ulcer* ADJ3 colit*) OR (primar* ADJ3 (biliar* OR scleros*) ADJ3 (cirrhosis* OR cholangit*)) OR ((liver* OR hepatic OR kidney* OR renal* OR organ*) ADJ3 (transplant*)) OR ((lupus OR lupoid) ADJ3 (nephr* OR glomerulonephr* OR kidney* OR erythem*)) OR glomerulonephrit* OR (anti-glomerular ADJ3 basement ADJ3 membrane) OR (glomerul* ADJ3 (nephr* OR kidney*)) OR ((interstitial* OR tubulointerstitial*) ADJ3 nephrit*) OR sarcoidos* OR (besnier ADJ3 boeck) OR schaumann* OR (lymphogranulom* ADJ3 benign*) OR (minimal-change ADJ3 (disease)) OR (Membran* ADJ3 nephropa*) OR (dense ADJ3 deposit* ADJ3 disease*) OR cryoglobulin* OR cryoimmunoglobulin* OR ((immunoglobulin A OR iga) ADJ3 nephropat*) OR (Acute ADJ3 anterior ADJ3 uveitis)).ab,ti.) AND (exp Infertility, Male/ OR Sperm Count/ OR Sperm Motility/ OR exp Spermatozoa/ OR Spermatogenesis/ OR Semen/ OR exp Semen Analysis/ OR (((male OR man OR men) ADJ6 (fertil* OR infertil* OR subfertil* OR reproducti* OR steril*))

OR aspermi* OR asthenospermi* OR azoospermi* OR oligospermi* OR ejaculat* OR ((sperm* OR semen OR seminal) ADJ6 (count* OR motility OR abnormal* OR qualit* OR morpholog* OR dna OR characteristic* OR function* OR activit* OR damage OR analy*)) OR spermatoz* OR spermatogen* OR aspermatogen*).ab,ti. OR ((Paternal Exposure/ OR Fathers/ OR (paternal OR father* OR ((male OR men OR man OR paternal*) ADJ6 (exposure OR drug OR medication OR patient*))).ab,ti.) AND (exp Pregnancy Outcome/ OR exp Sexual Dysfunction, Physiological/ OR exp Infant, Newborn, Diseases/ OR exp "Congenital, Hereditary, and Neonatal Diseases and Abnormalities"/ OR exp Obstetric Labor Complications/ OR exp Placenta/ OR exp Reproduction/ OR exp Parturition/ OR Fertilization/ OR Embryology/ OR Infertility/ OR Abortion, Spontaneous/ OR (((pregnan* OR obstetr* OR labor OR labour) ADJ3 (outcome* OR disorder* OR complication*)) OR (Sexual* ADJ3 Dysfunction*) OR (Erect* ADJ3 Dysfunct*) OR (impoten* ADJ3 vascul*) OR dyspareun* OR (Prematur* ADJ3 ejaculat*) OR placenta* OR ((newborn* OR neonat* OR fetus OR fetal OR foetus OR foetal) ADJ3 (health* OR disease OR death)) OR birth weight OR birthweight OR lbw OR vlbw OR elbw OR (small ADJ3 (date OR gestation*)) OR congenital* OR preeclamp* OR eclamp* OR miscarriag* OR abort* OR reproduct* OR Childbirth* OR Conception* OR progeny OR offspring OR (prenatal* ADJ3 develop*)).ab,ti.))) NOT (exp animals/ NOT humans/) NOT (letter* OR news OR comment* OR editorial* OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. AND english.la. NOT (exp animals/ NOT humans/)

Cochrane CENTRAL 40

((Autoinflammat* OR auto-inflammat* OR autoimmun* OR auto-immun* OR autoantibod* OR auto-antibod* OR ((Rheumatoid OR Idiopath* OR Undifferentiat* OR Psoria* OR enteropa*) NEAR/3 Arthritis) OR (Ankylos* NEAR/3 Spondyl*) OR spondyloarthropath* OR (Reactive NEAR/3 arthropath*) OR (systemic NEAR/3 (sclero* OR lupus)) OR (mixed NEAR/3 connective NEAR/3 disease*) OR Sjoegren* OR Sjogren* OR antiphospholipid* OR vasculitis OR (rheuma* NEAR/3 polymyalg*) OR (aortic-arch NEAR/3 syndrome*) OR (Takayasu NEAR/3 arterit*) OR (Granulomatosis NEAR/3 (Wegener OR polyangiitis)) OR (microscop* NEAR/3 polyangiit*) OR (Churg NEAR/3 Strauss) OR (Eosinophilic NEAR/3 granulomatosis NEAR/3 polyangii*) OR Goodpasture OR anti-GBM OR ((giant-cell* OR cranial*) NEAR/3 arterit*) OR ((polyarteritis OR poliarteritis OR arteritis OR periarteri* OR panarteritis) NEAR/3 (nodosa OR nodular)) OR kussmaul OR (cryoglobulin* NEAR/3 vasculit*) OR

((anaphylact* OR allergic) NEAR/3 (purpura* OR diathesis)) OR (Henoch NEAR/3 (Schonlein OR Schoenlein)) OR ((IgA OR 'immunoglobulin A') NEAR/3 vasculitis) OR (mucocutan* NEAR/3 (lymph-node* OR lymphadenopat*)) OR Kawasaki OR Behcet* OR dermatomyosit* OR Dermatopolymyos* OR dermatomucomyosit* OR poikilodermatomyosit* OR (hepp NEAR/3 unverrricht) OR ((famil* OR inherit*) NEAR/3 (Hibernian OR Mediterran* OR period*) NEAR/3 fever*) OR (paroxysma* NEAR/3 polyserosit*) OR ((period* OR recurr*) NEAR/3 polyserosit*) OR ((Periodic* OR recurr*) NEAR/3 Fever NEAR/6 Mevalona* NEAR/3 Deficien*) OR ((TNF* OR 'tumor necrosis factor') NEAR/3 Receptor NEAR/6 Periodic*) OR CINCA OR (Cryopyrin NEAR/3 Periodic*) OR (chronic* NEAR/3 infantil* NEAR/3 neurolog* NEAR/3 cutan* NEAR/3 articul*) OR still*-disease* OR (systemic* NEAR/3 juvenil* NEAR/3 idiopath* NEAR/3 arthrit*) OR (famil* NEAR/3 cold NEAR/3 urticar*) OR (Muckle NEAR/3 Wells) OR (urticar* NEAR/3 deaf* NEAR/3 amyloidos*) OR (NLRP12 NEAR/3 Periodic NEAR/3 Fever) OR psoria* OR ((atopic* OR infant*) NEAR/3 (dermatit* OR eczem*)) OR ((atopic*) NEAR/3 disease*) OR (neurodermatitis NEAR/3 (constitutional* OR dissemina*)) OR (suppurat* NEAR/3 hidradenit*) OR pemphigus* OR (bullous* NEAR/3 pemphigoid*) OR (dermatit* NEAR/3 herpetiform*) OR duhrig OR duehrig OR hidroa OR hydroa OR (linear NEAR/3 (iga OR 'immunoglobulin A') NEAR/3 dermatos*) OR (chronic* NEAR/3 urticar*) OR ((leukocytoclast* OR hypersensitiv* OR allerg*) NEAR/3 vasculit*) OR (allergic* NEAR/3 arteriolit*) OR (lichen NEAR/3 (planus OR ruber)) OR ((skin OR cutane* OR cutis) NEAR/3 (lupus OR sarcoidos*)) OR morphea OR (circumscri* NEAR/3 scleroder*) OR (alopec* NEAR/3 areat*) OR (pyoderm* NEAR/3 (gangre* OR ulcer*)) OR (dermatit* NEAR/3 ulcer*) OR (acute NEAR/3 (febrile OR fever) NEAR/3 neutroph* NEAR/3 dermato*) OR (sweet* NEAR/3 syndrom*) OR (Acne NEAR/3 (vulgar* OR juvenil* OR conglobat* OR fulminan*)) OR (perifolliculi* NEAR/3 conglumerat*) OR (Rosacea* NEAR/3 papulopustul*) OR neurodermatit* OR (Prurigo NEAR/3 nodula*) OR (erythem* NEAR/3 (nodos* OR contusifor*)) OR (inflammat* NEAR/3 bowel*) OR IBD OR Crohn OR (Ulcer* NEAR/3 colit*) OR (primar* NEAR/3 (biliar* OR scleros*) NEAR/3 (cirrhosis* OR cholangit*)) OR ((liver* OR hepatic OR kidney* OR renal* OR organ*) NEAR/3 (transplant*)) OR ((lupus OR lupoid) NEAR/3 (nephr* OR glomerulonephr* OR kidney* OR erythem*)) OR glomerulonephrit* OR (anti-glomerular NEAR/3 basement NEAR/3 membrane) OR (glomerul* NEAR/3 (nephr* OR kidney*)) OR ((interstitial* OR tubulointerstitial*) NEAR/3 nephrit*) OR sarcoidos* OR (besnier NEAR/3 boeck) OR schaumann* OR (lymphogranulom* NEAR/3 benign*) OR (minimal-change NEAR/3 (disease))

OR (Membran* NEAR/3 nephropa*) OR (dense NEAR/3 deposit* NEAR/3 disease*) OR cryoglobulin* OR cryoimmunoglobulin* OR (('immunoglobulin A' OR iga) NEAR/3 nephropat*) OR (Acute NEAR/3 anterior NEAR/3 uveitis)):ab,ti) AND ((((male OR man OR men) NEAR/6 (fertil* OR infertil* OR subfertil* OR reproducti* OR steril*)) OR aspermi* OR asthenospermi* OR azoospermi* OR oligospermi* OR ejaculat* OR ((sperm* OR semen OR seminal) NEAR/6 (count* OR motility OR abnormal* OR qualit* OR morpholog* OR dna OR characteristic* OR function* OR activit* OR damage OR analy*)) OR spermatoz* OR spermatogen* OR aspermatogen*):ab,ti OR (((paternal OR father* OR ((male OR men OR man OR paternal*) NEAR/6 (exposure OR drug OR medication OR patient*))):ab,ti) AND ((((pregnan* OR obstetr* OR labor OR labour) NEAR/3 (outcome* OR disorder* OR complication*)) OR (sexual* NEAR/3 dysfunction*) OR (Erect* NEAR/3 Dysfunct*) OR (impoten* NEAR/3 vascul*) OR dyspareun* OR (Prematur* NEAR/3 ejaculat*) OR placenta* OR ((newborn* OR neonat* OR fetus OR fetal OR foetus OR foetal) NEAR/3 (health* OR disease OR death)) OR 'birth weight' OR birthweight OR lbw OR vlbw OR elbw OR (small NEAR/3 (date OR gestation*)) OR congenital* OR preeclamp* OR eclamp* OR miscarriag* OR abort* OR reproduct* OR Childbirth* OR Conception* OR progeny OR offspring OR (prenatal* NEAR/3 develop*)):ab,ti)))

Web of science 1666

TS=(((Autoinflammat* OR auto-inflammat* OR autoimmun* OR auto-immun* OR autoantibod* OR auto-antibod* OR ((Rheumatoid OR Idiopath* OR Undifferentiat* OR Psoria* OR enteropa*) NEAR/2 Arthritis) OR (Ankylos* NEAR/2 Spondyl*) OR spondyloarthropath* OR (Reactive NEAR/2 arthropath*) OR (systemic NEAR/2 (sclero* OR lupus)) OR (mixed NEAR/2 connective NEAR/2 disease*) OR Sjoegren* OR Sjogren* OR antiphospholipid* OR vasculitis OR (rheuma* NEAR/2 polymyalg*) OR (aortic-arch NEAR/2 syndrome*) OR (Takayasu NEAR/2 arterit*) OR (Granulomatosis NEAR/2 (Wegener OR polyangiitis)) OR (microscop* NEAR/2 polyangiit*) OR (Churg NEAR/2 Strauss) OR (Eosinophilic NEAR/2 granulomatosis NEAR/2 polyangii*) OR Goodpasture OR anti-GBM OR ((giant-cell* OR cranial*) NEAR/2 arterit*) OR ((polyarteritis OR poliarteritis OR arteritis OR periarteri* OR panarteritis) NEAR/2 (nodosa OR nodular)) OR kussmaul OR (cryoglobulin* NEAR/2 vasculit*) OR ((anaphylact* OR allergic) NEAR/2 (purpura* OR diathesis)) OR (Henoch NEAR/2 (Schonlein OR Schoenlein)) OR ((IgA OR "immunoglobulin A") NEAR/2 vasculitis) OR (mucocutan* NEAR/2 (lymph-node* OR lymphadenopat*))

OR Kawasaki OR Behcet* OR dermatomyosit* OR Dermatopolymyos* OR dermatomucomyosit* OR poikilodermatomyosit* OR (hepp NEAR/2 unverrricht) OR ((famil* OR inherit*) NEAR/2 (Hibernian OR Mediterran* OR period*) NEAR/2 fever*) OR (paroxysma* NEAR/2 polyserosit*) OR ((period* OR recurr*) NEAR/2 polyserosit*) OR ((Periodic* OR recurr*) NEAR/2 Fever NEAR/5 Mevalona* NEAR/2 Deficien*) OR ((TNF* OR "tumor necrosis factor") NEAR/2 Receptor NEAR/5 Periodic*) OR CINCA OR (Cryopyrin NEAR/2 Periodic*) OR (chronic* NEAR/2 infantil* NEAR/2 neurolog* NEAR/2 cutan* NEAR/2 articul*) OR still*-disease* OR (systemic* NEAR/2 juvenil* NEAR/2 idiopath* NEAR/2 arthrit*) OR (famil* NEAR/2 cold NEAR/2 urticar*) OR (Muckle NEAR/2 Wells) OR (urticar* NEAR/2 deaf* NEAR/2 amyloidos*) OR (NLRP12 NEAR/2 Periodic NEAR/2 Fever) OR psoria* OR ((atopic* OR infant*) NEAR/2 (dermatit* OR eczem*)) OR ((atopic*) NEAR/2 disease*) OR (neurodermatitis NEAR/2 (constitutional* OR dissemina*)) OR (suppurat* NEAR/2 hidradenit*) OR pemphigus* OR (bullous* NEAR/2 pemphigoid*) OR (dermatit* NEAR/2 herpetiform*) OR duhrig OR duehrig OR hidroa OR hydroa OR (linear NEAR/2 (iga OR "immunoglobulin A") NEAR/2 dermatos*) OR (chronic* NEAR/2 urticar*) OR ((leukocytoclast* OR hypersensitiv* OR allerg*) NEAR/2 vasculit*) OR (allergic* NEAR/2 arteriolit*) OR (lichen NEAR/2 (planus OR ruber)) OR ((skin OR cutane* OR cutis) NEAR/2 (lupus OR sarcoidos*)) OR morphea OR (circumscri* NEAR/2 scleroder*) OR (alopec* NEAR/2 areat*) OR (pyoderm* NEAR/2 (gangre* OR ulcer*)) OR (dermatit* NEAR/2 ulcer*) OR (acute NEAR/2 (febrile OR fever) NEAR/2 neutroph* NEAR/2 dermato*) OR (sweet* NEAR/2 syndrom*) OR (Acne NEAR/2 (vulgar* OR juvenil* OR conglobat* OR fulminan*)) OR (perifolliculi* NEAR/2 conglumerat*) OR (Rosacea* NEAR/2 papulopustul*) OR neurodermatit* OR (Prurigo NEAR/2 nodula*) OR (erythem* NEAR/2 (nodos* OR contusifor*)) OR (inflammat* NEAR/2 bowel*) OR IBD OR Crohn OR (Ulcer* NEAR/2 colit*) OR (primar* NEAR/2 (biliar* OR scleros*) NEAR/2 (cirrhosis* OR cholangit*)) OR ((liver* OR hepatic OR kidney* OR renal* OR organ*) NEAR/2 (transplant*)) OR ((lupus OR lupoid) NEAR/2 (nephr* OR glomerulonephr* OR kidney* OR erythem*)) OR glomerulonephrit* OR (anti-glomerular NEAR/2 basement NEAR/2 membrane) OR (glomerul* NEAR/2 (nephr* OR kidney*)) OR ((interstitial* OR tubulointerstitial*) NEAR/2 nephrit*) OR sarcoidos* OR (besnier NEAR/2 boeck) OR schaumann* OR (lymphogranulom* NEAR/2 benign*) OR (minimal-change NEAR/2 (disease)) OR (Membran* NEAR/2 nephropa*) OR (dense NEAR/2 deposit* NEAR/2 disease*) OR cryoglobulin* OR cryoimmunoglobulin* OR (("immunoglobulin A" OR iga) NEAR/2 nephropat*) OR (Acute NEAR/2 anterior NEAR/2 uveitis))) AND ((((male OR man OR men) NEAR/5 (fertil* OR infertil* OR subfertil*

OR reproducti* OR steril*)) OR aspermi* OR asthenospermi* OR azoospermi* OR oligospermi* OR ejaculat* OR ((sperm* OR semen OR seminal) NEAR/5 (count* OR motility OR abnormal* OR qualit* OR morpholog* OR dna OR characteristic* OR function* OR activit* OR damage OR analy*)) OR spermatoz* OR spermatogen* OR aspermatogen*) OR (((paternal OR father* OR ((male OR men OR man OR paternal*) NEAR/5 (exposure OR drug OR medication OR patient*)))) AND ((((pregnan* OR obstetr* OR labor OR labour) NEAR/2 (outcome* OR disorder* OR complication*)) OR (sexual* NEAR/2 dysfunction*) OR (Erect* NEAR/2 Dysfunct*) OR (impoten* NEAR/2 vascul*) OR dyspareun* OR (Prematur* NEAR/2 ejaculat*) OR placenta* OR ((newborn* OR neonat* OR fetus OR fetal OR foetus OR foetal) NEAR/2 (health* OR disease OR death)) OR “birth weight” OR birthweight OR lbw OR vlbw OR elbw OR (small NEAR/2 (date OR gestation*)) OR congenital* OR preeclamp* OR eclamp* OR miscarriag* OR abort* OR reproduct* OR Childbirth* OR Conception* OR progeny OR offspring OR (prenatal* NEAR/2 develop*)))))) AND DT=(article) AND

CHAPTER 3

Male sexual health and reproduction in cutaneous immune-mediated diseases: a systematic review

Published

Perez-Garcia LF, Dolhain R, Te Winkel B, Carrizales JP, Bramer WM, Vorstenbosch S, van Puijenbroek E, Hazes M, van Doorn MBA.

Sex Med Rev. 2021 Jul;9(3):423-433.

ABSTRACT

Background

Information about the possible effects of cutaneous immune-mediated diseases (cIMD) on male sexual function and reproduction is scarce. Factors known to impair sexual health and reproduction, such as inflammation, medication use and hypogonadism can be present in a significant proportion of male patients with cIMD.

Objectives

To systematically review the literature for the influence of paternal cIMD on many aspects of male sexual and reproductive health, such as sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes.

Methods

A systematic literature search was performed. The searches combined keywords regarding male sexual function and fertility, pregnancy outcomes and offspring's health with a list of cIMD.

Results

The majority of the identified studies included patients with psoriasis (22/27) and sexual function was the most common outcome of interest (20/27). For patients diagnosed with psoriasis, the prevalence of male sexual dysfunction reported in these studies ranged from 34-81%. Hypogonadism in patients with psoriasis was reported in 2 out of 3 studies. Sperm analysis abnormalities in patients with psoriasis were reported in 3 out of 4 studies. No information about the effect of paternal disease on pregnancy and offspring outcomes was identified.

Conclusion

Disease activity in psoriasis might play an important role in the development of sexual dysfunction, hypogonadism and abnormal sperm quality. For the other cIMD included in this review, there is insufficient information regarding male sexual and reproductive health to draw firm conclusions. More research is needed to understand the association between cIMD and impaired male sexual and reproductive health.

INTRODUCTION

Sexual and reproductive health (SRH) is defined as a state of complete physical, mental and social well-being in all matters relating to the reproductive system and every individual should have access to relevant information to make their own decisions about their SRH (1).

In the general population, it is estimated that sexual dysfunction (SD) can affect up to 52% of men older than 40 years old (2) and that the fertility rate in men younger than age 30 years is decreasing worldwide (3). In addition, poor semen quality is now considered as a biomarker of poor general health and it has been associated with an increased mortality rate (4).

Cardiovascular disease, obesity, smoking, depression and anxiety are among the "classic" risk factors that are associated with this increased rate of SRH problems. In addition, an association between inflammation and SD has been described. Recently, a systematic review concluded that evidence suggests a role for the immune system in the generation of an inflammatory environment that contributes to vascular impairments and the development of erectile dysfunction (5). Inflammation of the reproductive tract is also considered as a significant cause of male factor infertility (6)

Immune-mediated diseases (IMD) are characterized by dysregulated immune responses leading to tissue-damaging inflammation and are also strongly associated with cardiovascular disease and comorbidities such as depression and anxiety (7, 8).

Altogether, this evidence led us to believe that systemic inflammation associated with IMD could also have a significant role in the development of SD and/or infertility. We began to test our hypothesis in the field of Rheumatology, considered the hallmark field of autoimmunity. In rheumatic diseases such as rheumatoid arthritis or systemic lupus erythematosus a link between inflammation and an impaired SRH seems plausible (9).

The skin, a physical barrier that protects internal systems from foreign bodies also participates actively as an immune organ. Dermatologic lesions of the external genitalia are common in men with psoriasis (30-40%) and can also be found in men diagnosed with other cIMD. These lesions are associated with considerable physical symptoms and psychological distress that can directly impact male SRH (10). Furthermore, SRH in men diagnosed with cIMD without genital lesions can also be impaired due to other factors such as inflammation, medication or associated comorbidities.

A review article published in 2009 concluded that "sexual dysfunction (SD) should be investigated and treated in patients with skin diseases"(11). A recent meta-analysis that included data from 9 studies and included 36,242 psoriasis patients concluded that psoriasis

was associated with an increased risk of erectile dysfunction (ED) (12). Nonetheless, except for psoriasis, male SRH can still be considered as a neglected topic in Dermatology.

Men diagnosed with a cIMD should receive proper SRH counselling. This information should not be limited to discussing the possible side effects from drugs on a future pregnancy (reproductive toxicology) but the impact that disease itself has on SRH should also be considered.

Our objective was to systematically review the literature for the influence of paternal cIMD on many aspects of SRH, such as sexual function, male fertility, pregnancy outcome and on their offspring health outcome.

METHODS

This review is part of a larger systematic review (SR) that also included IMD from Rheumatology and Gastroenterology. The complete protocol was written according to the PRISMA-P statement (9-10) and registered in PROSPERO and is available in https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=99845. The results from the Rheumatology section have been published elsewhere (9).

Search

A search strategy was developed by an experienced medical librarian (WB) using a structured methodology (13). The searches combined keywords regarding male sexual function and fertility, pregnancy outcomes and offspring's health with a list of cIMDs. Our full search strategy is provided in supplement 1.

Information sources

A systematic literature search was performed in the bibliographic databases: Embase (via Elsevier embase.com), MEDLINE via Ovid, Cochrane Central Register of Trials (CENTRAL) and Web of Science Core Collection. Additionally, Google Scholar and the Clinical trial registries of Europe and the USA were searched. We also contacted authors for further information and included references from the primary search publications, in case these were missed in our search. The databases were searched from inception until February 28th, 2019.

Eligibility criteria

The literature search was limited to the English language and human subjects. Case-control studies, cohort studies, cross-sectional studies, case reports and case series were included. Publications without original data, such as reviews, were excluded.

In the case of studies reporting pregnancy and offspring outcomes, publications were included if the diagnosis of the IMD took place before conception. In case of studies just reporting fertility parameters (i.e. semen analysis, SD) we included publications were the diagnosis was taken into consideration. No restrictions were made regarding the comparison groups. The outcome data should include at least one of the following outcomes; sexual function, reproductive hormones, fertility, pregnancy or offspring outcomes.

Study selection

All articles were imported into EndNote X9. After removal of duplicates, two reviewers (LP and JC) independently and blindly screened titles, abstracts and full-text of the records for eligibility. Disagreements were resolved by consensus with the help of a third reviewer; RD.

Data collection process

One reviewer (LP) extracted relevant information for each studied outcome from the included studies.

Risk of bias in individual studies

The methodological quality of the studies was assessed with the Newcastle Ottawa Scale (NOS), developed for case-control and cohort studies (14). In the case of cross-sectional studies, an adapted scale was used (15). One reviewer, LP, assessed the quality of the studies. Using this method, points were awarded to each publication, related to the selection of the study group, the comparability of the study groups and the ascertainment of the outcomes. The score ranges from 0-9, with scores >5 representing good-quality studies (Scores per study are presented in tables 2-4).

RESULTS

A total of 9735 references were identified. After removing 2851 duplicates, 6884 articles were eligible for title/abstract screening, resulting in 289 articles eligible for full-text reading. 27 articles fulfilled the inclusion criteria for cIMD (see Fig. 1 and table 1).

Results are presented per disease (when available) and were divided into 4 categories (*sexual function, reproductive hormones, fertility outcomes and pregnancy and offspring outcomes)*.

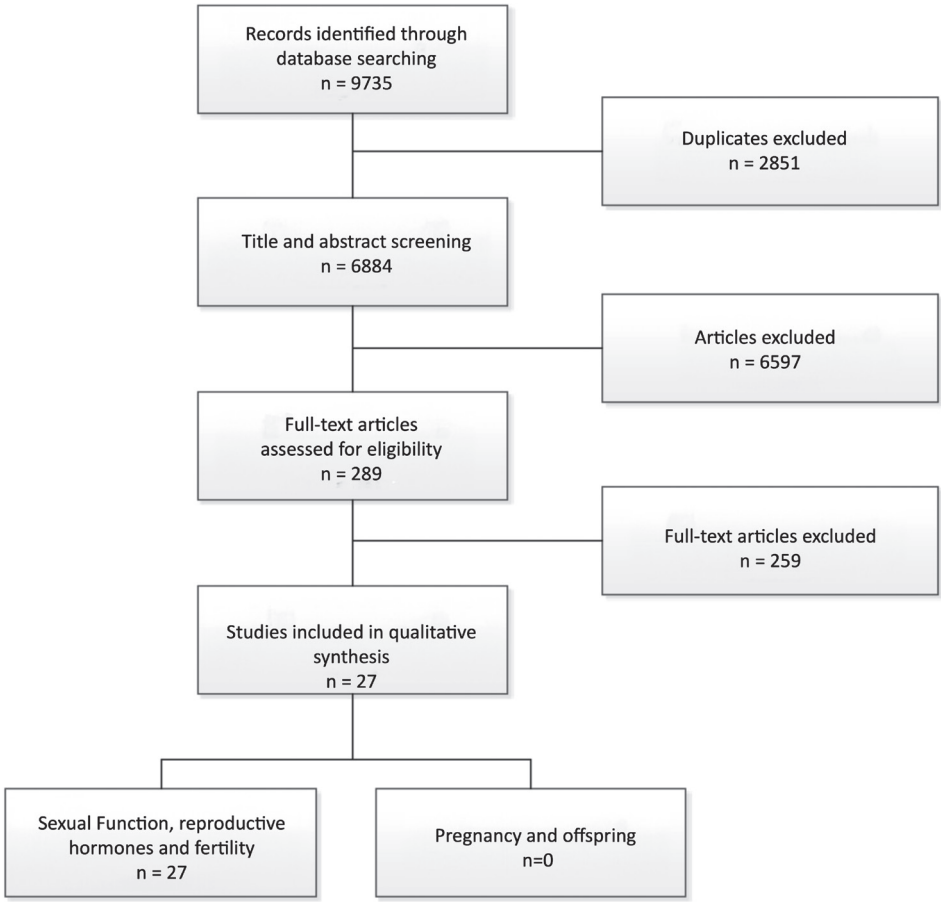


Figure 1. Flow diagram for study selection

- **Sexual function**

Sexual function in men with cIMD was the most common outcome found in our search, these studies represent 74% of the total included studies in this SR (for in-depth information, see table 2).

The importance of this topic is illustrated by the results from a European multicenter study where 24.9% of male patients diagnosed with a dermatologic disease reported sexual difficulties that were strongly associated with depression and anxiety. The highest prevalence of sexual difficulties was found in patients diagnosed with hidradenitis suppurativa (HS) (66.7%), blistering disorders (34.9%) and psoriasis (34.8%) (16).

Table 1. Description of characteristics and key findings of studies regarding sexual function

Article	Country	Number of participants	SD or ED prevalence	Association with psoriasis	Association with depression	Association with disease activity	Association with other factors	NOS Quality assessment and study type
Psoriasis								
Tasliyurt (17)	Turkey	37	81.08% (ED)	NA	+ (Independent risk factor for ED)	+	Significant: Age, smoking	4 Case control
Cabete (18)	Portugal	135	61.5% (ED)	+	NA	NA	Significant: Age, height and diabetes	6 Cross-sectional
Ji S (19)	China	191	52.9% (ED)	-	+	NA	Significant: Hypertension, hyperlipidemia and age	6 Cross-sectional
Molina-Leyva (20)	Spain	40	53.7% (SD)	+	+	+	Significant: Age and anxiety	Case series
Molina-Leyva (21)	Spain	79	34.2% (ED)	-	+	-	Significant: Age and smoking	Case series
Turel Ermertcan (25)	Turkey	39	NA	+	-	-	NA	5 Cross-sectional
Bardazzi (27)	Italy	120	51.6% (ED)	+	NA	+	Not significant: Diabetes Mellitus, smoking, hypertension	6 Cross-sectional
Wojciechowska-Zdrojowy (22)	Poland	76	43.8% (ED)	NA	NA	+	Significant: Age, genitourinary diseases, duration of psoriasis, Not significant: Cardiovascular diseases, diabetes	5 Cross-sectional
Goulding (23)	United Kingdom	92	58% (ED)	-	NA	NA	Significant: Age and hypertension	5 Cross-sectional
Egeberg (26)	Denmark	26,536	12.8% (ED)	+	NA	+	NA	7 Cohort

Table 1. Continued

Article	Country	Number of participants	SD or ED prevalence	Association with psoriasis	Association with depression	Association with disease activity	Association with other factors	NOS Quality assessment and study type
Meeuwis (28)	Netherlands	278	NA	NA	NA	NA	Significant: Genital psoriasis	7 Cross-sectional
Sampogna (24)	Italy	244	34.4-67.9% *4 questionnaires were used	NA	NA	+	Significant: Age	5 Cross-sectional
Hidradenitis suppurativa								
Alavi (31)	Canada	17	NA	NA	NA	NA	NA	6 Cross-sectional
Janse (32)	Netherlands	66	52% (ED)	NA	NA	-	NA	6 Cross-sectional
Kurek (33)	Germany	NA	NA	NA	NA	-	NA	5 Cross-sectional
Lichen simplex								
Juan (34)	Taiwan	5,611	3.37% (SD) *Incidence	NA	+	NA	Significant: Diabetes Mellitus, hypertension, hyperlipidemia Cardiovascular diseases and anxiety	7 Cohort
Vitiligo								
Sukan (35)	Turkey	26	11.5% (SD)	NA	-	NA	NA	4 Cross-sectional
Chronic urticaria								
Sukan (35)	Turkey	16	31.2% (SD)	NA	+	NA	NA	4 Cross-sectional
Atopic dermatitis								
Egeberg (26)	Denmark	26,536	6.7% (ED)	+	NA	+	NA	7 Cohort

2. Description of characteristics and key findings of studies regarding reproductive hormones

Study	Number of cases/ controls (mean age in years)	Main findings	Study type and Quality assessment (NOS)
Psoriasis			
Caldarola (17)	Cases: 50 (34) Controls: 50 (33.4)	• Testosterone was found to be significantly decreased in patients with psoriasis compared to the control group (3.7 ± 1.3 vs 4.8 ±1.2 ng/mL, respectively). • Estradiol (E2) levels were higher in patients with psoriasis than in the control group (43.8 ± 8.1 vs 29.1 ±8.2 pg/mL).	4 Cross-sectional
Cemil (37)	Cases: 47 (55.9 ± 4.1) Controls: NA	• Testosterone was found to be significantly decreased in patients with psoriasis compared to the control group (3.9 ± 1.8 vs 5.1 ±1.2 ng/mL, respectively). • Estradiol (E2) levels were higher in patients with psoriasis than in the control group (37.5 ± 17.1 vs 29.9 ± 8.7 pg/mL). o Inverse correlation was detected between PASI and serum level of estradiol in the psoriasis group.	4 Cross-sectional
Saad (38)	Cases: 15 (53) Controls: 131 (NA)	Observational study. 15 men diagnosed with late-onset hypogonadism and psoriasis. Treatment with testosterone undecanoate every 12 weeks for up to 93 months was associated with: • Testosterone levels rose significantly to an eugonadal state. • PASI declined from 19.3 ± 2.3 to 1.8 ± 0.4 ($p < 0.0001$). • Serum CRP levels decreased significantly over the first 24 months.	Case series
Tehranchinia (39)	Cases: 43 (34.1 ± 10.5) Controls: 42 (31.8 ± 8.9)	• Testosterone levels were not statistically different between the two groups. • Psoriasis patients had significantly higher levels of leptin than healthy controls (5.4 vs 2.7 ng/mL, respectively) and lower levels of FSH (1.4 vs 2 IU/L). • A positive correlation was reported between serum leptin levels and disease activity.	4 Cross-sectional
Atopic dermatitis			
Ebata (40)	Cases: 40 (24) Controls: 40 (24)	Serum levels of testosterone, free testosterone and estradiol were significantly lower and serum levels of H were significantly higher in male patients with atopic dermatitis	4 Cross-sectional

-

- **Psoriasis**

Sexual function in psoriasis was studied in 14 studies that included 29,410 patients with a mean age of 41.07 years. Cross-sectional studies were the most frequent study type and the overall quality of these studies was graded as 'good quality'. To assess sexual function, eight of the studies used the International Index of Erectile Function (IIEF). Other tools also used were; Massachusetts General Hospital-Sexual Functioning Questionnaire (MGH-SFQ) in 2 studies and the Sexual Quality of Life-Men (SQoL_M) in one study. Disease activity in psoriasis was reported using the Psoriasis Area and Severity Index (PASI) which combines the assessment of the severity of the skin lesions and the affected area into a single score in the range of 0 (no disease) to 72 (maximal disease) (17-30).

Using validated questionnaires, the prevalence of SD in psoriasis (including ED) ranged from 34.4% to 81% (17-27). When compared to a control group, the prevalence of SD was significantly higher in psoriasis patients than in controls. Using the IIEF questionnaire, the highest prevalence of ED was reported by Tasliyurt et al. In their study a prevalence of 81.08% was found in a population of 37 psoriasis patients (mean age 45.19 ± 13.82, mean PASI 8.25 ± 4.42) compared to 53.57% in 28 healthy men (mean age 40.89 ± 12.91 years), this difference was statistically significant (p=0.018). IIEF scores had a significant negative correlation with age, body mass index and PASI scores. Depression, older age and smoking were found to be independent risk factors for ED (17).

In the study from Cabete et al, the prevalence of ED (IIEF-5 score $\leq$21) was higher in psoriasis patients than in controls (61.5% vs 43.8%, p=0.001). Furthermore, it was reported that psoriasis patients had a 2.69- and 5.3-fold increased risk of having mild-moderate and moderate-severe ED, respectively (18).

In a study from Poland, 42% of patients diagnosed with psoriasis reported that sexual activity decreased due to their skin problems. ED was diagnosed in 43.8% of these patients and its severity was correlated with age (r=-0.42; p=$<$0.001) and with disease activity (r=-0.26: p=0.03) (22).

Psoriasis was found to be an independent risk factor for ED (odds ratio of 2.28 [CI 95%, 1.40-3.27]) in one study (18) and with SD in two studies (19, 21). No association was reported in one study (25).

The association between disease activity and SD was further analyzed in 8 studies. Six studies reported an association between disease activity and SD (17, 20, 22, 24, 26, 27). Conversely, in 2 studies such an association was not significant (21, 25).

The association between SD and depression, a known factor that adversely affects male sexual function, was analyzed in 5 studies. An association between depression and the presence of SD was reported in 3 studies (17, 19-21). No association between depression and SD in patients with psoriasis was reported in one study (25).

In a study that included 191 psoriasis patients, Ji et al reported that severe depressive symptoms increased the risk of ED (19). Similarly, Molina-Leyva et al reported that depression was significantly associated with ED and that psoriasis per se was not independently associated with ED (21).

No significant association between depression and SD was reported in a study that included 70 men from Turkey (39 diagnosed with psoriasis and 27 healthy controls, mean age 41.42 and 41.77 years, respectively). Interestingly, total IIEF scores were not correlated with disease activity (PASI) (25).

Other relevant factors associated with SD were; increasing age, smoking and hypertension (17-24). Bardazzi et al reported that psoriatic patients with ED were younger and had a more severe form of ED in comparison to non-psoriasis patients diagnosed with ED (27).

Communication between patients and health care professionals was analyzed in two studies from the UK. Only 9% of psoriatic patients had been previously asked by a healthcare professional about erectile problems while 68% admitted dissatisfaction with their erectile ability and wanted more information on this topic (23). Similarly, in a study from the Netherlands that included 278 men diagnosed with psoriasis (mean age 53.9 ± 12.3 years) only 9% of patients believed that there was sufficient attention given by their doctors to possible sexual problems and 43% thought that healthcare professionals should ask more frequently about possible sexual problems (28).

Three studies used diagnosis codes to report the prevalence or incidence of SD in patients with psoriasis. Data from 1,593 psoriasis patients from the United States (aged 18-42 years) reported that a diagnosis of SD (ICD-9 and ICD-10 codes) was present in 7.2% of men on systemic medications compared to 3.6% of those treated with topical or no medications, this difference was statistically significant (29).

A recent observational nationwide study from Egeberg et al included 1,756,679 Danish men from which 1.5% were diagnosed with psoriasis. The prevalence of ED was 12.8% for patients with psoriasis compared to 8.7% in the general population. The risk of ED was significantly increased in patients with mild psoriasis (adjusted HR 1.14; 1.09-1.20) and severe psoriasis (adjusted HR 1.17; 1.04-1.32) (26).

A nationwide study from Taiwan reported a significantly higher incidence of SD (3.03%) among 12,300 patients (median age 46 years) compared to age-matched controls (2.34%) during 7 years The most prevalent SD was ED (30).

- **Hidradenitis suppurativa**

Sexual function in hidradenitis suppurativa (HS) was reported in 3 studies. The IIEF questionnaire was used in all 3 studies. The quality of these studies was graded as 'good quality'. These studies included data on 103 patients (mean age of 41.6 years) and 42 healthy controls (mean age of 37.8 years). The prevalence of SD in HS was reported in one study. Overall, compared to healthy controls, patients with HS reported more sexual function problems that contribute to a lower quality of life. No association was found between disease activity and SD.

In a cross-sectional study from Canada that included 17 HS patients (mean age 40.47 ± 15.49 years) and 22 healthy age-matched control, significant differences in sexual function assessments were identified. Patients with HS had significantly lower Sexual Quality of Life Questionnaire for Use in Men (SQoLM) scores ($p<0.001$) and lower IIEF scores ($p=0.019$). The authors concluded that SD is an important contributor to impaired QoL in patients with HS (31) .

A multicenter cross-sectional study from the Netherlands (n=66, mean age 48.4 ± 12.3 years) reported a prevalence of ED of 52%. No association was reported between the IIEF total score and age of onset, duration of disease, VAS pain score, PGA score, Hurley stage or DLQI score. 58% of men with HS indicated that their sexual activity declined after disease onset (32).

SD was more severe in 20 patients with HS compared to 20 age-matched controls as evidenced by a lower IIEF total score (42.6 ± 27.1 vs 62.6 ± 10.8, $p = 0.01$). No significant correlation between disease activity and the IIEF was reported (33).

- **Lichen simplex**

From 2000 to 2004, 5611 male patients (mean age 49.46 years) were diagnosed with lichen simplex in Taiwan. The incidence of SD in this group was higher than in the general population (3.37 vs 1.74 per 1000 person-years). After adjusting for age and comorbidities and using data from 22444 age-matched patients without lichen simplex as controls, patients with lichen simplex had a 1.74-fold greater risk of developing ED compared to controls ($p<0.001$) (34).

- **Vitiligo**

The prevalence of SD was not significantly different among patients with vitiligo and healthy controls (11.5 and 16%) in one study from Turkey that included 26 patients and 25 healthy controls (mean age 35.8 and 35.9 years, respectively) (35).

- **Chronic Urticaria**

The prevalence of SD was not significantly different among patients with chronic urticaria and healthy controls (31.2 and 16%) in a study that included 26 patients and 25 healthy controls from Turkey (mean age 38.6 and 35.9 years, respectively) (35).

- **Atopic dermatitis**

In the study from Egeberg et al, patients diagnosed with atopic dermatitis were also included. Interestingly, patients with atopic dermatitis had a lower prevalence of SD than the general population (6.7% vs 8.7%, respectively) (26).

- **Reproductive hormones**

Regarding reproductive hormones, 5 studies were identified. The quality of these studies was graded as 'low quality' (for in-depth information, see table 3).

- **Psoriasis**

The androgenic status of 50 patients (mean 34 ± 8.4 years) with moderate psoriasis (PASI 8 ± 5.5) was investigated by Caldarola et al. Testosterone and sex hormone-binding globulin (SHBG) were significantly decreased in patients compared to age-matched controls (n=50). Estradiol (E2) levels were higher in patients than controls (36).

An association between disease activity and low estradiol levels was reported by Cemil et al. In a cross-sectional study that included 47 patients and 20 controls (42.87 ± 15.56 and 38.05 ± 10.14 years, respectively) serum testosterone levels were significantly decreased in psoriatic patients compared to controls (392.29 ± 181.91 ng/mL and 506.91 ± 117.7 ng/mL, respectively). Estradiol levels were significantly increased in psoriatic patients (37.52 ± 17.16 vs 29.9 ± 8.77) and an inverse correlation was detected between PASI and estradiol levels in psoriatic patients ($p < 0.05$) (37).

In an observational study, testosterone replacement therapy declined PASI scores by >75% within 2 years in 15 patients diagnosed with psoriasis and late-onset hypogonadism. This was an observational study without controls. The possible role of testosterone as an anti-inflammatory agent is discussed (38).

Table 3. Description of characteristics and key findings of studies regarding fertility

Study	Number of cases/ controls (mean age in years)	Main findings	NOS Quality assessment and study type
Psoriasis			
Caldarola	Cases: 50 (34) Controls: 50 (33.4)	Total sperm count, sperm motility and percent of spermatozoa with normal morphology were significantly reduced in patients compared to controls. • Sperm concentration, n X 10^6/mL: 18.6 ± 11. 6 vs 62.8 ± 20.5 • Total motility, %: 29.7 ± 22.7 vs 60.2 ± 10.2 • Normal morphology, %: 13.3 ± 9 vs 32.9 ± 5.5	4 Cross sectional
Heppt	Cases: 27 (37.5) Controls: NA	• Only 4 (14.8%) patients with psoriasis showed normozoospermia at baseline. • 85.2% of the patients had at least one sperm/seminal abnormality, including two patients showing an azoospermia. • 48.1% of the patients showed semen parameters indicating a genital tract inflammation.	5 Cohort
Grunnet	Cases: 20 (32.4) Controls: 10 (NA)	16 out of 20 psoriasis patients (80%) treated with topical glucocorticoids or methotrexate had abnormal semen parameters.	3 Cross sectional
Liu	Cases: 31 (18-24) Controls: 14 (18-24)	Semen quality did not differ between patients and controls.	4 Cross sectional

Leptin, a hormone secreted by the adipose tissue that plays an important role in reproductive function, was found to be significantly higher in patients with psoriasis (n=43, mean age 34.09 ± 10.53) compared to age-matched healthy controls (n=42). This was associated with lower level of FSH in patients compared to controls. Serum concentrations of LH, total testosterone, SHBG, and prolactin were comparable among the two groups. In psoriatic patients, disease activity and duration were significantly correlated with log-transformed leptin levels (adjusted R2=0.50, F=21.87, p<.0001) (39).

- **Atopic dermatitis**

The prevalence of hypogonadism was significantly higher in 40 patients diagnosed with atopic dermatitis compared to age-matched healthy controls. This was evidenced as patients had lower serum levels of testosterone, free testosterone (447 ± 96 vs 593 ± 149 ng/dl and 14.6 ± 3.2 vs 20.0 ± 5.1 pg/ml, both p<0.001) and higher levels of LH than controls (4.57 ± 1.6 vs 3.11 ± 1.2 mIU/ml, p<0.001) (40).

- **Fertility**

- **Psoriasis**

Regarding fertility parameters, 4 studies that reported sperm analysis results were identified. The quality of these studies was graded as 'low quality'. Sperm analysis abnormalities in patients with psoriasis were reported in 3 out of 4 studies (one study included untreated patients, one study included patients treated with methotrexate and one study did not report treatment characteristics of the patients) (for in-depth information, see table 4).

Table 4. Number of studies included per disease and topic

Disease	Total number of studies	Sexual function	Reproductive hormones	Fertility	Pregnancy outcomes
Psoriasis	21	13	4	4	0
Hidradenitis suppurativa	3	3	0	0	0
Lichen simplex	1	1	0	0	0
Vitiligo	1	1	0	0	0
Chronic urticaria	1	1	0	0	0
Atopic dermatitis	2	1	1	0	0

Sperm analysis was performed in 27 untreated patients (mean age of 37.5 years) with moderate to severe psoriasis (mean PASI score, 11.05). Interestingly, 85.2% had at least one sperm/seminal abnormality and 48.1% showed parameters indicative of genital tract inflammation (41).

Grunnet et al reported sperm analysis abnormalities in all 10 patients with severe psoriasis treated with topical corticosteroids included in their study. Based on semen quality, 30% were classified with 'severely impaired fertility' (oligospermia 70%, asthenospermia 90%) and 30% were unwillingly childless. In contrast, sperm analysis was normal in 40% of the patients included in their comparison group (n=10 patients with severe psoriasis treated with methotrexate, this was statistically significant (p=0.04) (42).

In the study from Caldarola et al semen analysis was also performed. Sperm count, motility and morphology were significantly reduced in patients compared to controls. 50% of patients showed 1 or more seminal parameters abnormalities (36).

Sperm quality was investigated in 31 young Chinese soldiers diagnosed with psoriasis (aged 18-24 years). Compared to a group of 14 healthy volunteers from the same population, conventional sperm analysis and the measurement of sperm nuclear DNA fragments was comparable among the 2 groups (43).

- **Pregnancy and offspring outcomes**

No articles were identified.

DISCUSSION

Sexual function

Patients with psoriasis, hidradenitis suppurativa and lichen simplex have a higher prevalence of SD. Along with the classical risk factors, a positive correlation between psoriasis disease activity and SD was reported in several studies. This finding invites a discussion about how inflammation secondary to psoriasis can contribute to the development of SD in a young population.

Although there is evidence suggesting an influence of disease itself (via inflammation) in the development of SD, we were not able to conclude whether the disease itself plays a role in this association.). After carefully analyzing our data, we concluded that performing a meta-analysis was not ideal. Our main reason behind this decision was that the type of studies included and the extracted heterogeneous data might lead to erroneous assumptions.

Epidemiological, clinical and basic science studies are needed to investigate the association between sexual function and cIMD. These studies should be executed in such a way that results can be compared among different populations.

Before there is more research on this topic and in order to improve the overall quality of it, agreement should be pursued on the definitions and diagnostic tools to use. Discussion on these issues between experts from different fields such as Andrology, Sexology, Dermatology and Epidemiology is needed. Such an agreement will have a positive effect on future research projects trying to summarize the available data (see also table 5, Research recommendations to conduct future research on these topics).

Adult men consider sexual health as a highly important aspect of quality of life (49) thus, dermatologists with a commitment to improving patient's overall health should address sexual concerns with their patients and partners.

Table 5. Research recommendations

Sexual function	Use standardized screening questionnaires (IIEF). Case-control studies and well-designed prospective cohort studies are encouraged over cross-sectional studies. Consider relevant comorbidities and potential confounders (Depression, anxiety, disease activity). Collaboration with experts in the field of Sexology is encouraged.
Sperm quality	Use standardized methods to report sperm quality (WHO) (primary endpoint). DNA fragmentation index could provide more information regarding male fertility potential and can be considered as a secondary endpoint. Ideally, technicians should be blinded regarding the drug-exposure. RCTs are ideal but case-control and well-designed prospective cohort studies are also encouraged over cross-sectional studies. Consider disease activity, relevant medication history, comorbidities and potential confounders (age, smoking, varicocele).
Reproductive hormones	Use standardized methods to measure hormones. RCTs are ideal but case-control and well-designed prospective cohort studies are also encouraged over cross-sectional studies. Consider disease activity, relevant comorbidities and potential confounders (age, medication history).
Pregnancy and offspring outcomes	Collect data prospectively or report cases with all the relevant information. For instance: Source of the information, indication, disease activity, clear description of medication use and timing paternal age. Regarding pregnancy/child outcome; pregnancy outcome, gestational age, birthweight, infant health, genetic testing, follow up period, Partner's relevant medical history.

Reproductive hormones

In psoriasis, evidence suggests a possible association between disease activity and abnormalities in the reproductive endocrine axis. This is a topic where surprisingly few studies were found. Nonetheless, these studies provide interesting information; inflammation secondary to disease activity, via aromatase activity stimulation, might contribute to the development of hypogonadism in these men. Consequently, hypogonadism can be in part responsible for the high prevalence of SD in this population.

The anti-inflammatory effects of testosterone have been previously described and low testosterone levels are correlated with increased expression of inflammation markers (44). Nonetheless, in men diagnosed with cIMD a valid estimation of the prevalence of hypogonadism and the influence that this has on the development of the disease is still unknown. More research is needed to fully understand the role of reproductive hormones on cIMD.

Fertility

Sperm quality can be impaired in patients diagnosed with psoriasis (independent of treatment) and this could be associated with disease activity. Systemic inflammation can cause impaired spermatogenesis by mechanisms that have not been fully elucidated. For men diagnosed with psoriasis and a desire to become a father, disease activity should be monitored before and during the conception period. Importantly, medication is not the only factor that can contribute to impaired fertility in men diagnosed with psoriasis.

Pregnancy and offspring outcomes

Considering the extensive list of diseases included in this SR, the complete lack of studies included in this section warrants discussion. The paternal contributions to pregnancy are vital for a successful pregnancy. These men need to receive proper counselling to limit the potential negative effects of disease and/or medication on a future pregnancy. Nonetheless, currently, there is not enough information regarding the possible influence of paternal cIMD on pregnancy and offspring outcomes.

Strengths and limitations

Several limitations should be addressed. First, a limited amount of studies that included a small number of participants were identified. In addition, studies about sexual function and fertility in men with cIMD suffer from an inconsistent methodological quality mainly because a wide variety of screening questionnaires and/or diagnostic tools were used. In consequence, the definition of SD and ED was not uniformly reported. Altogether, these limitations contributed to heterogeneous data, which we consider to be too large to perform a meta-analysis. Lastly, relevant comorbidities that can also have a direct effect on sexual function such as depression and anxiety were not analyzed or reported in all studies.

Although we were able to provide a summary of the available information, we consider that the major strength of this SR is its ability to identify a large knowledge gap in this

topic. Regarding fertility and pregnancy outcomes, the complete lack of information available should be acknowledged and prioritized for future research plans.

CONCLUSION

Evidence suggests that male SRH can be impaired in a significant proportion of men diagnosed with psoriasis. Nonetheless, for the other cIMD included in this SR, information on this topic is scarce and no strong conclusions can be drawn other than more research is needed and that this is still an important neglected topic in Dermatology. Future research on this topic can provide us with relevant scientific information that can help us understand the role of inflammation in SRH.

We encourage dermatologists to consider male SRH in their clinical practice. Timely detection, referral and treatment of SD and fertility problems can have a significant impact on the quality of life of patients and reduce the use of costly medical care. To achieve this, dermatologists and patients must have the opportunity and necessary tools to discuss this topic.

REFERENCES

1. Glasier A, Gülmezoglu AM, Schmid GP, Moreno CG, Van Look PFA. Sexual and reproductive health: a matter of life and death. The Lancet. 2006;368(9547):1595-607.
2. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol. 1994;151(1):54-61.
3. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S. Births: final data for 2004. Natl Vital Stat Rep. 2006;55(1):1-101.
4. Eisenberg ML, Li S, Cullen MR, Baker LC. Increased risk of incident chronic medical conditions in infertile men: analysis of United States claims data. Fertil Steril. 2016;105(3):629-36.
5. Calmasini FB, Klee N, Webb RC, Priviero F. Impact of Immune System Activation and Vascular Impairment on Male and Female Sexual Dysfunction. Sex Med Rev. 2019;7(4):604-13.
6. Fijak M, Pilatz A, Hedger MP, Nicolas N, Bhushan S, Michel V, et al. Infectious, inflammatory and 'autoimmune' male factor infertility: how do rodent models inform clinical practice? Hum Reprod Update. 2018.
7. Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, et al. Psoriasis and comorbid diseases: Epidemiology. J Am Acad Dermatol. 2017;76(3):377-90.
8. Shlyankevich J, Chen AJ, Kim GE, Kimball AB. Hidradenitis suppurativa is a systemic disease with substantial comorbidity burden: A chart-verified case-control analysis. Journal of the American Academy of Dermatology. 2014;71(6):1144-50.
9. Perez-Garcia LF, Te Winkel B, Carrizales JP, Bramer W, Vorstenbosch S, van Puijenbroek E, et al. Sexual function and reproduction can be impaired in men with rheumatic diseases: A systematic review. Semin Arthritis Rheum. 2020.
10. Gabrielson AT, Le TV, Fontenot C, Usta M, Hellstrom WJG. Male Genital Dermatology: A Primer for the Sexual Medicine Physician. Sex Med Rev. 2019;7(1):71-83.
11. Ermertcan AT. Sexual dysfunction in dermatological diseases. Journal of the European Academy of Dermatology and Venereology. 2009;23(9):999-1007.
12. Wu T, Duan X, Chen S, Chen X, Yu R, Yu X. Association Between Psoriasis and Erectile Dysfunction: A Meta-Analysis. J Sex Med. 2018;15(6):839-47.
13. Bramer WM, de Jonge GB, Rethlefsen ML, Mast F, Kleijnen J. A systematic approach to searching: an efficient and complete method to develop literature searches. J Med Libr Assoc. 2018;106(4):531-41.
14. Wells G SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013.
15. Modesti PA, Reboldi G, Cappuccio FP, Agyemang C, Remuzzi G, Rapi S, et al. Panethnic Differences in Blood Pressure in Europe: A Systematic Review and Meta-Analysis. PLoS One. 2016;11(1):e0147601.
16. Sampogna F, Abeni D, Gieler U, Tomas-Aragones L, Lien L, Titeca G, et al. Impairment of Sexual Life in 3,485 Dermatological Outpatients From a Multicentre Study in 13 European Countries. Acta Derm Venereol. 2017;97(4):478-82.
17. Tasliyurt T, Bilir Y, Sahin S, Seckin HY, Kaya SU, Sivgin H, et al. Erectile dysfunction in patients with psoriasis: Potential impact of the metabolic syndrome. Eur Rev Med Pharmacol Sci. 2014;18(4):581-6.
18. Cabete J, Torres T, Vilarinho T, Ferreira A, Selores M. Erectile dysfunction in psoriasis patients. Eur J Dermatol. 2014;24(4):482-6.
19. Ji S, Zang Z, Ma H, Gu M, Han Y, Wang L, et al. Erectile dysfunction in patients with plaque psoriasis: The relation of depression and cardiovascular factors. Int J Impotence Res. 2016;28(3):96-100.

20. Molina-Leyva A, Almodovar-Real A, Carrascosa JC, Molina-Leyva I, Naranjo-Sintes R, Jimenez-Moleon JJ. Distribution pattern of psoriasis, anxiety and depression as possible causes of sexual dysfunction in patients with moderate to severe psoriasis. An Bras Dermatol. 2015;90(3):338-45.
21. Molina-Leyva A, Molina-Leyva I, Almodovar-Real A, Ruiz-Carrascosa JC, Naranjo-Sintes R, Jimenez-Moleon JJ. Prevalence and Associated Factors of Erectile Dysfunction in Patients With Moderate to Severe Psoriasis and Healthy Population: A Comparative Study Considering Physical and Psychological Factors. Arch Sex Behav. 2016;45(8):2047-55.
22. Wojciechowska-Zdrojowy M, Reid A, Szepietowski JC, Wojciechowski A. Analysis of sexual problems in men with psoriasis. J Sex Marital Ther. 2018;44:8:735-45.
23. Goulding JM, Price CL, Defty CL, Hulangamuwa CS, Bader E, Ahmed I. Erectile dysfunction in patients with psoriasis: increased prevalence, an unmet need, and a chance to intervene. Br J Dermatol. 2011;164(1):103-9.
24. Sampogna F, Gisondi P, Tabolli S, Abeni D, investigators IDIMPRoVE. Impairment of sexual life in patients with psoriasis. Dermatology. 2007;214(2):144-50.
25. Turel Ermertcan A, Temeltas G, Deveci A, Dinc G, Guler HB, Ozturkcan S. Sexual dysfunction in patients with psoriasis. J Dermatol. 2006;33(11):772-8.
26. Egeberg A, Hansen PR, Gislason GH, Skov L, Thyssen JP. Erectile Dysfunction in Male Adults With Atopic Dermatitis and Psoriasis. J Sex Med. 2017;14(3):380-6.
27. Bardazzi F, Odorici G, Ferrara F, Magnano M, Balestri R, Patrizi A. Sex and the PASI: patients affected by a mild form of psoriasis are more predisposed to have a more severe form of erectile dysfunction. J Eur Acad Dermatol Venereol. 2016;30(8):1342-8.
28. Meeuwis KA, de Hullu JA, van de Nieuwenhof HP, Evers AW, Massuger LF, van de Kerkhof PC, et al. Quality of life and sexual health in patients with genital psoriasis. Br J Dermatol. 2011;164(6):1247-55.
29. Orrell KA, Nardone B, Serrano L, Lund EB, Grushchak S, Rangel S, et al. Psoriasis and sexual dysfunction in young adult males: A cross-sectional study in a large U.S. population. J Invest Dermatol. 2017;137(5):S27.
30. Chen YJ, Chen CC, Lin MW, Chen TJ, Li CY, Hwang CY, et al. Increased Risk of Sexual Dysfunction in Male Patients with Psoriasis: A Nationwide Population-Based Follow-Up Study. J Sex Med. 2013;10(5):1212-8.
31. Alavi A, Farzanfar D, Rogalska T, Lowes MA, Chavoshi S. Quality of life and sexual health in patients with hidradenitis suppurativa. Int J Women's Derm. 2018.
32. Janse IC, Deckers IE, van der Maten AD, Evers AWM, Boer J, van der Zee HH, et al. Sexual health and quality of life are impaired in hidradenitis suppurativa: a multicentre cross-sectional study. Br J Dermatol. 2017;176(4):1042-7.
33. Kurek A, Peters EMJ, Chanwangpong A, Sabat R, Sterry W, Schneider-Burrus S. Profound disturbances of sexual health in patients with acne inversa. J Am Acad Dermatol. 2012;67(3):422-8.e1.
34. Juan CK, Chen HJ, Shen JL, Kao CH. Lichen simplex chronicus associated with erectile dysfunction: A population-based retrospective cohort study. PLoS ONE. 2015;10(6).
35. Sukan M, Maner F. The problems in sexual functions of vitiligo and chronic urticaria patients. J Sex Marital Ther. 2007;33(1):55-64.
36. Caldarola G, Milardi D, Grande G, Quercia A, Baroni S, Morelli R, et al. Untreated Psoriasis Impairs Male Fertility: A Case-Control Study. Dermatology. 2017;233(2-3):170-4.
37. Cemil BC, Cengiz FP, Atas H, Ozturk G, Canpolat F. Sex hormones in male psoriasis patients and their correlation with the Psoriasis Area and Severity Index. J Dermatol. 2015;42(5):500-3.
38. Saad F, Haider A, Gooren L. Hypogonadal men with psoriasis benefit from long-term testosterone replacement therapy - a series of 15 case reports. Andrologia. 2016;48(3):341-6.

39. Tehranchinia Z, Niroomand M, Kazeminejad A, Ghahari MJ, Radvar SE, Sadat-Amini SH, et al. Leptin and sex hormones in psoriasis and correlation with disease severity. Iran J Dermatol. 2014;17(68):43-8.
40. Ebata T, Itamura R, Aizawa H, Niimura M. Serum sex hormone levels in adult patients with atopic dermatitis. J Dermatol. 1996;23(9):603-5.
41. Heppt F, Colsman A, Maronna A, Uslu U, Heppt MV, Kiesewetter F, et al. Influence of TNF-alpha inhibitors and fumaric acid esters on male fertility in psoriasis patients. J Eur Acad Dermatol Venereol. 2017;31(11):1860-6.
42. Grunnet E, Nyfors A, Brogaard Hansen K. Studies on human semen in topical corticosteroid treated and in methotrexate treated psoriatics. Dermatologica. 1977;154(2):78-84.
43. Liu H, Li J, Yu L. Effects of acitretin on semen quality and reproductive hormone levels in patients with psoriasis vulgaris. Dermatol Sin. 2017;35(2):55-8.
44. Bianchi VE. The Anti-Inflammatory Effects of Testosterone. J Endocr Soc. 2019;3(1):91-107.

PART III

Can inflammatory arthritis impair male reproductive health?

CHAPTER 4

Impaired fertility in men diagnosed with inflammatory arthritis: results of a large multicentre study (iFAME-Fertility)

Published

Perez-Garcia LF, Röder E, Goekoop RJ, Hazes JMW, Kok MR, Smeele HTW, Tchetverikov I, van der Helm-van Mil AHM, van der Kaap JH, Kok P, Krijthe BP, Dolhain RJEM.

Ann Rheum Dis. 2021 Dec;80(12):1545-1552.

ABSTRACT

Objectives

The impact of inflammatory arthritis (IA) on male fertility remains unexplored. Our objective was to evaluate the impact of IA on several male fertility outcomes; fertility rate (number of biological children per man), family planning, childlessness and fertility problems.

Methods

We performed a multicenter cross-sectional study (iFAME-Fertility).Men with IA 40 years or older who indicated that their family size was complete were invited to participate. Participants completed a questionnaire that included demographic, medical and fertility-related questions. To analyze the impact of IA on fertility rate, patients were divided into groups according to the age at the time of their diagnosis: ≤30 years (before the peak of reproductive age), between 31-40 years (during the peak) and ≥41 years (after the peak).

Results

In total 628 participants diagnosed with IA were included. Men diagnosed ≤30 years had a lower mean number of children (1.32 [SD 1.14]) than men diagnosed between 31-40 years (1.60 [SD 1.35]) and men diagnosed ≥41 years (1.88 [SD 1.14]).This was statistically significant (p=0.0004).The percentages of men diagnosed ≤30 and 31-40 years who were involuntary childless (12.03% vs 10.34% vs 3.98%, p=0.001) and who reported having received medical evaluations for fertility problems (20.61%, 20.69% and 11.36%, p=0.027) were statistically significant higher than men diagnosed ≥41 years.

Conclusion

This is the first study that shows that IA can impair male fertility. Men diagnosed with IA before and during the peak of reproductive age had a lower fertility rate, higher childlessness rate and more fertility problems. Increased awareness and more research into the causes behind this association are urgently needed.

INTRODUCTION

Spondyloarthritis (SpA) and Rheumatoid Arthritis (RA) are frequent causes of Inflammatory Arthritis (IA) that can affect men before or during the peak of their reproductive age (1-4). Even though IA is associated with male infertility, erectile dysfunction and hypogonadism (5, 6) the impact of IA on male fertility remains largely unexplored. This is even more striking if we consider that several frequently prescribed anti-rheumatic drugs have been associated with reversible or irreversible testicular toxicity (7).

The majority of people aspire to have children and it is known that men desire parenthood as much as women do (8-10). Nonetheless, the impact of IA on one of the most important markers of fertility, the male fertility rate (total number of children per man) (11-13), has never been studied before.

Childbearing decisions and reproductive potential are strongly influenced by multiple psychosocial, demographic and biological factors (9, 14). Furthermore, it has been demonstrated that men diagnosed with chronic diseases are exposed to additional factors that have an effect on their childbearing decisions and their reproductive potential (15, 16).

In women diagnosed with IA, several factors related to IA have been associated with lower fertility rates (17-19). It can be expected that some of these factors could also influence the fertility rate of men diagnosed with IA , such as impaired sexual function, lower intercourse frequency, deciding not to have a family or to have smaller families due to concerns about the impact of IA or anti-rheumatic treatment.

Therefore, we aimed to evaluate the impact of IA on relevant markers of male fertility. Our primary objective was to compare the fertility rate of men diagnosed with IA based on their age at diagnosis. Additionally, we compared the fertility rate of men diagnosed with IA with the general male population of the Netherlands. To further evaluate the impact of IA on male fertility, as secondary objectives we compared the total number of pregnancies per man, desired family size (family planning), the proportion of childless men and fertility outcomes based on the results from medical evaluations for fertility problems.

METHODS

Study design and patient selection

We conducted a multicenter cross-sectional study in eight Dutch hospitals (iFAME-Fertility study). In the Netherlands, most men become a father between the age of 30 and 40 years and this period is considered to be the peak of reproductive age (20).

Therefore, men who were diagnosed with IA based on the expert opinion of their rheumatologists (RA, Juvenile Idiopathic Arthritis (JIA) and SpA (Ankylosing Spondylitis (AS), Psoriatic Arthritis, Reactive Arthritis, Enteropathic Arthritis), who at the time of inclusion were 40 years or older and who indicated that their "family size" was completed were included. Men who were still planning on having biological children in the future were excluded.

To evaluate the impact of IA on male fertility we considered the age at diagnosis of IA and divided participants into three study groups: diagnosis ≤30 years (before the peak of reproductive age), diagnosis between 31-40 years (during the peak of reproductive age) and diagnosis ≥41 years (after the peak reproductive age).

We estimated the mean number of children number per men without IA in their reproductive lifespan at 1.7 (standard deviation: 1.0) and estimated a mean number of 1.4 children as significantly different. Using data simulation that accounted for dispersion and under-dispersion, to reject the null hypothesis with a 80% power (alpha=0.05; two-sided), it was estimated that 548 men were needed to be included in the study (n=137, n=137 and n=274 per group, respectively).

Data collection

A self-reported questionnaire developed for this study was used. The design of this questionnaire was based on the 'fertility experiences questionnaire (FEQ)'. The FEQ was validated in women with subfertility and when compared to medical records it was proven to be over 90% sensitive for fertility outcomes (21). In addition, we adapted the questionnaire to our population using previous questionnaires that have evaluated fertility outcomes in male kidney transplant recipients (22) and in women with rheumatic diseases (23, 24). Our questionnaire was divided into four sections: general demographic information, medical history, family planning and fertility outcomes (See Supplement 1). The digital version of the questionnaire that was distributed to participants was built using the survey software GemsTracker/LimeSurvey® (LimeSurvey GmbH, Hamburg, Germany).

Men who fulfilled the inclusion criteria of being 40 years or older and diagnosed with IA were invited to participate in the study. These men received a letter from their hospital that included information about the study. To ensure the protection of privacy data, the letter included a personalized link to complete the digital questionnaire. To increase the number of responders, a second letter was sent to all non-responders.

Our primary outcome, the male fertility rate, was calculated using the answers to the question "How many biological children did you have?". This is a validated method that has been used to evaluate fertility. For secondary outcomes, other collected data include, but are not limited to, total number of pregnancies, desired family size, satisfaction with final family size and relevant medical history regarding fertility and pregnancy outcomes. A pregnancy was defined as "any positive pregnancy test (even if it did not result in a live born child)" and time to pregnancy (TTP) was determined with the answers provided to the question "How many months did it take for your partner to get pregnant?".

A Likert scale questionnaire (scale ranging from completely disagree (0) to completely agree (10)) was used to evaluate the impact of IA on family planning/desired number of children.

Statistical analysis

Comparisons between the three groups and between the groups and the general population were tested. Categorical variables were presented as number (percentage), and continuous variables are reported as mean ±SD, or median ±IQR, as appropriate. Continuous variables were compared using a one-way analysis of variance (ANOVA), Tukey post-hoc test, paired t-test and Wilcoxon rank. Categorical variables were compared using $\chi 2$ tests and Fisher's exact tests. To control for confounders, multivariate regression model (analysis of covariance/ANCOVA) was used. All potential confounders were fitted into the model. The level of significance was set as a two-tailed $p \leq 0.05$, and statistical analyses were completed using Stata V.15 (StataCorp-LP).

Ethics

This study was reviewed by the ethics review boards of all participating centers in compliance with the Declaration of Helsinki. All patients gave their informed consent.

Patient and public involvement

Six male patients diagnosed with IA and who are active members of the research advisory board from the Department of Rheumatology of the Erasmus University Medical Center were involved in the design of the questionnaire and the invitation letter. We carefully assessed the burden on participating patients. We intend to share the results to participating patients and will appropriately disseminate the results.

RESULTS

Between September 2019 and January 2021, a total of 1841 men were invited to participate in the study. All hospitals invited men from the three study groups using a 1:1:2 ratio until the necessary number of patients per group to achieve statistical power was reached. In total, 628 men agreed to participate (response rate of 34.1%). A detailed description of the demographics characteristics of these men is presented in table 1. Due to current privacy regulations that are applicable in the Netherlands, it was not possible to describe the demographic characteristics of the non-responders.

Table 1. Demographic characteristics.

	All patients (N=628)	**IA diagnosed ≤30 years (N=137)**	**IA diagnosed 31-40 years (N=149)**	**IA diagnosed ≥41 years (N=342)**	**P value**
General information					
Age at inclusion in the study, mean (SD)	57.17 (9.98)	53.01 (9.96)[a]	52.76 (7.35)[a]	61.06 (9.47)	P=0.001
Born in the Netherlands, n (%)	531 (94.48)	117 (92.13)	132 (94.96)	277 (95.19)	P=0.143
Education Bachelor degree or higher, n (%)	223 (35.51)	61 (44.53)[a]	51 (34.23)	111 (32.46)	P=0.048
Currently in a relationship, n (%)	423 (67.36)	89 (64.96)	100 (67.11)	234 (68.42)	P=0.765
Inflammatory arthritis					
Diagnosis, n (%) RA JIA SpA (incl. PsA)	 297 (47.29) 10 (1.59) 320 (50.96)	 42 (30.66)[a b] 10 (6.45) 90 (65.69)[a]	 67 (44.97) 0 83 (55.70)	 188 (55.32) 0 147 (42.98)	 P=0.001 - P=0.001
Age at diagnosis, mean (SD)	41.30 (13.08)	23.76 (6.17)[a b]	36.52 (2.48)[a]	51.25 (7.77)	P=0.001
Disease duration, mean (SD)	15.89 (11.88)	29.51 (11.30)[a b]	16.30 (8.29)[a]	9.68 (7.77)	P=0.001
Concerning your IA, have you ever received information about your desire to have children? Yes, n (%)	139 (22.13)	45 (33.83)[a]	36 (24.66)[a]	37 (11.31)	P=0.001
Comorbidities					
Type 2 diabetes mellitus, n (%)	54 (8.60)	13 (9.49)	10 (6.71)	31 (9.06)	P=0.635
Cardiovascular disease*, n (%)	98 (15.61)	17 (12.41)	13 (8.72)[a]	68 (19.88)	P=0.006
Inflammatory bowel disease, n (%)	21 (3.34)	5 (3.65)	7 (5.04)	7 (2.05)	P=0.278
Urogenital comorbidities**, n (%)	27 (4.30)	6 (4.38)	3 (2.01)	18 (5.26)	P=0.264

[a] p≤ 0.05 compared to those diagnosed age ≥41 years, [b] p≤ 0.05 compared to those diagnosed age ≥31-40 years.
* Arterial hypertension, angina pectoris, myocardial infarction, heart failure, stroke, peripheral vascular disease and dyslipidemia.
** Urogenital infection, sexually transmitted disease, cryptorchidism, varicocele, testicular torsion, epididymitis, prostatitis, inguinal hernia, urogenital surgery, urogenital trauma and exposure to chemicals or radiation that can result in DNA damage.

Total number of biological children (fertility rate)

Men diagnosed ≤30 years had a lower number of children (1.32 [SD 1.14]) than men diagnosed between 31-40 years (1.56 [SD 1.27]) and men diagnosed ≥41 years (1.88 [SD 1.14]) (See figure 1). There was a statistically significant difference between groups (p =0.0004). The total number of children was statistically significant lower in men diagnosed <30 years and in men diagnosed 31-40 years compared to men diagnosed >41 years (p<0.001 and p=0.020, respectively). The difference between men diagnosed <30 and 31-40 years was not statistically significant (p=0.264)

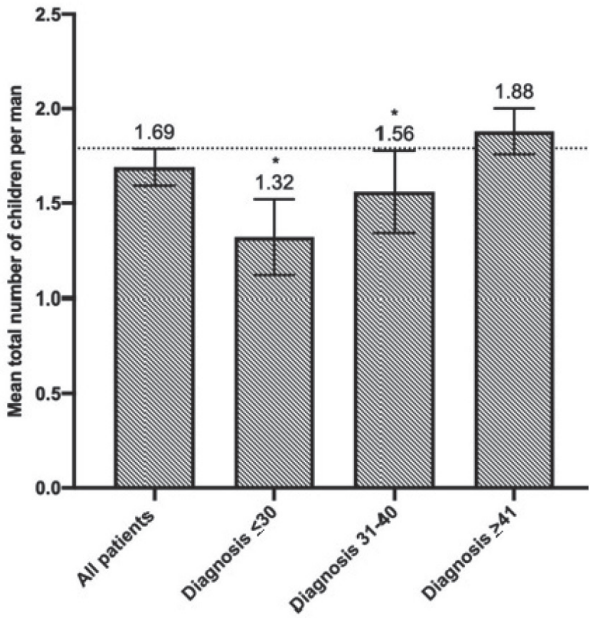


Figure 1. Mean total number of children per man for all participants and per group. Error bars represent 95% CI. The dotted line represents the mean number of children per man for men older than 40 years in the Netherlands. *Statistically significantly different compared with men diagnosed ≥41 years.

After adjusting for potential confounders (current age, education level, history of cardiovascular disease, diagnosis of infertility in partner and diagnosis of RA, JIA and SpA) and considering the total number of children of men diagnosed ≥41 years as our reference group, we observed a statistically significant negative effect on the total number of children of men diagnosed ≤30 years (p=0.002) (See table 2). Furthermore, the total number of children per disease was not statistically significant between diseases.

Table 2. Analysis of covariance: effect of dichotomized age at diagnosis of IA (based on our study groups) on total number of children per man and considering the total number of children of men diagnosed ≥41 years as our reference group.

	Crude (n=615)		Adjusted* (n=609)	
	B (95% CI)	**P value**	**B (95% CI)**	**P value**
31-40 years	-0.398 (-0.624 to -0.171)	0.001	-0.207 (-0.455 to 0.040)	0.101
≤30 years	-0.517 (-0.744 to -0.291)	0.000	-0.406 (-0.660 to -0.152)	0.002

Lastly, we compared the fertility rate of the study groups with the fertility rate of all men living in the Netherlands who at the time of our last inclusion were 40 years or older (1.79, Statistics Netherlands (CBS), personal communication, August 18, 2020). Compared to the fertility rate of men ≥40 years from the general population, the fertility rate of men diagnosed ≤30 and 31-40 years was statistically significant lower (1.32, p=0.001 and 1.56 p=0.03, respectively). The fertility rate of men diagnosed ≥41 years was not statistically significant different (1.88, p=0.128).

Total number of pregnancies per man

In contrast to the fertility rate, where only live births are taken into account, the total number of pregnancies per man includes any positive pregnancy test independent of the final pregnancy outcome. Men diagnosed ≤30 years had a lower total number of pregnancies (1.45 [SD 1.37]) than men diagnosed between 31-40 years (1.73 [SD 1.69]) and men diagnosed ≥41 years (1.98 [SD 1.45]). There was a statistically significant difference between groups (p =0.0023). The total number of pregnancies was statistically significant lower in men diagnosed ≤30 years compared to men diagnosed ≥41 years (p=0.002). There were no statistically significant differences between men diagnosed <30 and 31-40 years (p=0.261) and between men diagnosed 31-40 and ≥41 years (p= 0.219).

Childlessness

In the Netherlands, the percentage of childless men ranges between 20-25% (25). In total, 143 men (22.27%) were childless most of whom were voluntary childless (n=99 (69.23%)). The percentage of childless men was significantly higher in men diagnosed ≤30 years (n=45 [33.83%]) and in men diagnosed 31-40 years (n=39 [26.90%]) compared to men diagnosed ≥41 years (n=59 [17.25%], p=0.001).

In addition, we compared the percentages of voluntary and involuntary childlessness between the groups. The proportion of men who were voluntary childless was statistically significant different (29 [24.79], 24 [18.32] and 46 [14.64], p=0.048). The proportion of men who were involuntary childless was also statistically significant different between

our groups (16 [12.03%], 15 [10.34%] and 13 [3.98%], p=0.001). Amongst childless men, the percentage of men who were involuntary childless was statistically significant between our groups (35.56% vs 38.46% vs 22.03%, p=0.046).

Desired number of children and family planning

The desired number of children was not statistically different between the three groups (1.75 [SD 1.32] vs 1.86 [SD 1.22] vs 2.03 [SD 1.18], p=0.083). Statistically significant more men diagnosed ≤31 years and 31-40 years reported feeling unsatisfied with their final number of children than men diagnosed ≥41 years (n=22 [16.67%], n=14 [9.66%] and n=18 [5.50%], p=0.010). Approximately one third of these men reported that the diagnosis of IA and/or the medical treatment associated with it, were the main reason to have less children (31% and 28%, respectively).

The difference between desired and final number of children was significantly wider in men diagnosed ≤30 years (0.41 [SD 0.98]) compared to men diagnosed ≥41 years (0.14 [SD 0.77], p=0.003). Compared to men diagnosed 31-40 years, the difference between desired and final number of children was not statistically significant different (0.29 [SD 0.74], p=0.181) (See figure 2).

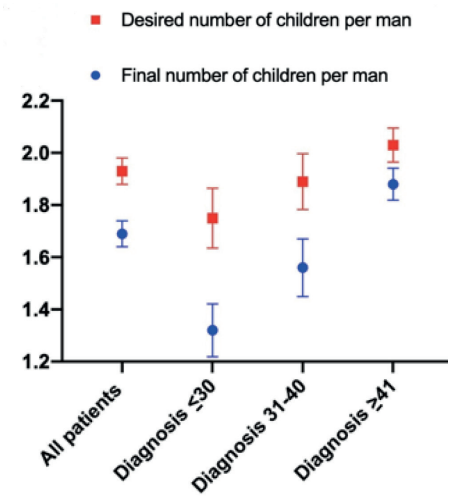


Figure 2: Comparison of the desired and final number of children per man for all participants and per group (Mean + 95% CI).

Furthermore, to analyze the impact of IA on the fertility rate of men who wanted to become a father, we conducted a subgroup analysis where all men who were voluntary childless were excluded (See table 3).

Table 3. Analysis of covariance: effect of dichotomized age at diagnosis of IA (based on our study groups) on total number of children per man (excluding men who were voluntary childless) and considering the total number of children of men diagnosed ≥41 years as our reference group.

	Crude (n=507)		Adjusted* (n=501)	
	B (95% CI)	**P value**	**B (95% CI)**	**P value**
31-40 years	-0.279 (-0.501 to -0.058)	0.013	-0.205 (-0.434 to 0.022)	0.078
≤30 years	-0.474 (-0.702 to -0.246)	0.000	-0.352 (-0.550 to -0.113)	0.004

*Adjusted for confounders (Age at inclusion in the study, education level, cardiovascular disease, diagnosis of infertility in partner and diagnosis of RA, JIA and SpA).

Using a Likert scale questionnaire, a significant negative effect of IA on family planning was reported by men diagnosed ≤30 and 31-40 years (See figure 3). Statements such as "I was concerned that my medications would harm my child" or "I was afraid that my child would get the same disease as me" were graded with a significantly higher degree of agreement amongst men diagnosed ≤30 and 31-40 years.

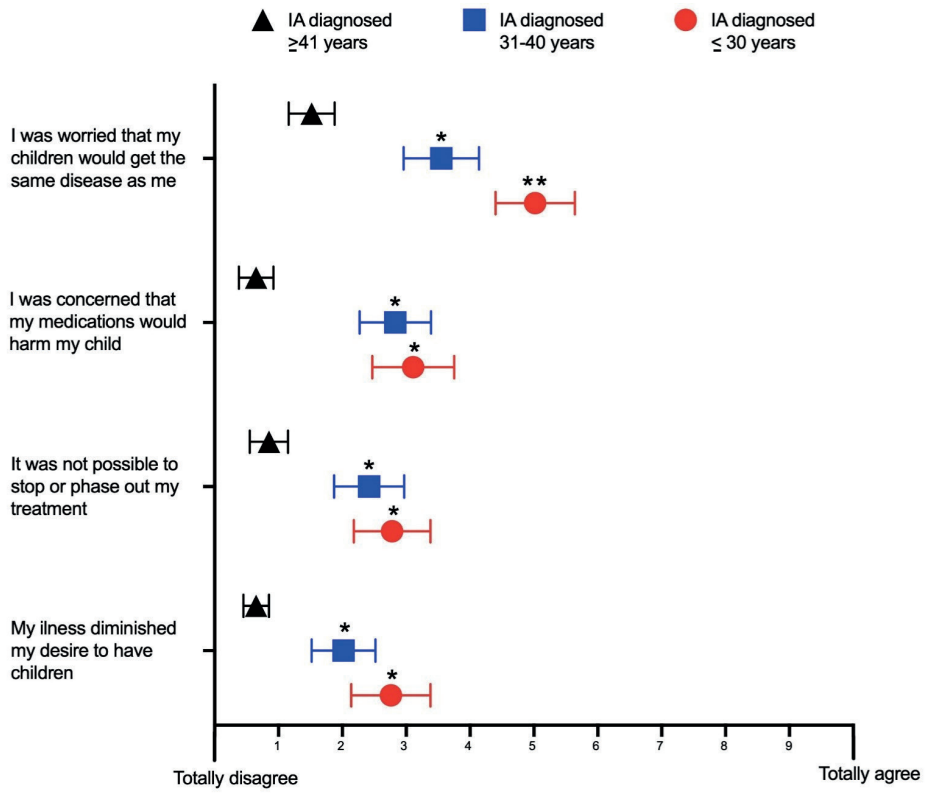


Figure 3: Likert scale questionnaire regarding the influence of IA on family planning. Men answered the questions using a 0-10 scale where 0 meant 'totally disagree' and 10 "totally agree" (Mean with SD) *p≤ 0.05 compared to those diagnosed age ≥41 years. **p≤ 0.05 compared to those diagnosed 31-40 years and ≥41 years.

Moreover, amongst men who remained voluntary childless, the statement "My disease reduced my desire to have children" was graded higher by men diagnosed ≤30 years (5.93 [2.42]) than by men diagnosed 31-40 years (3.73 [1.91]) and by men diagnosed ≥41 years (1.35 [1.14]). This was statistically significant different (p=0.001).Amongst men who remained involuntary childless and compared to men diagnosed ≥41 years, the statement "Stopping of weaning off my medication because of my desire to have children was not possible because my disease was too active" was graded statistically significant higher by men diagnosed ≤30 years (See figure 4).

Fertility

Statistically significantly more men diagnosed ≤30 and 31-40 years reported having received medical evaluations for fertility problems, compared to men diagnosed ≥41 years (n=27 [20.61%], n=30 [20.69%] and n=35 [11.36%], p=0.027) and ultimately receiving a diagnosis of low sperm quality (n=9 [6.57%], n=12 [8.05%] and n=12 [3.51%], p=0.086). Statistically significant more female partners of men diagnosed ≤30 years received a diagnosis of infertility secondary to an unknown cause (See Table 4).

Table 4. Fertility evaluation.

	All patients (N=628)	IA diagnosed ≤30 years (N=137)	IA diagnosed 31-40 years (N=149)	IA diagnosed ≥41 years (N=342)	P value
Fertility					
Male fertility evaluation, n (%)	93 (15.74)	27 (20.61)[a]	30 (20.69)[a]	35 (11.36)	P=0.027
Female fertility evaluation (partner), n (%)	71 (15.04)	18 (18.56)	24 (20.69)	29 (11.42)	P=0.069
Male fertility evaluation outcome					
No male fertility problem identified, n (%)	47 (7.48)	14 (10.22)	14 (9.40)	19 (5.56)	P=0.129
Low sperm quality, n (%)	33 (5.45)	9 (6.77)	12 (8.22)	12 (3.67)	P=0.086
Infertility secondary to unknown cause, n (%)	7 (1.16)	3 (2.26)	3 (2.05)	1 (0.31)	P=0.105
Female fertility evaluation outcome					
No female fertility problem identified, n (%)	34 (5.41)	8 (6.02)	11 (7.53)	15 (4.59)	P=0.066
Female infertility secondary to known cause*, n (%)	24 (3.96)	6 (4.51)	9 (6.16)	9 (2.75)	P=0.199
Female infertility secondary to unknown cause, n (%)	7 (1.16)	4 (3.01)[a]	2 (1.37)	1 (0.31)	P=0.047

[a] p≤ 0.05 compared to those diagnosed age ≥41 years, [b] p≤ 0.05 compared to those diagnosed age ≥31-40 years.
* Endometriosis, fallopian tube obstruction, polycystic ovary syndrome, uterine abnormality, early menopause.

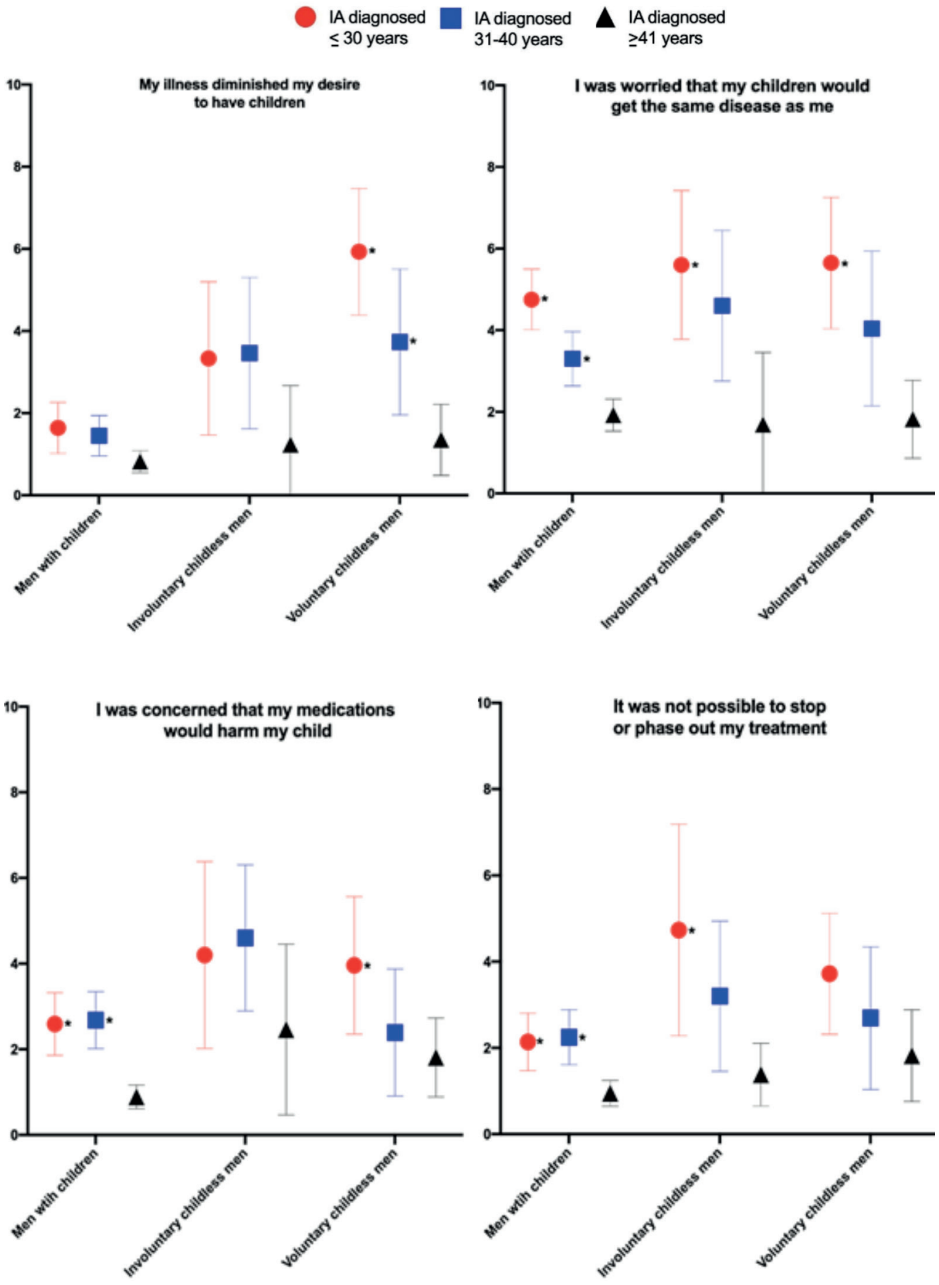


Figure 4: Comparison of the reported impact of IA on different aspects of family planning in men with children, involuntary and voluntary childless men. A Likert scale with 0 meaning 'totally disagree' and 10 'totally agree' was used (Mean with SD). *p≤ 0.05 compared to those diagnosed age ≥41 years.

In men who achieved a pregnancy, TTP was statistically significant higher in men diagnosed 31-40 years (6.74 [SD 11.12] months) compared to men diagnosed ≤41 years (4.77 [SD 8.47] months, p=0.045) and not statistically significantly different when compared to men diagnosed ≤30 years (5.69 [SD 10.93], p=0.623).

DISCUSSION

Our study is the first of its kind to demonstrate that IA can significantly impair male fertility. The diagnosis of IA before or during the peak of the male reproductive age was associated with a lower fertility rate, lower number of pregnancies, higher rates of involuntary childlessness and fertility problems.

Respecting family planning we observed that the number of desired children per man was lower in men diagnosed before and during the peak of male reproductive age. Nonetheless, this was not statistically significant different between our groups and it was similar to the number of desired children per man reported for the general population of the Netherlands (1.81-2.29) (26).Conversely, the difference between the desired and final number of children was significantly larger in men diagnosed before and during the reproductive age, indicating that the lower fertility rates are primarily affected by reduced fertility potential and not by a reduced desire for parenthood.

In this regard, men diagnosed with IA before and during the peak of their reproductive age were two times more likely to remain involuntary childless (12% and 10%). To put this into perspective, it is estimated that around 4% of healthy couples who want children remain involuntary childless (27).

Moreover, it was shown that the diagnosis of IA may have a major impact on family planning. Not only did IA significantly reduce the desire to have children of men diagnosed before and during the peak of reproductive age who remained voluntary childless but also concerns or difficulties with regard to pharmacological treatment were larger in men diagnosed with IA before the peak of reproductive age who remained involuntary childless.

Lastly, the diagnosis of IA before and during the peak of reproductive age is associated with male fertility problems. These men were twice as likely to be evaluated for fertility problems and being subsequently diagnosed with abnormal sperm quality. In this regard, it has been estimated that abnormal sperm quality affects 2% of adult men (28). This estimation is considerably lower compared to the 6.5% and 8% reported by men diagnosed with IA before and during the peak of reproductive age.

Similar to our results, Uzunaslan et al. reported that, compared to healthy men, men diagnosed with AS had statistically significant fewer children (1.9 vs 2.5) and a higher rate of infertility (9.1 vs 2.9%) (29). These findings could be in part explained by the high incidence of varicocele and sperm abnormalities that have been reported for men diagnosed with AS (6, 30, 31). Nonetheless, this study was primarily designed to study the impact of Behçet's syndrome on male fertility and only included 79 male patients diagnosed with AS.

Multiple mechanisms can be responsible for our findings. Biological mechanisms, namely inflammation, may contribute to the impaired fertility in men with IA. Several cytokines that are characteristic of the immune response associated with IA, such as tumor necrosis factor, play important roles in modulating testicular homeostasis and regulating spermatogenesis (32, 33). Increased expression of mRNA for IL1-beta, TNF and IFN-gamma has been observed in testicular tissue of men with disturbed spermatogenesis (34). Correspondingly, inflammation may impair normal reproductive development before or during puberty, or have a direct negative impact on the spermatogenesis during the reproductive age (35-40).

Beyond inflammation, pharmacological treatment associated with IA can also result in damage to the male reproductive axis (41, 42). Moreover, side effects such as hypogonadism and low sperm quality have been associated with frequently used immunosuppressive agents (13). It has been estimated that among involuntary childless men that present to infertility clinics, 25% take drugs that have the potential to negatively impact male sexual function and 10% take drugs associated with male fertility impairment (42).

Furthermore, several psychosocial factors, associated with a diagnosis of IA, may have contributed to the lower fertility rate as observed in this study (43). In our study, due to problems or concerns associated with IA and its treatment and based on medical advice (or the lack of), men with IA and their partners decided to become voluntarily childless or to delay their plans to become parents. These psychosocial factors were of special importance for men diagnosed before the peak of reproductive age. Moreover, some of these psychosocial factors could be associated with psychological comorbidities that are highly prevalent in patients diagnosed with IA such as depression and anxiety. These comorbidities have also been associated with sexual health problems (44-46).

Our study has several strengths. It is the first large study (≥600 participants) specifically designed to detect statistically significant differences in a robust outcome measure (fertility rate). In addition, we used an extensive questionnaire to gain insight into most

of the factors that might have influenced our primary outcome measure. Our study has important limitations. First, our response rate was low. However, the response rate is comparable to similar studies that explored male fertility rate in chronic diseases (22). Second, men diagnosed with chronic diseases and especially those who use pharmacological therapy are more aware of potential fertility problems (47, 48) and it can be expected that these men are more likely to seek fertility evaluation. Furthermore, men who experience fertility problems might be more willing to participate in these type of studies. Both factors are potential sources of selection bias in our study. In this respect, in the Netherlands, strict health care policies and referral guidelines reduce the possibility of self-referrals or unnecessary fertility evaluations. It is also reassuring that the response rates were similar between the three groups of men and that the results from our control group, men diagnosed ≥41 years, were strikingly similar to the data available in the general population further strengthening our comparisons. Lastly, this was a retrospective study. Recently, it has been shown that the sperm quality of male patients diagnosed with AS improved after being treated with TNF- α inhibitors (49, 50). Furthermore, to get approval, new drugs are facing more strict protocols with regard to testicular toxicity. Therefore, the current conditions for men with IA, regarding treatment options and treatment strategies (biological therapy, shared-decision process, treat to target strategies), might be different than they were when our participants were in the peak of their reproductive age.

The results of this study may have several implications. In the clinical setting, rheumatologists should be aware that IA and/or the pharmacological treatment associated with IA may impair male fertility. Accordingly, they should discuss this with their patients, inform them about the impact of IA on male fertility and if indicated, adjust treatment aiming at low disease activity with the safest treatment strategy possible (6, 50). For research purposes, basic, translational and epidemiological studies are needed to understand the impact of inflammation, pharmacological treatment and psychosocial factors associated with IA on male fertility. To corroborate our findings and to further describe the magnitude of the impact of IA on male fertility, large prospective studies are strongly recommended.

In conclusion, the diagnosis of IA before or during the peak of reproductive age can result in impaired male fertility. Rheumatologists should be aware of this novel association and approach their patients accordingly. Multiple biological and non-biological mechanisms can be responsible for this association and more research is urgently needed to improve the quality of care for men diagnosed with IA and a desire for parenthood.

REFERENCES

1. Stolwijk C, van Onna M, Boonen A, van Tubergen A. Global Prevalence of Spondyloarthritis: A Systematic Review and Meta-Regression Analysis. Arthritis Care Res (Hoboken). 2016;68(9):1320-31.
2. Hootman JM, Helmick CG, Barbour KE, Theis KA, Boring MA. Updated Projected Prevalence of Self-Reported Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation Among US Adults, 2015-2040. Arthritis & rheumatology (Hoboken, N J). 2016;68(7):1582-7.
3. Ackerman IN, Pratt C, Gorelik A, Liew D. Projected Burden of Osteoarthritis and Rheumatoid Arthritis in Australia: A Population-Level Analysis. Arthritis Care Res (Hoboken). 2018;70(6):877-83.
4. van der Woude D, van der Helm-van Mil AHM. Update on the epidemiology, risk factors, and disease outcomes of rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2018;32(2):174-87.
5. Brubaker WD, Li S, Baker LC, Eisenberg ML. Increased risk of autoimmune disorders in infertile men: analysis of US claims data. Andrology. 2018;6(1):94-8.
6. Perez-Garcia LF, Te Winkel B, Carrizales JP, Bramer W, Vorstenbosch S, van Puijenbroek E, et al. Sexual function and reproduction can be impaired in men with rheumatic diseases: A systematic review. Semin Arthritis Rheum. 2020;50(3):557-73.
7. Perez-Garcia LF, Dolhain RJEM, Vorstenbosch S, Bramer W, van Puijenbroek E, Hazes JMW, et al. The effect of paternal exposure to immunosuppressive drugs on sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes: a systematic review. Human Reproduction Update. 2020.
8. Hammarberg K, Collins V, Holden C, Young K, McLachlan R. Men's knowledge, attitudes and behaviours relating to fertility. Hum Reprod Update. 2017;23(4):458-80.
9. Bodin M, Plantin L, Elmerstig E. A wonderful experience or a frightening commitment? An exploration of men's reasons to (not) have children. Reproductive Biomedicine & Society Online. 2019;9:19-27.
10. Vassard D, Lallemant C, Nyboe Andersen A, Macklon N, Schmidt L. A population-based survey on family intentions and fertility awareness in women and men in the United Kingdom and Denmark. Upsala Journal of Medical Sciences. 2016;121(4):244–51.
11. Schoumaker B. Across the world, is men's fertility different from that of women? Population & Societies. 2017;548(9):1-4.
12. Schoumaker B. Measuring male fertility rates in developing countries with Demographic and Health Surveys: An assessment of three methods. Demographic Research. 2017;36(28):803-50.
13. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al. The International Glossary on Infertility and Fertility Care, 2017. Fertil Steril. 2017;108(3):393-406.
14. Agarwal A, Baskaran S, Parekh N, Cho C-L, Henkel R, Vij S, et al. Male infertility. The Lancet. 2021;397(10271):319-33.
15. Sato A, Naganuma M, Asakura K, Nishiwaki Y, Yajima T, Hisamatsu T, et al. Conception outcomes and opinions about pregnancy for men with inflammatory bowel disease. J Crohns Colitis. 2010;4(2):183-8.
16. Glazer CH, Bonde JP, Eisenberg ML, Giwercman A, Hærvig KK, Rimborg S, et al. Male Infertility and Risk of Nonmalignant Chronic Diseases: A Systematic Review of the Epidemiological Evidence. Semin Reprod Med. 2017;35(3):282-90.
17. Smeele HTW, Dolhain R. Current perspectives on fertility, pregnancy and childbirth in patients with Rheumatoid Arthritis. Semin Arthritis Rheum. 2019;49(3S):S32-S5.
18. Ostensen M. Sexual and reproductive health in rheumatic disease. Nat Rev Rheumatol. 2017;13(8):485-93.

19. de Jong PH, Dolhain RJ. Fertility, Pregnancy, and Lactation in Rheumatoid Arthritis. Rheum Dis Clin North Am. 2017;43(2):227-37.
20. Statistiek CBvd. One in six first-time fathers over 402011. Available from: https://www.cbs.nl/en-gb/news/2011/39/one-in-six-first-time-fathers-over-40.
21. Thomas FS, Stanford JB, Sanders JN, Gurtcheff SE, Gibson M, Porucznik CA, et al. Development and initial validation of a fertility experiences questionnaire. Reproductive Health. 2015;12(1):62.
22. Boyer A, Lobbedez T, Ouethrani M, Thuillier Lecouf A, Bouvier N, Châtelet V, et al. Paternity in male kidney transplant recipients: a French national survey, the PATeRNAL study. BMC Nephrol. 2020;21(1):483.
23. Brouwer J, Fleurbaaij R, Hazes JMW, Dolhain R, Laven JSE. Subfertility in Women With Rheumatoid Arthritis and the Outcome of Fertility Assessments. Arthritis Care Res (Hoboken). 2017;69(8):1142-9.
24. Eudy AM, McDaniel G, Clowse ME. Pregnancy outcomes, fertility, and family planning in women with psoriatic arthritis. Obstet Med. 2020;13(2):70-5.
25. Statistiek CBvd. More childless men2010. Available from: https://www.cbs.nl/en-gb/news/2010/27/more-childless-men.
26. Ideal and actual number of children [Internet]. 2016. Available from: http://www.oecd.org/els/family/database.htm.
27. Lechner L, Bolman C, van Dalen A. Definite involuntary childlessness: associations between coping, social support and psychological distress. Human Reproduction. 2006;22(1):288-94.
28. Kumar N, Singh AK. Trends of male factor infertility, an important cause of infertility: A review of literature. J Hum Reprod Sci. 2015;8(4):191-6.
29. Uzunaslan D, Saygin C, Hatemi G, Tascilar K, Yazici H. No appreciable decrease in fertility in Behçet's syndrome. Rheumatology (Oxford). 2014;53(5):828-33.
30. Nukumizu LA, Saad CG, Ostensen M, Almeida BP, Cocuzza M, Gonçalves C, et al. Gonadal function in male patients with ankylosing spondylitis. Scand J Rheumatol. 2012;41(6):476-81.
31. Ozgocmen S, Kocakoc E, Kiris A, Ardicoglu A, Ardicoglu O. Incidence of varicoceles in patients with ankylosing spondylitis evaluated by physical examination and color duplex sonography. Urology. 2002;59(6):919-22.
32. Hedger MP, Meinhardt A. Cytokines and the immune-testicular axis. J Reprod Immunol. 2003;58(1):1-26.
33. Ware CF. The TNF receptor super family in immune regulation. Immunol Rev. 2011;244(1):5-8.
34. Klein B, Haggeney T, Fietz D, Indumathy S, Loveland KL, Hedger M, et al. Specific immune cell and cytokine characteristics of human testicular germ cell neoplasia. Human Reproduction. 2016;31(10):2192-202.
35. Fijak M, Pilatz A, Hedger MP, Nicolas N, Bhushan S, Michel V, et al. Infectious, inflammatory and 'autoimmune' male factor infertility: how do rodent models inform clinical practice? Hum Reprod Update. 2018.
36. Agarwal A, Rana M, Qiu E, AlBunni H, Bui AD, Henkel R. Role of oxidative stress, infection and inflammation in male infertility. Andrologia. 2018;50(11):e13126.
37. Bachir BG, Jarvi K. Infectious, Inflammatory, and Immunologic Conditions Resulting in Male Infertility. Urologic Clinics of North America. 2014;41(1):67-81.
38. Nistal M, Paniagua R. Non-neoplastic diseases of the testis. Urologic Surgical Pathology. 2008:614-755.
39. Silva CA, Cocuzza M, Carvalho JF, Bonfá E. Diagnosis and classification of autoimmune orchitis. Autoimmun Rev. 2014;13(4-5):431-4.
40. Chan PT, Schlegel PN. Inflammatory conditions of the male excurrent ductal system. Part I. J Androl. 2002;23(4):453-60.

41. Sasaki JC, Chapin RE, Hall DG, Breslin W, Moffit J, Saldutti L, et al. Incidence and nature of testicular toxicity findings in pharmaceutical development. Birth Defects Res B Dev Reprod Toxicol. 2011;92(6):511-25.
42. Pompe SV, Strobach D, Stief CG, Becker AJ, Trottmann M. Drug use among men with unfulfilled wish to father children: a retrospective analysis and discussion of specific drug classes. Pharmacoepidemiol Drug Saf. 2016;25(6):668-77.
43. Buhr P, Huinink J. Why Childless Men and Women Give Up on Having Children. Eur J Popul. 2017;33(4):585-606.
44. Perez-Garcia L.F., Röder E., Pastoor H., Bolt H., van Exel J., Dolhain R. It is not just about the sex: viewpoints of Dutch adult men with inflammatory arthritis regarding the impact of the disease on their sexual health. Ann Rheum Dis. 2021;80:186.
45. Hill J, Bird H, Thorpe R. Effects of rheumatoid arthritis on sexual activity and relationships. Rheumatology. 2003;42(2):280-6.
46. Kraaimaat FW, Bakker AH, Janssen E, Bijlsma JWJ. Intrusiveness of rheumatoid arthritis on sexuality in male and female patients living with a spouse. Arthritis & Rheumatism. 1996;9(2):120-5.
47. Tielemans E, Burdorf A, te Velde E, Weber R, van Kooij R, Heederik D. Sources of Bias in Studies among Infertility Clients. American Journal of Epidemiology. 2002;156(1):86-92.
48. Pedro J, Brandão T, Schmidt L, Costa ME, Martins MV. What do people know about fertility? A systematic review on fertility awareness and its associated factors. Upsala journal of medical sciences. 2018;123(2):71-81.
49. Villiger PM, Caliezi G, Cottin V, Forger F, Senn A, Ostensen M. Effects of TNF antagonists on sperm characteristics in patients with spondyloarthritis. Ann Rheum Dis. 2010;69(10):1842-4.
50. Ramonda R, Foresta C, Ortolan A, Bertoldo A, Oliviero F, Lorenzin M, et al. Influence of tumor necrosis factor alpha inhibitors on testicular function and semen in spondyloarthritis patients. [Erratum appears in Fertil Steril. 2014 May;101(5):1058]. Fertil Steril. 2014;101(2):359-65.

CHAPTER 5

Paternal inflammatory arthritis is associated with a higher risk of miscarriage: results of a large multicentre study (iFAME-Fertility)

Published

Perez-Garcia LF, Röder E, Smeele HTW, Goekoop R, Hazes JMW, Kok MR, Tchetverikov I, van der Helm-van Mil A, van der Kaap J, Kok P, Krijthe BP, Dolhain RJEM.

Rheumatology (Oxford). 2022 Aug 3;61(8):3390-3395.

ABSTRACT

Objectives

Paternal preconception health is recognized as an important contributor to pregnancy outcomes. Nonetheless, pregnancy outcomes of partners of men with inflammatory arthritis (IA) have never been studied. Our objective was to describe the pregnancy outcomes of partners of men diagnosed with IA.

Methods

We performed a multicenter cross-sectional retrospective study conducted in the Netherlands. Men with IA who were over 40 years old that reported at least one positive pregnancy test were included. To analyze the impact of IA on pregnancy outcomes, pregnancies were classified into two groups; pregnancies conceived after the diagnosis of IA and before the diagnosis of IA.

Results

In total 408 male participants diagnosed with IA reported 897 singleton pregnancies that resulted in 794 live births. Pregnancies conceived after the diagnosis of IA had higher rate of miscarriage (12.27 vs 7.53%, p=<0.05). This increased risk was still present after adjusting for confounders (OR 2.03 [95%CI 1.12-3.69], p=0.015).

Conclusions

This is the largest study to describe the pregnancy outcomes of partners of men diagnosed with IA and the first to demonstrate that paternal IA is associated with a higher risk of miscarriage. Notwithstanding, the overall rate of miscarriage reported in our study could be comparable to previously reported population estimates.

INTRODUCTION

Paternal preconception health is recognized as an important contributor to pregnancy outcomes (1). It has been shown that increased abnormalities in sperm DNA (2), low sperm quality (3), oxidative stress (4) and epigenetic changes in sperm (5) are potential mechanisms that could lead to worse pregnancy outcomes. Furthermore, it has been suggested that pregnancies conceived by men diagnosed with chronic diseases are at higher risk of ending in losses (miscarriage, ectopic pregnancy or stillbirth) (6). However, the impact of paternal inflammatory arthritis (IA) on pregnancy outcomes has never been studied.

Rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) are frequent causes of IA that have been associated with impaired male fertility (7, 8). Since human reproduction failure ranges from the inability to conceive to the incapacity to maintain pregnancy after successful conception (9) it is of the utmost importance to evaluate the impact of paternal IA on pregnancy outcomes.

Therefore, our objective was to describe the pregnancy outcomes of partners of men diagnosed with IA.

METHODS

Study design and patient selection

This study is part of the iFAME-Fertility study (8). Briefly, the iFAME-Fertility study is a multicenter cross-sectional study that was primarily designed to evaluate the impact of IA on the male fertility rate (total number of children per man). Men diagnosed by their rheumatologists with IA (RA, JIA, PsA and AS), who at the time of inclusion were 40 years or older and who indicated that their 'family size' was completed participated in the study. Participants completed a self-reported questionnaire that included demographic, medical history, family planning and fertility related questions. Additionally, participants who reported at least one pregnancy ("any positive pregnancy test, even if it did not result in a live born child") completed a different questionnaire that included questions regarding pregnancy outcomes.

To evaluate the impact of paternal IA on pregnancy outcomes we classified pregnancies into two groups; pregnancies conceived after diagnosis of IA and before the diagnosis of IA.

Data collection

A self-reported questionnaire developed for this study was used. The design of this questionnaire was based on the 'fertility experiences questionnaire' (FEQ) (10). A

miscarriage was defined as a pregnancy loss that occurred before the 16th week of gestation and a stillbirth as a pregnancy loss at or after 16 weeks of gestation.

Statistical analysis

Comparisons between the two groups were tested. Categorical variables were presented as number (percentage), and continuous variables are reported as mean ±SD, or median ±IQR, as appropriate. Continuous variables were compared using a paired t-test and Wilcoxon rank. Categorical variables were compared using $\chi 2$ tests and Fisher's exact tests.

To control for confounders, multivariate logistic regression model was used. All clinically considered important potential confounders (paternal age at conception, paternal and maternal smoking exposure, paternal medication preconception exposure, diagnosis of IA, conception by assisted reproductive technology (ART) and consecutive pregnancy number) were fitted into the model. The level of significance was set as a two-tailed $p \leq 0.05$, and statistical analyses were completed using Stata V.15 (StataCorp-LP).

Ethics

This specific study was reviewed by the ethics review boards of all participating centers in compliance with the Declaration of Helsinki (Erasmus MC - Ethics Committee: MEC-2018-1418, Admiraal de Ruyter Hospital - Ethics Committee: ADRZ2019-010 iFAME-Fertility, Franciscus Hospital - Ethics Committee: T-110. 4, Leiden University Medical Center, Reinier de Graaf Hospital, Haga Hospital – Ethics Committee: N19.081. 5, Maasstad Hospital - Ethics Committee: L2020040). All patients gave their written informed consent.

RESULTS

Between September 2019 and January 2021, a total of 1841 men were invited to participate. In total 628 male participants diagnosed with IA were included in the iFAME-Fertility study. Of them, 408 men reported at least one positive pregnancy test and were included in this part of the study. In total, these men reported 897 singleton pregnancies that resulted in 794 live births.

A detailed description of the differences in pregnancy characteristics between the study groups is presented in table 1.In line with our previous findings (8), pregnancies after IA diagnosis were characterized by a statistically significant longer time to pregnancy (TTP) (6.99 (SD 11.79) vs 4.83 (SD 8.71), p=0.002) and by a statistically significant larger rate

of pregnancies that were conceived by ART (20 (9.09%) vs 23 (3.40%), p=0.0001). As expected, paternal and maternal age at conception were statistically significant higher in pregnancies after IA diagnosis (34.27 (SD 6.08) vs 30.49 (SD 5.34) and 30.69 (SD 5.16) vs 28.45 (SD 4.83), respectively, both p=0.0001). The percentage of pregnancies with paternal exposure to anti-rheumatic drugs 3 months before conception was statistically significant higher in pregnancies after IA diagnosis (110 (50.23%) vs 40 (5.91%, p=0.0001).

The rates of pregnancy outcomes related to maternal and neonatal comorbidity were calculated for all pregnancies with a gestational age ≥16 weeks (n=806) and were not statistically significant different between our groups. (See table 1).

Table 1. Pregnancy characteristics and outcomes.

	All pregnancies	Pregnancy after IA diagnosis	Pregnancy before IA diagnosis	P value
Total number of pregnancies	**897**	**220**	**677**	**-**
1st pregnancy, n (%)	408 (45.48)	103 (46.82)	305 (45.05)	p=0.87
Year of pregnancy, mean (SD)	1990 (12.76)	1996 (12.96)	1989 (12.12)	p≤0.05
TTP, months (SD)	5.35 (9.59)	6.99 (11.79)	4.83 (8.71)	p≤0.05
Spontaneous pregnancies, n (%)	854 (95.21)	200 (90.91)	654 (96.60)	p≤0.05
Conceived by ART , n (%)	43 (4.79)	20 (9.09)	23 (3.40)	p≤0.05
Pregnancy duration, weeks (SD)	38.31 (4.06)	38.57 (3.22)	38.23 (4.30)	p=0.66
Paternal demographic characteristics				
Paternal age at conception, mean (SD)	31.31 (5.72)	34.27 (6.08)	30.49 (5.34)	p≤0.05
Paternal age at conception >40 years, n (%)	78 (8.70)	53 (24.09)	25 (3.69)	p≤0.05
Paternal education higher than bachelor, n (%)	363 (40.47)	94 (42.73)	269 (39.73)	p=0.44
Paternal preconception exposure*				
Paternal smoking exposure, n (%)	344 (38.39)	67 (30.59)	277 (40.92)	p≤0.05
Paternal alcohol exposure, n (%)	613 (68.42)	136 (62.10)	447 (70.46)	p=0.07
Paternal medication exposure, n (%)	150 (16.74)	110 (50.23)	40 (5.91)	p≤0.05
Paternal diagnosis of IA				
Age at diagnosis IA, years (SD)	42.99 (12.65)	26.99 (7.85)	47.59 (9.69)	p≤0.05
Diagnosis RA, n (%)	451 (50.28)	82 (37.27)	369 (54.51)	p≤0.05
Diagnosis JIA, n (%)	15 (1.67)	15 (6.82)	0 (0.00)	-
Diagnosis AS, n (%)	181 (20.18)	75 (34.09)	106 (15.66)	p≤0.05
Diagnosis PsA, n (%)	286 (31.88)	68 (30.91)	218 (32.20)	p=0.72
Paternal fertility evaluation outcomes*				
Fertility evaluation, n (%)	138 (15.38)	57 (25.91)	81 (11.96)	p≤0.05
Low sperm quality, n (%)	45 (5.02)	20 (35.09)	25 (30.85)	p=0.60
Maternal demographic characteristics				
Maternal age at conception, mean (SD)	29.00 (5.00)	30.69 (5.16)	28.45 (4.83)	p≤0.05
Maternal age at conception >40 years, n (%)	10 (1.11)	5 (2.27)	5 (0.74)	p=0.06

Table 1. Continued

	All pregnancies	Pregnancy after IA diagnosis	Pregnancy before IA diagnosis	P value
Maternal preconception* and pregnancy exposure				
Maternal preconception smoking exposure, n (%)	171 (19.08)	32 (14.61)	139 (20.53)	p=0.06
Maternal smoking exposure during pregnancy, n (%)	58 (6.47)	13 (5.94)	45 (6.65)	p=0.93
Maternal alcohol exposure, n (%)	329 (36.72)	73 (33.33)	256 (37.81)	p=0.31
Maternal alcohol exposure during pregnancy, n (%)	53 (5.92)	16 (7.31)	37 (5.47)	p=0.45
Maternal fertility evaluation outcomes**				
Fertility evaluation, n (%)	116 (12.93)	40 (18.18)	76 (11.23)	p≤0.05
				p=0.07
Female infertility secondary to known cause**, n (%)	37 (31.90)	19 (47.50)	18 (57.89)	p≤0.05
Female infertility secondary to unknown cause, n (%)	11 (9.48)	6 (15.00)	5 (6.58)	p≤0.05
Pregnancy outcomes				
Live births, n (%)	794 (88.52)	190 (86.36)	604 (89.22)	p=0.05
Miscarriage, n (%)	78 (8.70)	27 (12.27)	51 (7.53)	p≤0.05
Induced abortion, n (%) *Medical indication *Personal reasons	25 (2.78) 5 (20.00) 20 (80.00)	3 (1.36) 0 (0.00) 3 (100.00)	22 (3.25) 5 (22.73) 17 (77.27)	p=0.13
Stillbirths, n (%)	6 (0.67)	0 (0.00)	6 (0.89)	p=0.16
Pregnancy outcomes related to maternal and neonatal morbidity***				
Pre-term birth, n (%)	149 (16.61)	31 (14.09)	118 (17.43)	p=0.24
Hypertensive disorders (hypertension, pre/eclampsia), n (%)	41 (4.57)	8 (3.64)	33 (4.87)	p=0.45
Gestational Diabetes Mellitus, n (%)	11 (1.28)	2 (0.94)	9 (1.38)	p=0.62
Intrauterine growth restriction, n (%)	12 (1.34)	1 (0.45)	11 (1.65)	p=0.19
Maternal anemia, n (%)	15 (1.67)	6 (2.73)	9 (1.33)	p=0.16

Abbreviations: TTP – Time to pregnancy, ART – Assisted Reproductive Technology, IA – Inflammatory arthritis, RA – Rheumatoid arthritis, JIA – Juvenile idiopathic arthritis, AS – Ankylosing Spondylitis, PsA – Psoriatic arthritis.
* 3 months before conception
** Endometriosis, fallopian tube obstruction, polycystic ovary syndrome, uterine abnormality, early menopause.
*** Maternal and neonatal morbidity reported for pregnancies≥16 weeks of gestation (n=806).

Pregnancy outcomes

The rate of miscarriage was statistically significant higher in pregnancies after IA diagnosis (27 (12.27%)) compared to pregnancies before IA diagnosis (51 (7.53%), p=0.030) (See table 1). The rate of live births was lower in pregnancies before IA diagnosis but this difference was not statistically significant when compared to pregnancies after IA diagnosis (190 (86.36%) vs 604 (89.22%), p=0.053). The rates of induced abortions, stillbirths and pre-term births were statistically similar between the two groups.

After adjusting for confounders, compared to pregnancies before IA diagnosis, the difference remained significant (OR miscarriage in pregnancies after IA diagnosis (2.03 (95% CI 1.12 -3.69)) (See Figure 1). Furthermore, a subgroup analysis based on the specific diagnosis of IA (RA, AS, PsA) revealed that the adjusted OR for a miscarriage was highest in pregnancies after the diagnosis of PsA and RA (4.35 (95% CI 1.65-11.49) and 2.96 (95% CI 1.19-7.36), respectively) (See supplementary figure S1).

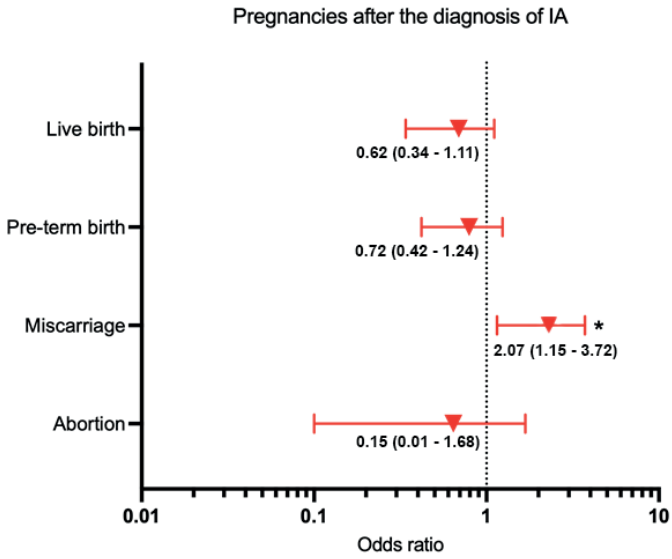


Figure 1. Adjusted OR (point estimate and 95% CI) for pregnancy outcomes with paternal IA exposure. Multivariate logistic regression models adjusted for confounders (paternal age at conception, paternal and maternal smoking exposure, paternal medication preconception exposure, diagnosis of IA, conception by ART, year of pregnancy and consecutive pregnancy number). (Because of a high degree of correlation between paternal and maternal age at conception (r=0.70), only paternal age at conception was included in the model).

* Statistically significant, p<0.05

DISCUSSION

Consistent with findings that have suggested that impaired preconception paternal health is associated with adverse pregnancy outcomes (6), our study is the first of its kind to demonstrate that paternal IA is significantly associated with a higher risk of miscarriage. Notably, this was independent of traditional risk factors for miscarriage such as advanced paternal and maternal age. The risk of miscarriage was highest in pregnancies after the diagnosis of PsA and RA.

The mechanism responsible for an increased risk of miscarriage in pregnancies after IA diagnosis is complex and probably multifactorial. First, abnormal sperm DNA is considered

as one of the most important paternal factors associated with pregnancy loss (11). In this regard, it has been shown that systemic inflammation and certain andrological comorbidities frequently present in men with IA (i.e. hypogonadism or varicocele) (7) have been associated with abnormal sperm DNA and low sperm quality (12, 13).

Second, since drug exposure has also been associated with abnormal sperm DNA and low sperm quality (14), paternal preconception exposure to anti-rheumatic drugs warrants discussion. Based on limited paternal exposure data, it has been concluded that paternal anti-rheumatic drug exposure is not associated with an increased risk for adverse pregnancy outcomes (15, 16). Nonetheless, pregnancy loss and specifically miscarriage, were not assessed as a pregnancy outcome.

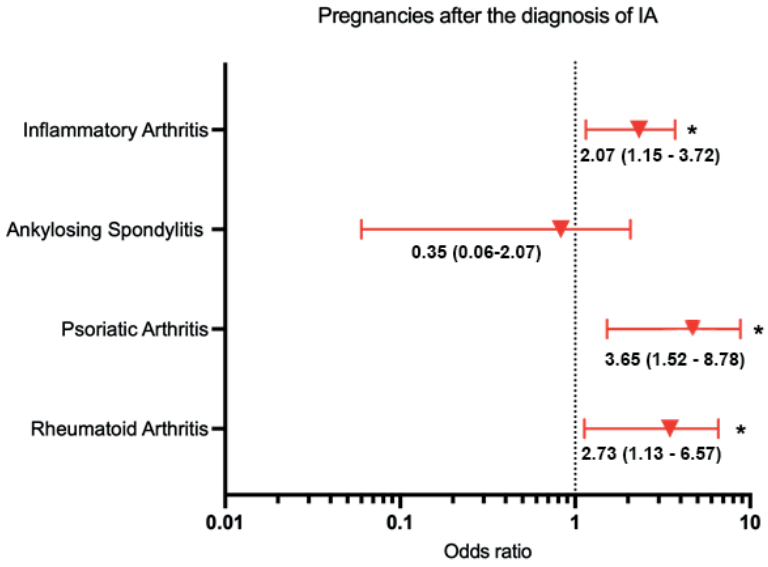
Third, it has been shown that poor paternal health can negatively impact pregnancy outcomes (6). Epigenetic changes in sperm can impact reproductive health (17) and were suggested as a potential cause of this association. Although epigenetic changes in several immune cells have been identified as important mechanisms associated with the pathogenesis and progression of RA (18), the occurrence of epigenetic changes on spermatozoa of men diagnosed with IA has not been studied before.

Our study is the first large study (897 pregnancies) to evaluate the impact of paternal IA exposure on pregnancy outcomes, including miscarriage. In addition, we used an extensive questionnaire to gain insight into most of the factors that might have influenced our results. Nonetheless, our study has important limitations. First, the study was not primarily designed to evaluate pregnancy outcomes. Second, men who experience negative pregnancy outcomes might be more willing to participate in these type of studies and this is a potential source of selection bias in our study. Furthermore, some pregnancies occurred more than 30 years ago which can lead to non-differential misclassification bias. For this same reason, and to minimize the risk of misclassification bias regarding paternal preconception anti-rheumatic drug exposure, we did not collect information on specific preconception anti-rheumatic drug exposure. Therefore, the potential impact of specific paternal pharmacological therapy on pregnancy outcomes was not assessed in our study. Third, although some of the most important maternal risk factors for miscarriage were taken into account in our analysis (maternal age, smoking and alcohol exposure), our study lacks information on other maternal factors such as anatomical abnormalities and relevant comorbidities. Lastly, our subgroup analysis revealed that the OR for miscarriage was different amongst the different diagnosis of IA. Although this finding is relevant for future research and for the clinical setting, the total number of pregnancies per diagnosis were low and these findings should be treated with caution.

Albeit these findings need to be corroborated by large prospective studies, rheumatologists should be aware that paternal IA may increase the risk of miscarriage. Although in various studies, different incidences of miscarriage have been described (dependent on the population studied and methodology used), the overall incidence of miscarriages found in our study is in line with data from a large Danish cohort that included more than 1,221,546 pregnancies and reported that 10.9% of clinically recognized pregnancies end in a miscarriage (19).

For specific advice and interventions on minimizing the negative impact of paternal IA on reproductive health (fertility and pregnancy outcomes), basic, translational and epidemiological studies are urgently needed. These studies should focus on understanding how inflammation (i.e. disease activity at the time of conception), pharmacological treatment, epigenetics and other factors associated with paternal IA influence pregnancy outcomes and male reproductive health. Until more is known about the potential effect of paternal IA on pregnancy outcomes, we recommend that all men diagnosed with arthritis and a wish to conceive should receive, at a minimum, general preconception counseling (20)

In conclusion, this study shows an association between paternal preconception IA and an increased risk of miscarriage. Notwithstanding, the overall rate of miscarriage reported in our study could be comparable to previously reported population estimates. Multiple biological mechanisms can be responsible for this association and more research is urgently needed to understand how paternal preconception IA influences pregnancy outcomes and ultimately to improve the quality of care for men diagnosed with IA and a desire for fatherhood.



Supplementary figure S1. Adjusted OR (point estimate and 95% CI) for miscarriage in pregnancies after IA diagnosis (per specific IA diagnosis). Multivariate logistic regression models adjusted for confounders (paternal age at conception, paternal and maternal smoking exposure, paternal medication preconception exposure, conception by ART, year of pregnancy and consecutive pregnancy number). Because of the low number of pregnancies reported by patients diagnosed with JIA (n=15), a multivariate logistic regression analysis was not performed for this group.

* Statistically significant, $p<0.05$

REFERENCES

1. Soubry A. POHaD: why we should study future fathers. Environ Epigenet. 2018;4(2):dvy007.
2. Simon L, Murphy K, Shamsi MB, Liu L, Emery B, Aston KI, et al. Paternal influence of sperm DNA integrity on early embryonic development. Hum Reprod. 2014;29(11):2402-12.
3. Lee SH, Song H, Park YS, Koong MK, Song IO, Jun JH. Poor sperm quality affects clinical outcomes of intracytoplasmic sperm injection in fresh and subsequent frozen-thawed cycles: potential paternal effects on pregnancy outcomes. Fertil Steril. 2009;91(3):798-804.
4. Wright C, Milne S, Leeson H. Sperm DNA damage caused by oxidative stress: modifiable clinical, lifestyle and nutritional factors in male infertility. Reprod Biomed Online. 2014;28(6):684-703.
5. Abbasi J. The Paternal Epigenome Makes Its Mark. Jama. 2017;317(20):2049-51.
6. Kasman AM, Zhang CA, Li S, Lu Y, Lathi RB, Stevenson DK, et al. Association between preconception paternal health and pregnancy loss in the USA: an analysis of US claims data. Hum Reprod. 2021;36(3):785-93.
7. Perez-Garcia LF, Te Winkel B, Carrizales JP, Bramer W, Vorstenbosch S, van Puijenbroek E, et al. Sexual function and reproduction can be impaired in men with rheumatic diseases: A systematic review. Semin Arthritis Rheum. 2020;50(3):557-73.
8. Perez-Garcia LF, Röder E, Goekoop RJ, Hazes JMW, Kok MR, Smeele HTW, et al. Impaired fertility in men diagnosed with inflammatory arthritis: results of a large multicentre study (iFAME-Fertility). Ann Rheum Dis. 2021.
9. Choudhury SR, Knapp LA. Human reproductive failure I: Immunological factors. Human Reproduction Update. 2001;7(2):113-34.
10. Thomas FS, Stanford JB, Sanders JN, Gurtcheff SE, Gibson M, Porucznik CA, et al. Development and initial validation of a fertility experiences questionnaire. Reproductive Health. 2015;12(1):62.
11. Robinson L, Gallos ID, Conner SJ, Rajkhowa M, Miller D, Lewis S, et al. The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis. Hum Reprod. 2012;27(10):2908-17.
12. Finelli R, Pallotti F, Cargnelutti F, Faja F, Carlini T, Rizzo F, et al. Sperm DNA damage and cytokines in varicocele: A case-control study. Andrologia. 2021;53(5):e14023.
13. Finelli R, Leisegang K, Finocchi F, De Masi S, Agarwal A, Damiani G. The impact of autoimmune systemic inflammation and associated medications on male reproductive health in patients with chronic rheumatological, dermatological, and gastroenterological diseases: A systematic review. Am J Reprod Immunol. 2021:e13389.
14. Sakkas D, Alvarez JG. Sperm DNA fragmentation: mechanisms of origin, impact on reproductive outcome, and analysis. Fertil Steril. 2010;93(4):1027-36.
15. Wallenius M, Lie E, Daltveit AK, Salvesen KÅ, Skomsvoll JF, Kalstad S, et al. Brief Report: No Excess Risks in Offspring With Paternal Preconception Exposure to Disease-Modifying Antirheumatic Drugs. Arthritis & Rheumatology. 2015;67(1):296-301.
16. Perez-Garcia LF, Dolhain RJEM, Vorstenbosch S, Bramer W, van Puijenbroek E, Hazes JMW, et al. The effect of paternal exposure to immunosuppressive drugs on sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes: a systematic review. Human Reproduction Update. 2020.
17. Marcho C, Oluwayiose OA, Pilsner JR. The preconception environment and sperm epigenetics. Andrology. 2020;8(4):924-42.
18. Nemtsova MV, Zaletaev DV, Bure IV, Mikhaylenko DS, Kuznetsova EB, Alekseeva EA, et al. Epigenetic Changes in the Pathogenesis of Rheumatoid Arthritis. Frontiers in Genetics. 2019;10(570).
19. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. BMJ (Clinical research ed). 2000;320(7251):1708-12.
20. Frey KA, Navarro SM, Kotelchuck M, Lu MC. The clinical content of preconception care: preconception care for men. Am J Obstet Gynecol. 2008;199(6 Suppl 2):S389-95.

PART IV

Testicular toxicity of immunosuppressive agents

CHAPTER 6

The effect of paternal exposure to immunosuppressive drugs on sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes: a systematic review

Published

Perez-Garcia LF, Dolhain RJEM, Vorstenbosch S, Bramer W, van Puijenbroek E, Hazes JMW, Te Winkel B.

Hum Reprod Update. 2020 Nov 1;26(6):961-1001.

Abstract

Background

Information regarding the possible influence of immunosuppressive drugs on male sexual function and reproductive outcomes is scarce. Men diagnosed with immune-mediated diseases and a wish to become a father represent an important neglected population since they lack vital information to make balanced decisions about their treatment.

Objectives

To systematically review the literature for the influence of paternal immunosuppressive drug use on many aspects of male sexual health, such as sexual function, fertility, pregnancy outcomes and on their offspring health outcome.

Methods

A systematic literature search was performed in the bibliographic databases: Embase (via Elsevier embase.com), MEDLINE ALL via Ovid, Cochrane Central Register of Trials (via Wiley) and Web of Science Core Collection. Additionally, Google Scholar and the Clinical trial registries of Europe and the USA were searched. The databases were searched from inception until August 31th 2019. The searches combined keywords regarding male sexual function and fertility, pregnancy outcomes and offspring's health with a list of immunosuppressive drugs. Studies were included if they were published in English and if they included original data on male human exposure to immunosuppressive drugs. A meta-analysis was not possible to perform due to the heterogeneity of the data.

Results

A total of 5867 references were identified among which we identified 163 articles fulfilling the eligibility criteria. 50 articles included pregnancy and offspring outcomes and 130 articles included sexual health outcomes. Except for large Scandinavian cohorts, most of the identified articles included a small number of participants. While a clear negative effect on sperm quality was evident for sulfasalazine and cyclophosphamide, a dubious effect was identified for colchicine, methotrexate and sirolimus. In 3 articles, exposure to TNF- α inhibitors in patients diagnosed with ankylosing spondylitis resulted in improved sperm quality. The information regarding pregnancy and offspring outcomes was scant but no large negative effect associated with paternal immunosuppressive drug exposure was reported.

Conclusion

Evidence regarding the safety of immunosuppressive drugs in men with a wish to become a father is inconclusive. The lack of standardization on how to evaluate and report male sexual function, fertility and reproduction as study outcomes in men exposed to immunosuppressive drugs is an important contributor to this result. Future research on this topic is needed and should be preferably done using standardized methods.

INTRODUCTION

Men with immune-mediated diseases (IMDs) and a wish to become a father represent an important neglected population. The question on how they should be treated to improve (or at least not impair) their chances of achieving a successful pregnancy and a healthy offspring remains a challenge for physicians and researchers all around the world.

Based on data from Denmark, the Netherlands and Norway, it is estimated that 5.6-7.6% of fathers could be exposed to NSAIDs or anti-rheumatic drugs during the pre-conceptional period (3 or 6 months before pregnancy) (1-3). Many factors are contributing to a substantial number of men with a wish to become a father being exposed to immunosuppressive drugs; some IMDs can affect men at a young age (i.e. juvenile idiopathic arthritis), the prevalence of other IMDs increases during the peak of the male reproductive lifespan (i.e. rheumatoid arthritis or inflammatory bowel disease) and furthermore, in many parts of the world men are becoming fathers at an older age (4).

It is known that immunosuppressive drugs can affect male sexual health and reproduction via multiple mechanisms; altering reproductive hormone secretion and/or action, disrupting spermatogenesis or sperm motility and by causing sexual dysfunction (5).

Furthermore, many of the available immunosuppressive drugs like methotrexate or sulfasalazine were approved by the Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) before it was required to perform mandatory evaluations of male reproductive toxicity (6, 7)

On the contrary, to get approval, new drugs are facing more strict protocols. Testicular toxicity is first evaluated in animal studies. When evidence suggests adverse events on the male reproductive system, complex trials in humans should follow. Importantly, in animal studies, the FDA considers histopathological evaluation to be an appropriate endpoint. In the case of human studies, semen analysis (baseline, at 13 weeks (one spermatogenic cycle after exposure and at 13 weeks after drug discontinuation) becomes the most important marker of fertility. For further reassurance of testicular safety, the FDA recommends conducting randomized, double-blind, placebo-controlled, parallel-arm trials including approximately 200 men in a 1:1 ratio (drug:placebo) (7) .

For men in their reproductive age, the decision on which immunosuppressive drug to prescribe is not straightforward. Information regarding the possible effects on male sexual health and reproduction is still lacking for most of the commonly used immunosuppressive drugs.

The objective of our study is to provide this information in the form of a "state of the art" systematic review. Our goal is to review the available information over the influence of paternal immunosuppressive drug exposure on many aspects of male sexual and reproductive health, such as; sexual function, reproductive hormones and fertility and on pregnancy and offspring outcomes.

METHODS

Protocol and registration

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (Registration no. CRD42018096898, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=96898) and undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses protocols (PRISMA-P) guidelines (8).

Eligibility criteria

The literature search was limited to the English language and human subjects. Case-control studies, cohort studies, cross-sectional studies, case reports and case series were included. In-vitro studies using human material were also included. Conference abstracts published after April 2016 were included. Publications without original data, such as reviews, were excluded. Publications concerning the use of immunosuppressive drugs for the treatment of any form of cancer were excluded.

The outcome data should include at least one of the following outcomes; sexual function, reproductive hormones, fertility, pregnancy or offspring outcomes. For pregnancy outcomes, publications were included if paternal exposure of immunosuppressive drugs took place in the six months before or around the time of conception and in case of studies reporting sexual function or fertility parameters (i.e. semen analysis, sexual dysfunction, testosterone levels) publications were included if male exposure of immunosuppressive drugs was taken into consideration. For both categories, no restrictions were made regarding the comparison groups.

Information sources and search terms

A search strategy was developed by an experienced medical librarian (WMB) using a structured methodology (9, 10). The searches combined keywords regarding male sexual function and fertility, pregnancy outcomes and offspring's health with a list of immunosuppressive drugs collected by experts in the fields of Rheumatology,

Gastroenterology, Dermatology and Nephrology. Our full electronic search strategy is provided in supplement 1.

Subsequently, a systematic literature search was performed in the bibliographic databases: Embase (via Elsevier embase.com), MEDLINE ALL (via Ovid), Cochrane Central Register of Trials (via Wiley) and Web of Science Core Collection. Additionally, Google Scholar and the Clinical trial registries of Europe and the USA were searched. We also included references from the primary search publications, in case these were missed in our search and when relevant data was missing we contacted authors for further information. These databases were searched from inception until August 31 2019.

Study selection and data extraction

All articles were imported into EndNote X9. After removal of duplicates with the method described by Bramer et al. (11), two reviewers (LP and BW) independently screened titles, abstracts and full-text of the records for eligibility. Disagreements were resolved by consensus with the help of a third reviewer; RD. Two reviewers (LP and BW) extracted relevant information for each studied outcome from the included articles.

Risk of bias in individual studies

The methodological quality of the studies was assessed with the Newcastle Ottawa Scale (NOS), developed for case-control and cohort studies (12). In the case of cross-sectional studies, an adapted scale was used (13). Using these methods, points were awarded to each publication, related to the selection of the study group, the comparability of the study groups and the ascertainment of the outcomes. The score ranges from 0-9, with scores >5 representing good-quality studies. The results are presented in Tables 1-2. Case reports were not graded. Quality assessment was done by LP for the sexual function, reproductive hormones and fertility data, and by BW and SV for pregnancy and child outcome data.

Regarding pregnancy and child outcomes data the following ‘rules’ were applied:

- Ascertainment exposure/outcome; graded ‘1’ (structured questionnaire equals structured interview)
- The question ‘Outcome not present at the start’ was always graded ‘0’
- Follow up length was considered long enough if:
- Congenital anomalies; at least one year follow up was reported.
- Long term outcomes; if follow up lasted until children were 18 years of age.

Table 1. Summary of study characteristics and main findings for sperm quality, sexual function and reproductive hormones outcomes.

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Aminosalicylic acid and similar agents							
(Di Paolo et al. 2001) Italy	42 (NR) NR	IBD	All sperm samples had abnormalities, mainly in motility. Sperm quality improved after stopping SSZ or switching to 5-ASA.	-	-	NR	H CS
(Zelissen et al. 1988) Netherlands	11 (32.3) NR	IBD	Oligospermia was detected in 72% of samples. After switching to 5-ASA all samples showed improvement in sperm counts.	-	*	NR	L CS
(Riley et al. 1987) UK	15 (NR) NR	IBD	Oligospermia was detected on 40% of samples. After switching to mesalazine samples showed improvement in sperm counts.	-	NR	NR	H CS
(Cosentino et al. 1984) USA	10 (30) 19 (NR)	IBD	Mean number of sperm count and of normal morphology was significantly lower. In 5 patients that stopped SSZ, improvement in sperm quality was observed.	-	*	NR	H Ch
(Freixa et al. 1984) Spain	10 (NR) 0	Healthy participants	Prostaglandin levels in seminal plasma decreased by 36% secondary to SSZ exposure.	-	NR	NR	L CS
(O'Morain et al. 1984) UK	39 (NR) 9 (NR)	IBD	SSZ exposure was associated with significant decrease in sperm counts, motility and increase in abnormal sperm morphology.	-	*	NR	L CC
(Ragni et al. 1984) Italy	7 (NR) 7 (30.1)	IBD	Sperm motility was reduced in all cases and serum testosterone levels were significantly lower in exposed cases.	-	-	NR	L CC
(Hudson et al. 1982) UK	8 (NR) 10 (NR)	IBD	Sperm head size was significantly larger in cases than in controls.	-	NR	NR	L CS

Table 1. Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
(Freeman et al. 1982) UK	11 (28.8) 6 (36)	IBD	Lower progressive motility in SSZ exposed group	-	NR	NR	L CC
Tobias (Tobias et al. 1982) South Africa, 1982	1 (39) 0	IBD	Case report: reversible infertility after stopping SSZ, patient on high dose GCs	-	*	NR	NA CR
(Toovey et al. 1981) UK	28 (NR) 4 (NR)	IBD	Exposed samples showed reduced sperm motility and density and altered morphology. After withdrawal sperm density and motility improved significantly but not sperm morphology.	-	*	NR	H CS
(Levi et al. 1979) UK	4 (30) 0	IBD	Case series: One of the first case series where authors reported semen analysis abnormalities in SSZ exposed patients.	-	NR	NR	NR Case series
(Toth 1979) UK	6 (NR) 0	IBD	Head, midpiece and tail abnormalities were detected in spermatozoa of SSZ exposed patients.	-	NR	NR	L CS
(McIntyre et al. 1984) UK	3 (NR) 0	IBD	Case series: Sperm abnormalities detected after SSZ exposed patients were sent to the infertility clinic. Sperm quality improved after switching therapy to balsalazide.	-	NR	NR	NA Case series
(Iglesias-cortit et al. 1985) Spain	6 (NR) 0	Healthy participants	Sperm motility decreased 15% after exposure to SSZ.	-	NR	NR	L CS

Table 1. Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
(Cann et al. 1984) Austria	1 (33) 0	IBD	Case report: SSZ exposed patient that was diagnosed with infertility and achieved a successful pregnancy after switching therapy from SSZ to 5-ASA.	-	NR	NR	NA CR
(Ganatra et al. 2018) India	61 (NR) 0	IBD	26.23% of SSZ exposed patients developed oligospermia. This is the first article to comment on the possible effect by disease activity.	-	NR	NR	L CS
(Shaffer et al. 1984) UK	1 (32) 0	IBD	Case report: Oligospermia associated with exposure to SSZ	-	NR	NR	NA CR
(Traub et al. 1979) UK	1 (25) 0	IBD	Case report: Pregnancy achieved after stopping SSZ therapy.	-	NR	NR	NA CR
(Chatzinoff et al. 1988) USA	1 (32) 0	IBD	Case report: SSZ-induced infertility case confirmed by sperm penetration assay (sperm analysis was normal).	-*	NR	NR	NA CR
(Birnie et al. 1981) Scotland	21 (32.8) 0	IBD	86% of SSZ exposed patients had abnormal semen analysis (72% had oligospermia).	-	NR	NR	L CS
(Heineman et al. 1981) The Netherlands	2 (32) 0	IBD	Case report: Reversible oligospermia in 2 cases exposed to SSZ. Both cases achieved pregnancies after drug withdrawal.	-*	NR	NR	NA CS

Table 1. Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Antimalarials							
(Ejebe et al. 2008) Nigeria	5 (NR) 10 (NR)	Healthy participants	No differences in sperm quality parameters and reproductive hormones were found between exposed and non-exposed after exposure of chloroquine 1 g/d for 2 days and then 500 mg/d for 1 day.	*	*	NR	L CS
(Hargreaves et al. 1998) UK	NR	Healthy participants	Chloroquine had a dual in vitro effect, enhancing rapid motility at low concentrations but inhibiting it at higher concentrations. At 250 µg/ml chloroquine, all spermatozoa were static.	+ -	NR	NR	CS L
(Adeeko et al. 1994) Nigeria	8 (NR) 0 (NR)	Healthy participants	Chloroquine is present in seminal plasma even after long time of no exposure.	NR	NR	NR	L Ch
(Ette et al. 1988) Nigeria	4 (NR) 0 (NR)	Healthy participants	Chloroquine crosses the BTB, probably by passive diffusion.	NR	NR	NR	NA Case series
Calcineurin Inhibitors (CsP=ciclosporine, EVE=everolimus, SIR=sirolimus, TAC=tacrolimus)							
(Misro et al. 1999) India	NR	Healthy participants **CsP**	In vitro study showing that ciclosporine exerts deleterious effects on sperm, which become immotile and nonviable.	-	NR	NR	H CS
(Haberman et al. 1991) USA	9 (41.2) NR	Kidney transplantation **CsP**	With the exemption of a low semen volume ciclosporine A at 3 mg/kg/d did not result in other sperm quality or hormonal abnormalities.	*	*	NR	L CS
(Samojlik et al. 1992) USA	10 (NR) 0	Kidney transplantation **CsP**	Pretreatment (pretransplant) testosterone levels were below normal in 80%. After 12 months of treatment with CsP and other immunosuppressive drugs testosterone levels significantly increased in all 10 cases.	NR	+	NR	L CC

Table 1. Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
(Eid et al. 1996) Egypt	34 (32) 31 (31)	Kidney transplantation **CsP**	Sperm concentration was inversely correlated to the CsP whole blood levels.	-	*	+	H CC
(Kramer et al. 2005) Germany	256 (NR) 0	Kidney transplantation **CsP -EVE**	Testosterone levels increased from baseline in EVE and EVE-CsP groups.	NR	+	NR	L Ch
(Kantarci et al. 2004) Turkey	37 (38.1) 0	Kidney transplantation **CsP - TAC**	No statistical differences in baseline levels of serum FSH, LH, testosterone and PRL between CsP and TAC treated patients. All results were in normal ranges.	NR	*	NR	L CS
(Peces et al. 1994) Spain	19 (35) 0	Kidney transplantation **CsP**	Serum levels of reproductive hormones were normal in CsP exposed cases.	NR	*	NR	L CS
(Sajad Hussain et al. 2015) India	1 (40)	Kidney transplantation **SIR**	Case report, patient was infertile while on Sirolimus he developed oligospermia with normal hormone levels after switching to tacrolimus he was able to conceive	-*	*	NR	NA CR
(Boobes et al. 2010) UAE	6 (43) 0	Kidney transplantation **SIR**	Case series, infertile patients with oligospermia, after discontinuing SRL all patients had increased sperm counts and were able to conceive.	-*	NR	+	NA Case series
(Zuber et al. 2008) France	25 (32) 67 (NR)	Kidney transplantation **SIR**	Sirolimus exposed patients had lower sperm counts and motility. The fathered pregnancy rate was significantly lower in exposed patients than in non-exposed.	-	NR	NR	H CS
(Skrzypek et al. 2007) Germany	1 (29) 0	Kidney transplantation **SIR**	Recovery of spermatogenesis after cessation of sirolimus	-*	-	NR	NR CR

Table 1. Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
(Deutsch et al. 2007) Germany	1 (26)	Lung – heart transplantation **SIR**	Benign Leydig cell tumor in a patient exposed to sirolimus lead to testicular biopsy that showed testicular atrophy and signs of impaired spermatogenesis.	-*	-	NR	NA CR
(Bererhi et al. 2003) France	1 (36)	Kidney transplantation **SIR**	Case report: Low sperm count and motility with abnormal morphology associated with sirolimus exposure. This changes were reversed after switching therapy to tacrolimus*.	-*	NR	NR	NA
(Kaczmarek et al. 2004) Germany	66 (NR) 66 (NR)	Heart transplantation **SIR**	Patients exposed to sirolimus had significantly lower serum testosterone levels and higher FHS/LH levels than control group.	NR	-	NR	H CS
(Lee et al. 2005) USA	32 (41) 34 (47)	Kidney transplantation **SIR**	Patients exposed to sirolimus had significantly lower serum testosterone levels and higher FHS/LH levels than control group.	NR	-	NR	H CS
(Fritsche et al. 2004) Germany	28 (46.5) 28 (45.5)	Kidney transplantation **SIR**	Sirolimus daily dose and testosterone concentrations were significantly inversely correlated (r= –0.383)	NR	-	NR	H CC
(Tondolo et al. 2005) USA	59 (48) 0	Kidney transplantation **SIR**	Significantly reduced levels of circulating testosterone among patients receiving sirolimus alone compared to those treated with calcineurin inhibitors alone were identified.	NR	-	NR	L CS
Colchicine							
(Kastrop et al. 1999), Netherlands	2 (40) 0	Gout	Cytogenic analysis of sperm (FISH) revealed no damage secondary to colchicine use.	*	NR	NR	NA CR
(Kirchin et al. 1999) UK	1 (48) 0	Retinal vasculitis	Case report: reversible azoospermia	-	NR	NR	NA CR

Table 1. Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
(Sarica et al. 1995) Turkey	62 (32.4) 0	Behçet syndrome	The longer the use of colchicine the more serious the adverse events on sperm count	-	+	NR	L CS
(Ben-Chetrit et al. 1993) Israel	15 (NR) 0	Healthy participants	In vitro study, high concentrations of colchicine may affect in vitro motility of sperms, probably by its direct effect on the microtubules.	-	NR	NR	H CC
(Levy et al. 1978) Israel	6 (34.6) 0	FMF	After being advised to stop treatment with colchicine prior to attempt conception, sperm analysis were within normal limits in all 6 patients.	*	NR	NR	L CS
(Bremner et al. 1976) USA	7 (22) 0	Healthy participants	Colchicine caused no significant changes in sperm quality or reproductive hormones levels after 3 or 6 months of treatment.	*	*	NR	L CS
(Merlin 1972) USA	1 (36) 0	Gout	Case report: azoospermia believed to be associated to colchicine use. Colchicine was stopped and after 3 months, sperm count improved and wife became pregnant.	-	NR	NR	NA CR
(Kaya Aksoy et al. 2019) Turkey	72 (14.5) 0	FMF	Mean colchicine dose at the time of sperm analysis was higher in patients with low sperm motility than that with normal sperm motility.	-	NR	NR	H Ch
Cyclophosphamide							
(Suehiro et al. 2008) Brazil	13 (NR) NR	SLE	The median serum inhibin B was lower in patients treated with CYC compared with those without this therapy.	-	-	NR	L CS

Table 1. Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
(Soares et al. 2007) Brazil	14 (NR) NR	SLE	Semen analysis demonstrated that patients who had undergone IV CYC therapy had worse sperm quality (count, motility and morphology) compared with patients who did not undergo this treatment. Elevated FSH levels were detected in patients who underwent IV CYC therapy	-	-	NR	H CC
(Anserini et al. 2002) Italy	19 (NR) 0	Bone marrow transplantation	10% of patients who received CYC showed azoospermia and recovery of spermatogenesis was observed in 60% of patients.	-	NR	NR	NA Case series
(Bogdanovic et al. 1990) Yugoslavia	17 (NA) 0	Nephrotic syndrome	Significant inverse correlation between sperm density and CYC dosage and duration of treatment.	-	NR	NR	NA Case series
(Perrone et al. 1989) Italy	22 (NR) 20 (NR)	Nephrotic syndrome	Altered spermatogenesis was found in 41.6% of adult patients treated with CYC during childhood (1.8-5.5 mg/kg/d for 12 weeks) No significant inverse correlation of total dose of the drug with sperm density.	-	-	NR	H CC
(Watson et al. 1985) Canada	30 (22) 18 (28)	Nephrotic syndrome	A significant inverse correlation was evident between sperm density and CYC dosage. Recovery of sperm count after prolonged interval after treatment is possible.	-	-	*	L CC
(Ogata et al. 1982) Japan	6 (NR) 0	Nephrotic syndrome	Histologic oligospermic changes were observed in 3 patients treated with high doses (10.6-16.2 g during 125-432 days)	-	NR	NR	L Case series
(Fukutani et al. 1981) Japan	31 (33) 33 (NR)	Behcet syndrome	Azoospermia and oligospermia found in 13 out of 17 patients treated with CYC. High mean FSH levels in CYC treated patients	-	-	NR	L CS

Table 1. Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
(Trompeter et al. 1981) UK	19 (22) 17 (23)	Nephrotic syndrome	Lower ejaculate volumes and sperm densites and higher percentage of immotile and abnormal forms in CYC exposed group.	-	-	NR	L CS
Marina (Marina et al. 1979) Spain, 1979	3 (NR) 0	Nephrotic syndrome	All patients showed abnormalities: oligospermia (1), azoospermia (1) and aplasia of germinal epithelium (1).	-	NR	NR	NA Case series
(Hsu et al. 1979) Canada	16 (NR) 0	Nephrotic syndrome	Sperm quality abnormalities found in 63%. An increase in the total dosage and in duration of the treatment was associated with a higher incidence of testicular dysfunction.	-	-	NR	L Ch
(Etteldorf et al. 1976) USA	12 (NR) 0	Nephrotic syndrome	Low doses (2-4mg/kg/d) did not influence pituitary gonadal function (confirmed by biopsy)	-	-	NR	NA Case series
(Kirkland et al. 1976) USA	15 (NR) 0	Nephrotic syndrome	Serum testosterone levels were normal in CYC-treated patients	NR	*	NR	NA Case series
(Pennisi et al. 1975) USA	23 (NR) 0	Nephrotic syndrome	Sperm quality was uniformly decreased in CYC-treated patients and high FSH levels were common	-	-	NR	L Case series
(Kumar et al. 1972) UK	8 (NR) 0	Nephrotic syndrome	All 8 biopsy specimens had evidence of testicular atrophy, and it was profound in 6.	-	NR	NR	L CS
(Penso et al. 1974) USA	7 (NR) 0	Nephrotic syndrome	Biopsies confirmed absent spermatogenesis in azoospermic patients and FSH elevation correlated with degree of testicular damage	-	-	NR	L CS
(Feng et al. 1972) Singapore	1 (18) 0	Nephrotic syndrome	First case report that reported azoospermia associated with CYC exposure.	-	NR	NR	NA CR

Table 1. Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
(Masala et al. 1997) Italy	15 (NR) 0	Nephrotic syndrome	All 15 patients received CYC and became azoospermic or oligospermic. 5 patients received testosterone (100 mg intramuscularly every 15 days during CYC therapy). After CYC treatment normal sperm analysis were reported in all 5 patients that received testosterone (vs 1/10)	-	NR	NR	L CS
(Fairley et al. 1972) Australia	31 (31.2) 0	NR	Testicular biopsy was performed on 5 patients who were receiving CYC and no spermatogenesis was found.	-	NR	NR	L CS
Methotrexate							
(Sussman et al. 1980) USA	1 (26) 0	Psoriasis	Case report, reversible oligospermia secondary to MTX.	-	NR	NR	NA CR
(Van Scott et al. 1959) USA,	2 (NR) 0	Psoriasis	Sperm counts was reduced 63–97% at 2 weeks after a single IV injection of MTX.	-	NR	NR	NA Case series
(El-Beheiry et al. 1979) Egypt	26 (33-52) 0	Psoriasis	The mean difference in sperm count, motility, and abnormal forms before and after methotrexate therapy was not significant. 5 testicular biopsies performed where no alterations were found.	*	NR	NR	L CS
(Grunnet et al. 1977) Denmark	10 (23-46) 0	Psoriasis	Sperm abnormalities found in 40% of MTX treated patients but sperm quality was better than in patients treated with glucocorticoids.	+	NR	NR	L CS
(Ley et al. 2018) USA	7 (28) 1912 (NR)	IBD	In all MTX-treated patients, basic semen analyses were within normal limits	- DFI * sperm	NR	NR	L CC
(Pandhi et al. 2006) India	1 (50)	Psoriasis	Case report, gynecomastia and oligospermia secondary to MTX	-	NR	NR	NA CR

Table 1. Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
NSAIDs							
(Kristensen et al. 2018) Denmark	14 (NR) 17 (NR)	Healthy participants **Ibuprofen**	Experiment: Exposure to ibuprofen in adult testis explants caused a state of compensated hypogonadism.	NR	-	NR	NA RCT
(Poratsoldin et al. 1992) USA	19 (NR) 0	Healthy participants **Salicylate**	In vitro study: salicylate significantly decreases sperm motility	-	NR	NR	H CS
(Bendvold et al. 1985) Sweden	6 (NR) 0	Healthy participants **Naproxen**	Treatment with naproxen significantly reduces the concentration of all PGs present in human seminal fluid.	NR	NR	NR	H CC
(Albert et al. 2013) France	NA	Healthy participants **Aspirin and indomethacin**	In vitro study: Production of testosterone by Leydig cells was altered by exposure to all these drugs	NR	-	NR	L CS
(Knuth et al. 1989) Germany	10 (25.1) 12 (27.4)	Healthy participants **Indomethacin**	Exposure to indomethacin led to lower PGs levels in seminal plasma but unchanged sperm quality parameters and levels of reproductive hormones	*	*	NR	L CS
Retinoids							
(Liu et al. 2017) China	31 (NR) 14 (NR)	Psoriasis Acitretin	After 3 months of treatment at doses of 20 mg/d and 30 mg/d sperm quality did not differ between cases and controls.	*	*	NR	H CC
(Schmitt-Hoffmann et al. 2011) Switzerland	24 (30) 0	Healthy participants Acitretin	After 3 months of treatment at doses of 20 mg or 40 mg/d alitretinoin and 4-oxo-alitretinoin were detected in 11 of 12 semen samples. Concentrations detected are unlikely associated with teratogenicity.	NR	NR	NR	L CC

Table 1. Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
(Rossi et al. 2009) Italy	1 (39) 0	Psoriasis Acitretin	Case report: 39 year old diagnosed with psoriasis reported erectile dysfunction after starting treatment with acitretin (25 mg/d). After 2 weeks of drug withdrawal patient reported normalization of sexual activity	NR	NR	-	NA CR
(Parsch et al. 1990) Germany	5 (34) 6 (34)	Psoriasis Acitretin	After 3 months of treatment at doses of 25-50 mg/d sperm quality did not differ between cases and controls	*	*	NR	H CC
(Çinar et al. 2016) Turkey	81 (22.6) 0	Acne Isotretinoin	After 6 months of treatment at doses of 120 mg/d all the sperm quality parameters changed positively and reproductive hormone levels did not differ.	+	*	NR	H CS
(Torok et al. 1987) Hungary	13 (27) 0	Acne Isotretinoin	After 4 months of treatment at doses of 1 mg/kg/d, sperm motility increased significantly and the other sperm quality parameters did not differ.	+	NR	NR	H CS
(Coleman et al. 1994) UK	1 (29) 0	Acne Isotretinoin	Case report of ejaculatory failure associated with isotretinoin (1 mg/kg/d)	NR	NR	-	NA CR
(Healy et al. 2018) UK	47 (NR) 0	Acne Isotretinoin	Independent drug safety website (RxISK.org) data: isotretinoin commonly associated with SD	NR	NR	-	H Ch
Systemic glucocorticoids							
(McDonald et al. 1956) USA	4 (NR) 7 (NR)	RA	Case series: Biopsies performed after exposure to 75 mg of cortisone and no negative effect was observed.	*	NR	NR	NA Case series

Table 1. Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
(Martens et al. 1994) USA	36 (62) 70 (68)	RA	Compared to healthy controls, RA patients taking prednisone had significantly lower testosterone levels, and slightly elevated levels of FSH and LH.	NR	-	NR	L CS
Thiopurines (AZA=Azathioprine)							
(Dejaco et al. 2001) Austria	23 (32) 0 (NR)	IBD **AZA**	Semen analyses of 23 patients with IBD showed no negative association between AZA therapy and sperm quality.	*	NR	NR	L CS
(Farthing et al. 1983) UK	5 (NR) 0	IBD **AZA**	80% of patients had oligospermia	-	NR	NR	NA Case series
(Baumgarten et al. 1977) USA	7 (NR) 0	Kidney transplantation **AZA**	No correlation between poor spermatogenesis and AZA was reported.	*	*	NR	NA Case series
(Grosen, Nersting, et al. 2019) Denmark	40 (27.6) 40 (23.3)	IBD **AZA**	Sperm motility was decreased in patients, DFI was similar	- DFI * sperm	*	NR	H Ch
TNF-α inhibitors (INF=infliximab, ETN=etanercept, CZP=certolizumab pegol, ADA=adalimumab, GOL=golimumab)							
(Heppt et al. 2017) Germany	27 (37.5) 0	Psoriasis **ETN** **ADA**	Compared with baseline, no significant differences in mean total sperm number, sperm concentration, total and progressive motility nor other semen parameters were noticed during follow-up.	*	NR	NR	L Ch
(Pascarelli et al. 2017) Italy	10 (NR) 0	Healthy participants **ETN**	*In vitro study TNF- α had a detrimental effect on sperm function and in-vitro etanercept counteracted this toxic action of TNF- α	+	NR	NR	L CS

Table 1. Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
(Ramonda et al. 2014) Italy	10 (28.7) 20 (27.4)	SpA **ADA**	Improvement in semen parameters after 12 months of TNF- α inhibitor treatment was reported.	+	*	NR	H CC
(Micu et al. 2014) Rumania	23 (34.7) 42 (34.8)	AS **ETN (2) ADA (14) INF(4)**	Exposure of 20 patients to three different types of anti-TNFs did not have a negative impact on sperm quality after 3–6 months and in 6 cases after 12 months of treatment.	*	NR	NR	L CC
(Almeida et al. 2013) Brazil	10 (33) 24 (28.5)	AS **ETN (2) ADA (8)**	Sperm abnormalities were comparable in patients and controls after 6 months of TNF-α inhibitor therapy	*	*	NR	H CC
(Villiger et al. 2010) Switzerland	15 (29.5) 102 (30)	SpA **ETN ADA INF**	Impaired sperm quality was especially found in the group of anti-TNF naive patients with active disease. Sperm quality tended to improve within the five paired samples for sperm vitality (p=0.08) and sperm motility (p=0.08),	+	*	NR	L CC
(Mahadevan et al. 2005) USA	10 (31) 0	IBD **INF**	Sperm motility, or the percentage of sperm that show flagellar motion, was below normal in study patients after INF treatment	-	NR	NR	H CS
(Perrier d'Hauterive et al. 2012) Belgium	10 (NR) 10 (NR)	Healthy Participants **CZP**	CZP treatment was found to have no effect on the semen quality variables assessed vs placebo	*	NR	NR	NA RCT
(Grosen, Bungum, Christensen, et al. 2019) Denmark	28 (30.8) 17 (27.5)	IBD **INF (38) ADA(7)**	A statistically significant reduction in DFI was observed after the start of anti-TNF-α therapy [median DFI 12.8 off therapy versus 10.0 on therapy, p = 0.02. No differences in sperm quality parameters were found between groups.	* sperm + DFI	NR	NR	H Ch

Table 1. Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
(Montagna et al. 2005) Italy	3 (40) 0	AS **INF**	Case series reporting asthenoazoospermia in 2 out of 3 patients using infliximab.	-*	NR	NR	NA Case series
(Wildi et al. 2012) Canada	1 (35) 0	AS **ADA**	Case report: Oligoasthenozoospermia and decreased motility reversed after stopping drug.	-*	NR	NR	NA CR
(Younis et al. 2014) Israel	1 (50)	AS **INF**	Case report: Low sperm count, concentration increased after stopping IFX.	-*	NR	NR	NA CR
(Micu et al. 2019) Romania	5 (NR) 0	SpA **ADA**	Normospermia before and after TNF- α therapy initiation.	*	NR	NR	L Ch
(Kreitenberg et al. 2015) USA	1 (58)	RA **ADA**	Case report: Priapism associated with adalimumab	NR	NR	-	NA CR
(Oh et al. 2009) Korea	22 (37.8) 0	AS **ETN** **ADA** **INF**	Anti-TNF- α treated patients showed significant improvements in four out of the five IIEF domains.	NR	NR	+	L Ch
Verdolizumab							
(Grosen, Bungum, Hvas, et al. 2019) Denmark	15 (33) 33 (23)	IBD	Sperm quality and DFI was similar among cases and controls after exposure to verdolizumab. Verdolizumab was detected in seminal plasma at levels that correspondent to 0.3-1.1% of serum levels.	*	*	NR	L CC

Abbreviations in table:
H (high), L (low), NA (not applicable), NR (not reported), (*) no differences reported, (+) positive effect, (-) negative effect, (-*, reversible negative effect upon withdrawal.

In the case that publications included maternal and paternal outcomes, the score was based only on the paternal outcomes.

Synthesis of results

Sexual health outcomes were classified into 2 categories:

1. **Sexual function, reproductive hormones and fertility** (e.g. sexual dysfunction, testosterone, sperm quality)
2. **Pregnancy and offspring outcomes** (e.g. live births, spontaneous abortions, premature birth, low birth weight, congenital anomalies).

Additional analysis

A meta-analysis was not possible to perform due to the heretogenicity of the data.

RESULTS

Study selection and characteristics

A total of 5867 references were identified (2366 from Embase, 2023 from Medline, 1315 from Web of Science and 163 from Cochrane central) and imported into EndNote X9. After removing 1663 duplicates, 4204 articles were eligible for title and abstract screening. 3850 articles were excluded during this phase and 354 articles were eligible for full-text reading. 193 articles were excluded after full-text reading (see flowchart in figure 1). 15 articles that fulfilled the inclusion criteria and that were not identified by our search strategy or that were missed during the screening titles and abstracts procedure were identfied by cross-checking relevant literature. In total, 178 articles fulfilled the inclusion criteria.

Description of participants

A brief description of participants' characteristics is provided in the text and/or in the tables.

Description of interventions

In general, sexual function and fertility outcomes were evaluated in a few studies before and after exposure to immunosuppressive drugs. In cross-sectional studies, disease activity and co-medication used during the study were not uniformly reported.

The publications regarding pregnancy and child outcomes were observational, no standardized interventions were studied.

Risk of bias within studies

Regarding sexual function, reproductive hormones and male fertility the overall quality of the included studies was low to moderate and the number of exposed cases was low for all the drugs included in this systematic review. Regarding pregnancy outcomes case series and small cohorts were of low quality (<5) in general. High scores (≥5) were given to the population-based registries from Denmark and Norway and transplantation registries.

Outcomes

In the upcoming text, we provide a summary of the main outcomes from the included studies. More in-depth information regarding the findings and study quality per study is presented in tables 1-2 and in the supplementary material. Table 1 contains information regarding fertility, reproductive hormones and sexual function outcomes. Table 2 contains information about pregnancy outcomes, gestational age, birth weight and birth defects. Supplementary table 5 contains more study specifications. Reported specification of the birth defects is presented in supplementary table 6. Other maternal and child outcomes are reported in supplementary table 7.

Paternal exposure was included in this systematic review if paternal exposure occurred six months before conception or around the time of conception. Some of the included studies also presented results for exposure at any time before conception. Comparison between 'exposure three months prior to conception' and 'exposure at any time before conception' was possible in publications of the Danish registry data (14-16). See supplement table 8 for outcomes after any time before conception exposures. No major changes were found in the risk estimates, only in case of a very low number of cases.

Aminosalicylic acid and similar agents

- **Sexual function, reproductive hormones and fertility**

Twenty-two studies with data on a total of 329 exposed men to sulfasalazine were identified. Sperm analysis abnormalities were reported in 40-100% of those patients exposed to sulfasalazine (doses ranged from 2 to 4 mg per day). The most common sperm abnormality reported was asthenozoospermia (decreased motility) followed by decreased sperm counts and abnormal morphology. Data extracted from case reports and small case-series showed that oligospermia and asthenozoospermia were severe enough to cause male infertility. In all studies where follow up samples were available, sperm quality improved after sulfasalazine was withdrawn for 3 months. The majority of these studies were published between 1979-1987 and included patients diagnosed with Inflammatory bowel disease (IBD) (17-38). Importantly, most of these studies are case reports and case series.

Table 2. Summary of study characteristics and main findings for pregnancy and child outcomes.

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
Calcineurin Inhibitors (CsP=ciclosporine, SIR=sirolimus, TAC=tacrolimus)								
Hospital Germany Schopf 2017 (Schopf 2017, 2017)	Case report 1 male	3 months prior to conception	Ciclosporine	LB 1	NS	NR	BD 0	L
Hospital Sweden Holmgren 2004 (Holmgren et al. 2004)	Case series NR 3 children	long-term	1 Tacrolimus, 2 Ciclosporine	LB 3	NR	BW 3967	BD 0	L
TC* China Xu 2009 (Xu et al. 2009)	Case series 1981-2007 164 males	long-term	Ciclosporine	LB 167	PB 7	BW 3274±395	BD 1	L
Hospital Turkey Ecevit 2017 (Ecevit et al. 2012)	Case series 1997-2010 2 males	long-term	1 Sirolimus, 1 Tacrolimus	LB 2	PB 0	BW >3500	BD 0	L
TPR* USA Moritz 2017 (Moritz et al. 2017)	Case series 1991-2017 29 pregnancies	long-term	Sirolimus	LB 28 SA 1	NR	NR	BD 1	L

Table 2. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
PBR* Denmark Egeberg 2017 (Egeberg et al. 2017)	Cohort 2004-2010 67 / 417567 children	3 months prior to conception and during the first trimester	Ciclosporine / no immunosuppressants	NA	PB 4 (6.0) / 18968 (4.5) OR (95% CI) 1.34 (0.49-3.67) Adj. OR (95% CI) 1.40 (0.51-3.85)	LBW <3 / 22087 (5.3) OR (95% CI) 0.55 (0.14-2.25) Adj. OR (95% CI) 0.58 (0.14-2.39)	BD 7 (10.5) / 31231 (7.5) OR (95% CI) 1.44 (0.66-3.16) Adj. OR (95% CI) 1.45 (0.66-3.19)	H
Colchicine								
Hospital Israel Levy 1977 (Levy et al. 1977)	Case series 3 pregnancies	3 months prior to conception	Colchicine	LB 3	NR	NR	NR	L
Ehrenfeld 1985 (Ehrenfeld et al. 1986)	Case series 11 years 12 (8) children (fathers)	3 months prior to conception	Colchicine	LB 9 SA 3 SA 10 (6) / 6 (9)	NR	NR	NR	L
Ben-Chetrit 2004 (Ben-Chetrit et al. 2004)	Cohort 1995-2003 158 / 64 pregnancies	3 months prior to conception						

Table 2. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
Cyclophosphamide								
Hospital Turkey Balci 1983 (Balci et al. 1983)	Case report 1 child	long-term	Cyclophosphamide	LB 1	NR	NR	BD 1	L
Interleukin inhibitors								
TIS Germany Weber-Schoendorfer 2016 (Weber-Schoendorfer et al. 2016)	Case series 2011-2014 2 pregnancies	long-term	Tocilizumab	LB 1 SA 1	NR	NR	BD 0	L
MAH SD* Youngstein 2017 (Youngstein et al. 2017)	Case series Until 2012 6 (5) children (fathers) 5 (3) children (fathers)	long-term	Anakinra Canakinumab	NA NA	NR NR	NR NR	BD 0 BD 0	L

Table 2. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
MAH SD Warren 2018 (Warren et al. 2018)	Case series Until 2017 54 pregnancies	at the time of conception	Secukinumab	LB 29 (54) SA 4 (7) ET 1 (2) PL 20 (37)	PB 1 (2)	NR	BD 1 (2)	L
Methotrexate								
Hospital USA Perry 1983 (Perry 1983)	Case report 1 male	6 months prior to conception		LB 1	PT 0	BW 2730	BD 0	NA
Hospital USA Griggs 2006 (Griggs et al. 2006)	Case report 1 male	6 months prior to conception		LB 1	NR	BW 3500	BD 0	NA
Hospital Italy Lamboglia 2009 (Lamboglia et al. 2009)	Case report 1 male	at the time of conception		LB 1	NR	BW 2800	BD 0	NA
TIS France Beghin 2011 (Beghin et al. 2011)	Case series 1997-2009 42 pregnancies (40 fathers)	3 months prior to conception		LB 36 SA 3 ET 3	GA 39.2±1.1 PB 1	BW 3393±407	BD 0	L

Table 2. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
JuMBO registry Germany Drenches 2018 (Drenches et al. 2018)	Case series Up to 2018 9 pregnancies	at the time of conception		LB 6 SA 2 ET 1	NR	NR	BD 1	L
PBR* Norway England 2012 (Engeland et al. 2013)	Cohort 2004-2011 5 singleton pregnancies	3 months prior to conception		SA 0	PB 0	SGA 0	BD 0	L
TIS Germany Weber-Schoendorfer 2014 (Weber-schoendorfer et al. 2014)	Cohort 1995-2012 113 / 412 pregnancies	3 months prior to conception		LB 87 / 349 (84.7) SA 15 / 40 (10.2) ET 11 / 21 (5.1)	GA 39.1 / 39 PB 8 (9.2) / 54 (15.1)	BW 3380 / 3330	BD major 1 (1.1) / 4 (1.1) minor 4 (4.6) / 18 (5.0) genetic 1 (1.1) / 2 (0.55) all OR (95% CI) 1.02 (0.4-2.5)	L

Table 2. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
PBR Denmark Winter 2017 (Winter et al. 2017) Eck 2017(Eck et al. 2017) Egeberg 2017 (Egeberg et al. 2017)	Cohort 1997-2013 193 / 1013801 live born children (singleton)	3 months prior to conception	Methotrexate / No methotrexate	NA	PB 13 (6.7) / 57088 (5.6) OR (95% CI) 1.27(0.63-2.56) Adj. OR (95% CI) 1.38 (0.68-2.81)	SGA 6 (3.1) / 34236 (3.4) OR (95% CI) 0.92 (0.37-2.31) Adj. OR (95% CI) 0.98 (0.39-2.50)	BD 10 (5.2) / 48466 (4.8) OR (95% CI) 1.16 (0.62-2.18) Adj. OR (95% CI) 1.10 (0.57-2.13)	H
Andersen 2018 (Andersen et al. 2018) Andersen 2019 (Andersen et al. 2019)	Cohort 1997-2015 520 / 1363543 fathers	3 months prior to conception and during the first trimester	Methotrexate / No methotrexate	SA 46 (8.9) / 122929 (9.0) Adj. HR (95% CI) 0.99 (0.67-1.46)	GA 39.7 (38.7-41.0)/ 40.0 (39.0-41.0) NA	BW 3510 (3198-3915)/ 3540 (3200-3890) NA	NA	L
Mycophenolate acid products								
TPR* USA Moritz 2017 (Moritz et al. 2017)	Cohort 1991-2017 295 / 1092 pregnancies	long-term	MPA / No MPA	LB (90.2) / (91.9) SA (9.2) / (6.2) ET 0 / (0.6) SB (0.7) / (0.7) OT 0 / (0.6)	GA 39±2.5 / 39±2.3 PT (12.8) / (12.8)	BW 3323±635 / 3362±592 LBW (8.5) / (6.6)	BD (3.5) / (3.1)	H

Table 2. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
PBR* Norway Midtvedt 2017 (Midtvedt et al. 2017) Asberg 2017 (Åsberg et al. 2017)	Cohort 1995-2015 155 (112) / 195 (133) children (fathers)	long-term	MPA / No MPA	LB 154 (99.4) / 191 (97.9) SB 1 (0.6%) / 4 (2.1%)	GA 38.8±2.5 / 39.1±2.7	BW 3381±681 / 3429±714	BD 6 (3.9) / 5 (2.6)	H
PBR* Denmark Egeberg 2017 (Egeberg et al. 2017)	Cohort 2004-2010 6 / 417628 children	3 months prior to conception and during the first trimester	Mycophenolate mofetil/ no immunosuppressants	NA	PB 0 / 18972 (4.5)	LBW 0 / 22089 (5.3)	BD 0 / 31238 (7.5)	H
Hospital Spain Lopez-Lopez 2018 (Lopez-Lopez et al. 2018)	Cohort 1988-2015 28 (20) / 21 (13) children (fathers)	long-term	MPA / No MPA	LB 28 / 21 SA 6 / 2		BW 3298±646 / 3148±401	BD 0 / 1	L

Table 2. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
Other selective immunosuppressants								
TIS Italy De Santis 2005 (De Santis et al. 2005)	Case report 1 pregnancy	At the time of conception	Leflunomide	LB 1	GA 38	BW 3350	BD 0	NA
MAH SD* Kumar 2015 (Kumar et al. 2015)	Case series 1995-2014 10 pregnancies	At the time of conception	Abatacept	LB 9 ET 1	NR	NR	BD 0	L
MAH SD Mahadevan 2018 (Mahadevan et al. 2018) Clowse 2016 (Clowse et al. 2016)	Case series Until 2017 84 pregnancies	At the time of conception	Tofacitinib	LB 55 (65.5) SA 7 (8.3) PL 21 (25) ND 1 (1.2)	NR	NR	BD 0	L
Retinoids								
Hospital UK Katugampola 2006 (Katugampola et al. 2006)	Case series 1974-2004 3 (2) children (fathers)	long-term	etretinate	LB 3	NR	NR	BD 0	L

Table 2. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
PBR* Norway Engeland 2012 (Engeland et al. 2013)	Cohort 2004-2011 80 singleton pregnancies	3 months prior to conception	isotretinoin / NR	NR	PB 7 OR (95% CI) 1.8 (0.81-3.8)	NR	BD 1	L
PBR* Denmark Norgaard 2019 (Nørgaard et al. 2019)	Cohort 1996-2016 244 pregnancies 205 children	3 months prior to conception and during first trimester	acitretin / NR	SA Adj. HR (95% CI) 0.76 (0.38-1.51)	NR	NR	BD	L
Systemic corticosteroids								
Hospital USA Penn 1971 (Penn at al. 1971)	Case series 1962-1970 19 males 23 pregnancies	Long-term	Prednisone	LB 19 SA 1 PL 3	NR	NR	BD 1	L
Hospital UK McGeown 1978 (McGeown et al. 1978)	Case series 8 males	long-term	Prednisolone	LB 11	GA 40.5 PB 0	BW 3741	BD 1	L

Table 2. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
TC* China Xu 2009 (Xu et al. 2009)	Case series 1981-2007 164 males	long-term	Prednisone	LB 167	PB 7	BW 3274±395	BD 1	L
PBR* Norway Engeland 2012 (Engeland et al. 2013)	Cohort 2004-2011 1477 singleton pregnancies	3 months prior to conception	Prednisolone	SA 4 OR (95% CI) 0.99 (0.37-2.6)	PB 93 OR (95% CI) 1.0 (0.84-1.3)	SGA 163 OR (95% CI) 1.1 (0.53-2.1)	Any BD 75 OR (95% CI) 0.99 (0.71-1.4) Serious BD 35 OR (95% CI) 0.99 (0.71-1.4)	L
PBR* Denmark Larsen 2017 (Larsen et al. 2018)	Cohort 1997-2013 2380 (1558:1, 822:2) / 1011614 live born children (singletons)	3 months prior to conception	Filled prescriptions for systemic corticosteroids 81% prednisone, 12% prednisolone / No filled prescriptions for systemic corticosteroids in one year prior to conception	NA	PB 1 presc. 92 (5.91) / 56677 (5.63) OR (95% CI) 1.02(0.79-1.33) Adj. OR (95% CI) 1.05 (0.80-1.37) PB ≥2 presc. 40 (4.87) 56677 (5.63) OR (95% CI) 0.81 (0.55-1.19) Adj. OR (95% CI) 0.81 (0.55-1.21)	SGA 1 presc. 56 (3.61) / 33987 (3.39) OR (95% CI) 1.11 (0.82-1.50) Adj. OR (95% CI) 1.13 (0.83-1.56) SGA ≥2 presc. 30 (3.66) / 33987 (3.39) OR (95% CI) 1.06 (0.70-1.61) Adj. OR (95% CI) 1.06 (0.68-1.64)	BD 1 presc. 83 (5.33) / 50170 (4.98) OR (95% CI) 1.08 (0.86-1.35) Adj. OR (95% CI) 1.08 (0.86-1.36) BD ≥2 presc. 51 (6.20) / 50170 (4.98) OR (95% CI) 1.28 (0.95-1.72) Adj. OR (95% CI) 1.33 (0.99-1.79)	H

Table 2. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
Thiopurines (AZA=azathioprine, 6MP=6-mercaptopurine)								
Hospital USA Penn 1971 (Penn at al. 1971)	Case series 1962-1970 19 males 23 pregnancies	Long-term	Azathioprine	LB 19 SA 1 PL 3	NR	NR	BD 1	L
Hospital Israel Ben-Neriah 2001 (Ben-Neriah et al. 2001)	Case report 1 male	long-term	Azathioprine or 6-mercaptopurine	LB 1	NR	NR	BD 1	NA
Hospital UK McGeown 1978 (McGeown et al. 1978)	Case series NR 8 males (13 pregnancies)	long-term	Azathioprine	LB 11 SA 1 SB 1	GA 40.5 PB 0	BW 3741	BD 1	L
TC* China Xu 2009 (Xu et al. 2009)	Case series 1981-2007 164 males	long-term	Azathioprine	LB 167	PB 7	BW 3274±395	BD 1	L

Table 2. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
Hospital USA Rajapakse 2000 (Rajapakse et al. 2000)	Cohort 1970-1997 13 / 90 pregnancies	3 months prior to conception and during the first trimester	6-Mercaptopurine / never taken 6MP or only after conception	SA 2 (15) / 2 (2.2)	NR	NR	BD 2 (15) / 0	L
Hospital Spain Teruel 2003 (Teruel et al. 2010)	Cohort 2007-2008 46 / 84 pregnancies	3 months prior to conception	37 Azathioprine or 9 - Mercaptopurine / no exposure to thiopurines in 3 months prior to conception	SA 5 / 7 OT 0 / 4	GA 38.9 / 39.4 PB 2 (4.3) / 2 (2.4)	BW 3063±533 / 3248±493 LBW 3 (6.5) / 5 (6.0)	BD 1 (2.2) / 2 (2.4)	H
Hospital USA Francella 2003 (Francella et al. 2003)	Cohort 1950-1997 37 / 73 pregnancies	at the time of conception	6-Mercaptopurine / pregnancies prior to treatment 6 MP	LB 30 / 62 SA 6 / 11 ET 1 / 0	PB 3 / 3	LBW 2 / 3	BD 1 / 2	L
TIS* Germany Hoeltzenbein 2012 (Hoeltzenbein et al. 2012)	Cohort 1988-2010 115 / 340 pregnancies	101 until conception or longer, others not specified	108 Azathioprine, 7 6-Mercaptopurine / pregnancies not exposed to teratogens and no paternal reported immunosuppressive drugs or otherwise risky treatment	LB 100 / 319 SA 9 / 24 ET 7 / 3 SB 0 / 1	GA 40 / 40 PB 7 (7) / 32 (10)	BW 3520 / 3400	BD major 3 / 7 minor 8 /13 genetic 0 / 5	L

Table 2. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
PBR* Denmark Norgard 2017 (Nørgård et al. 2017) Egeberg 2017 (Egeberg et al. 2017)	Cohort 1997-2013 699/ /1012624 live born children (singletons)	3 months prior to conception	At least one filled prescription of AZA or 6MP within 3 months before the date of conception / no filled prescription of AZA or 6MP within 3 months before the date of conception	NA	PB 35 (5.01) / 49966 (4.93) OR (95% CI) 0.94 (0.61-1.43) Adj. OR (95% CI) 1.17 (0.72-1.92)	SGA 23 (3.31) / 29803 (2.93) OR (95% CI) 1.18 (0.72-1.91) Adj. OR (95% CI) 1.38 (0.76-2.51)	BD 32 (4.58) / 48456 (4.79) OR (95% CI) 0.95 (0.66-1.38) Adj. OR (95% CI) 0.82 (0.53-1.28)	H
TNF-α inhibitors (INF=infliximab, ETN=etanercept, CZP=certolizumab pegol, ADA=adalimumab, GOL=golalinumab)								
Hospital Italy Lamboglia 2009 (Lamboglia et al. 2009)	Case report 1 male	at the time of conception	Infliximab	LB 1	NR	BW 2800	BD 0	NA
Hospital Greece Paschou 2009 (Paschou et al. 2009) Saougou 2013 (Saougou et al. 2013)	Case series 2001-2007 4 males (6 children) 2001-2010 11 males (14 children)	long-term	Infliximab	LB 6 LB 14 ET 1+	NR NR	NR NR	BD 0 BD 0	L L

Table 2. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
Hospital Turkey Uyaroglu 2017 (Uyaroglu et al. 2017)	Case series 2015-2016 42 males	at the time of conception	TNF-α Inhibitor	LB 38 SA 3 ET 1	GA 39 PB 4 (10.5)	BW 3229±582 LBW 4	BD 0	L
Hospital Italy Hoxha 2017 (Hoxha et al. 2017)	Case series 2008-2015 3 males	NR	Etanercept	LB 3	NR	NR	BD 0	L
TREAT registry USA Lichtenstein 2018 (Lichtenstein et al. 2018)	Case series 1999-2012 42 pregnancies	at the time of conception	Infliximab	LB 41 (97.6) SA 1 (2.4)	PB 1	NR	BD 1 (2.4)	L
MAH SD* Clowse 2015 (Clowse et al. 2015)	Case series up to 2014 46 pregnancies	at the time of conception	Certolizumab Pegol	LB 27 SA 4 ET 1 SB 1 PL 13	NS	NS	NS	L

Table 2. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects (BD, n(%))	QA*
PBR Denmark Larsen 2016 (Larsen et al. 2016)	Cohort 2007-2013 372 / 399498 live born children (singletons)	3 months prior to conception	TNF-α I: 155 Infliximab, 136 Adalimumab, 69 Etanercept, 11 Golimumab* 1 Certolizumab pegol	NA	PB 21 (5.65) / 21745 (5.44) OR (95% CI) 1.00 (0.57-1.75) Adj. OR (95% CI) 0.97 (0.54-1.76)	SGA 16 (4.32) / 11871 (2.98) OR (95% CI) 1.51 (0.84-2.71) Adj. OR (95% CI) 1.70 (0.94-31.09)	BD 21 (5.65) / 23244 (5.82) OR (95% CI) 0.97 (0.62-1.54) Adj. OR (95% CI) 0.92 (0.57-1.48)	H
Hospital Romania Micu 2019 (Micu et al. 2019)	Cohort 2012-2017 33 / 12142 pregnancies	long-term	TNF-α I / General population data	LB 30 (91) / 9667 (79.6) SA 0 / 1135 (9.4) ET 3 (9.0) / 1233 (10.2) SB 0 / 107 (0.9)	GA 37.57±1.01 / NS PB 6 (20.0) / 1074 (11.1)	BW 3390±343 / NS SGA 0 / 101 (1.0)	BD 0 / 140 (1.4)	L

Abbreviations in table:
H (high), L (low), NA (not applicable), NR (not reported), PBR (population based registry), presc. (prescriptions), TC (transplantation centre), TIS (Teratology Information Service)

- **Pregnancy and child outcomes**

No studies were identified.

- **Antimalarials (chloroquine, hydroxychloroquine)**

Sexual function, reproductive hormones and fertility

Four studies that included data from 37 healthy men were identified. One study reported sperm quality parameters and three studies evaluated the ability of chloroquine to cross the blood-testis barrier (39-42). As it is the case for other human tissues and fluids, chloroquine can be found on seminal plasma even after long-term withdrawal. One in-vitro study reported that high concentrations of chloroquine in seminal plasma inhibited sperm motility. No studies reporting these outcomes were identified for hydroxychloroquine.

- **Pregnancy and child outcomes**

No studies were identified.

Calcineurin Inhibitors (ciclosporine, sirolimus, tacrolimus)

Sexual function, reproductive hormones and fertility

Fifteen studies including a total of 263 cases and 229 controls were identified. All of these cases were receiving sirolimus or ciclosporine for organ transplantation (mainly kidney transplantation). In all 11 studies included, sperm quality abnormalities and reproductive hormonal alterations (low testosterone and high FSH/LH levels) were reported after sirolimus exposure (43-53). In addition, reversible infertility associated to sirolimus was reported in three studies. One prospective study reported that testosterone levels increased from baseline levels (pre-transplant) in an undefined number of patients using everolimus (54). Despite the lack of reproductive safety information for tacrolimus in humans, in these studies, patients were switched from sirolimus to tacrolimus and their sperm quality improved.

Nine post kidney transplant patients exposed to ciclosporine provided semen samples and no relevant sperm quality abnormalities were reported. From this group of patients, 3 out of 4 patients were able to conceive while being exposed to ciclosporine (48, 55). A prospective study that included pre and post kidney transplantation data of 10 men, reported that hypogonadism was present before initiating treatment with ciclosporine. After 12 months of ciclosporine exposure levels of testosterone exceeded pre-transplant levels (56). Sexual hormone levels were normal and comparable among 21 ciclosporine and 16 tacrolimus exposed renal transplant male patients (57). Similar

results were reported by others (58). Sperm concentration was inversely correlated to the ciclosporine whole blood levels in one study (59).

- **Pregnancy and child outcomes**

Six studies were aimed at determining the impact of the use of ciclosporine, tacrolimus or sirolimus on pregnancy and child-related outcomes. Transplant recipients used these medications often in combinations with other drugs.

Three case reports/case series and two transplantation registries found no abnormal outcomes (60-65). A population-based registry found a higher risk of birth defects although this was not statistically significant (15). Seven of the 67 children were diagnosed with a congenital anomaly (CA) after paternal use of ciclosporine. No details of the CAs were provided.

Colchicine

- **Sexual function, reproductive hormones and fertility**

Eight studies including a total of 166 cases were identified. Most of these studies were published before 2000. Colchicine exposure (1-2 mg/day) was associated with low sperm counts and motility in 5 studies (66-70). Abnormal sperm analysis were reported in 40-58% of patients exposed to colchicine (67, 70). One study reported normal cytogenic sperm analysis in 2 patients diagnosed with gout exposed to colchicine (71), one study reported no significant sperm analysis abnormalities in patients previously exposed to colchicine (72) and lastly, one study reported no significant sperm abnormalities in healthy volunteers exposed to colchicine (73). A possible adverse effect on sperm quality associated with disease activity was discussed in the most recent study by Kaya et al (70).

- **Pregnancy and child outcomes**

Three older studies from an Israeli hospital followed patients with FMF treated with colchicine (72, 74, 75). Only one study reported specific data on colchicine and spontaneous abortions (no increased risk) (75), the other studies did not report specific outcomes for colchicine treated patients.

Cyclophosphamide

- **Sexual function, reproductive hormones and fertility**

Twenty studies were identified, most of them included patients that were exposed to cyclophosphamide (CYC) to treat nephrotic syndromes associated with glomerulonephritis (73%). Most of these studies reported fertility outcomes from young

adults that were exposed to CYC during their childhood. Unfortunately, the mean age of these participants was not reported in many studies. From these studies, a clear negative effect on sperm quality and reproductive hormones, mainly causing low sperm counts and high FSH levels, from CYC is evident (76-94). Reversibility (improvement in sperm counts after CYC withdrawal) with a possible dose-dependent effect was a repetitive finding in some studies. Because of substantial methodological problems (selection bias, loss of follow up, no baseline samples) reversibility and a dose-dependent effect cannot be interpreted as conclusive evidence.

- **Pregnancy and child outcomes**

In 1983 a case report was published, a child was born with an absent hand after paternal exposure to cyclophosphamide and dexamethasone (95).

Interleukin inhibitors

- **Sexual function, reproductive hormones and fertility**

No studies were identified.

- **Pregnancy and child outcomes**

Three case series from different sources focused mainly on maternal exposures and briefly mentioned paternal exposures (96-98). The paternal exposures included 2 pregnancies on tocilizumab, one healthy liveborn and one spontaneous abortion, and 54 pregnancies on secukinumab. Outcomes were not available for 20 pregnancies (13 pending and 24 lost to follow up), known outcomes were 29 liveborn with one malformation, 4 spontaneous abortions and one elective termination (82).

Younstein et al reported 6 children with paternal exposure of anakinra and 5 children with paternal exposure of canakinumab, no malformations were reported (81).

Methotrexate

- **Sexual function, reproductive hormones and fertility**

Six studies reporting fertility outcomes in patients exposed to methotrexate (MTX) were identified. These studies included a total of 47 cases (40 men diagnosed with psoriasis and 7 with IMD) and 1912 controls (all controls come from one study (99)). In patients exposed to MTX sperm concentration decreased in three studies (100-102), no differences were reported in two studies (one study reported five normal testicular biopsies after MTX exposure) (99, 103) and the sperm quality of one group of patients diagnosed with psoriasis and exposed to MTX was better than patients treated with high dose glucocorticoids (104).

- **Pregnancy and child outcomes**

Three case reports from the 20th century reported only healthy liveborn children (105-107). More recent case series and cohort studies (169 pregnancies and 193 liveborn children) found no increased risk of birth defects associated with paternal MTX exposure (1, 108-111). This also applies to the rate of spontaneous abortions, preterm birth and small for gestational age (110-112).

Friedman et al used the Danish registries to look at long term outcomes and no negative impact of paternal preconception use of MTX was reported (113).

Mycophenolate acid products

- **Sexual function, reproductive hormones and fertility**

No studies were identified

- **Pregnancy and child outcomes**

Four data sources have published data with 295 pregnancies and 189 children included; three registries, two population-based and one pregnancy transplantation, and medical records from one hospital in Spain (15, 60, 114-117). No major differences were found compared to transplantation patients not taking mycophenolate acid products (MPA). In these studies, MPA was often used in combination with calcineurin inhibitors and corticosteroids.

NSAIDs

- **Sexual function, reproductive hormones and fertility**

For NSAIDs as a group, no studies were identified in our population of interest. Nonetheless, 6 studies that included healthy participants were identified. Exposure to salicylate decreased sperm motility and for naproxen one study concluded that sperm quality abnormalities were similar between pre and post exposed samples (118-120). A study from Kristensen et al concluded that ibuprofen exposure results in a state of compensated hypogonadism (121). One in vitro study using adult human testis explants demonstrated that exposure to indomethacin and aspirin altered the production of testosterone by Leydig cells (122).

- **Pregnancy and child outcomes**

No studies were identified.

Retinoids (Acitretin/Etretinate/Isotretinoin)

- **Sexual function, reproductive hormones and fertility**

Eight studies that included a total of 203 cases and 20 controls were identified (123-130). Low concentrations of retinoids that are unlikely associated with a teratogenic risk can be found in seminal plasma of exposed patients (124). No negative effect on sperm quality was reported in four studies (130 exposed men). Sexual dysfunction in the form of ejaculatory failure and erectile dysfunction associated with acitretin has been reported (130).

- **Pregnancy and child outcomes**

Three studies report paternal retinoid use and pregnancy-related outcomes. Two included only liveborn children. A long term general follow up study after etretinate use, with 18 male patients, found three healthy children (131). Population-based registries from Norway found a higher risk (OR (95%CI) 1.8 (0.81-3.8) for preterm birth (live birth after at least 22 and prior to 37 weeks of gestation) based on 80 isotretinoin cases (1). Based on population-based registries a study from Denmark found no risk for spontaneous abortion after acitretin use (14).

Systemic corticosteroids

- **Sexual function, reproductive hormones and fertility**

Two studies were identified. In a study from 1956, seven patients diagnosed with rheumatoid arthritis (RA) were treated with 75 mg of cortisone over periods ranging from 23 to 334 days. Pre and post-treatment testicular biopsies were performed in 6 patients in which no significant changes were reported (132). In a small study that included 36 men with long standing active RA, the use of prednisone at doses ranging from 5 to 10 mg/day was associated with significantly lower testosterone levels and lower levels of FSH and LH compared to men with long standing RA but without prednisone treatment (133). Because of the scope of our SR, studies that reported the effect of corticosteroids on the male reproductive health of healthy controls were excluded. A review on this topic can be found elsewhere (134).

- **Pregnancy and child outcomes**

A high number of cases is reported in the PBRs of Norway and Denmark. Data from Norway refer to prednisolone (1). No drug-specific information about systemic corticosteroids in the Danish data was available and both registries have no information about the used dose or indication. Larsen only found a higher risk in the Danish registries, although

not statistically significant, after 1 or 2 redeemed prescriptions for birth defects (135). Smaller numbers are reported in transplantation patients (136-138).

Thiopurines

- **Sexual function, reproductive hormones and fertility**

Four studies that included a total of 75 cases and 40 controls exposed to azathioprine were included (139-142). Sperm quality, sperm DNA fragmentation index and the male endocrine reproductive axis appear not to be negatively affected by azathioprine exposure.

- **Pregnancy and child outcomes**

Azathioprine is the most frequently reported thiopurine followed by 6-mercaptopurine. The first hospital case series were reported in the 1970s. (136, 138). In the early 2000s, other case series followed and the largest study up to now was based on the Danish registries from 2017. No differentiation between the two drugs was made (64, 137, 143-147). In total 192 males, 211 pregnancies and 669 children were included in these studies. Overall no increased risks were detected.

Friedman et al used the Danish registries to look at long term outcomes and no negative impact of paternal preconception use of azathioprine or 6-mercaptopurine was reported (113).

TNF- α inhibitors

- **Sexual function, reproductive hormones and fertility**

We identified fifteen studies that evaluated the effect of TNF-α inhibitors on male sexual health. Thirteen studies reported fertility/sperm quality outcomes, one study reported sexual function as an outcome (148) and priapism secondary to the use of adalimumab was reported in one case report (149). In total, outcomes of interest were reported in 156 men diagnosed with ankylosing spondylitis (AS), psoriasis, RA and IBD exposed to TNF-α inhibitors and in 225 men that participated in these studies as healthy controls.

Regarding sperm quality before and after TNF- α inhibitor use, one small randomized control trial (RCT) that included data of 20 men concluded that certolizumab pegol had no adverse event on sperm quality compared to placebo (150). In studies where a comparison between baseline samples before TNF- α inhibitor exposure and follow up samples were available; no differences on sperm quality were reported in five studies (151-155), in three studies sperm quality improved after exposure (156-158) and in

one study sperm quality worsened after exposure (159). A possible positive effect on sperm quality using TNF-α inhibitors could be the result of decreasing disease activity in patients with AS. These findings should not be extrapolated into other diseases until more research is available.

One study showed that exposure to TNF- α inhibitors in a group of men diagnosed with AS resulted in improvement of sexual function scores (148).

- **Pregnancy and child outcomes**

Eight small studies and one large population-based cohort were identified (16, 107, 155, 160-165). In total 61 males, 121 pregnancies and 372 children were included. Overall no increased risk was found. Larsen found a higher risk for Small for Gestational Age (SGA) based on 16 cases, although this was not statistically significant.

Verdolizumab

- **Sexual function, reproductive hormones and fertility**

One study from Denmark that included data on 15 male patients diagnosed with IBD with a mean age of 33 years and 40 healthy controls with a mean age of 23 years was identified. After exposure to verdolizumab the sperm DNA fragmentation index (DFI) was similar among the two groups (166).

- **Pregnancy and child outcomes**

No studies were identified.

Other selective immunosuppressants

- **Pregnancy and child outcomes**

All publications contained mostly maternal exposure cases and briefly mention paternal exposures. The results for the paternal exposure were; one case report on leflunomide reported a healthy child (167). And two case series from the industry on abatacept (10 pregnancies) and tofacitinib (84 pregnancies) revealed no safety concerns (168, 169).

Immunosuppressive drugs without available information

For many immunosuppressive drugs, no studies were identified. In table 3 the most relevant immunosuppressive drugs where no available data was available are presented.

Table 3. Immunosuppressive drugs included in the search strategy without studies included in the final data analysis.

Sexual function, reproductive hormones and fertility.		Pregnancy outcomes	
Anakinra	JAK inhibitors	Apremilast	JAK inhibitors
Apremilast	Leflunomide	Belimumab	NSAIDs
Belimumab	Rituximab	Canakinumab	Rituximab
Canakinumab	Ruxolitinib	COX 2 inhibitors	Ruxolitinib
Human immunoglobulin	Secukinumab	Everolimus	Sulfasalazine
Hydroxychloroquine	Tacrolimus	Human immunoglobulin	Tioguanine
Ixekizumab	Tocilizumab	Ixekizumab	Tocilizumab

Treatment of antisperm antibodies

Antisperm antibodies are considered as an important cause of male infertility and often are associated with autoimmunity. Although not included in the original scope of our systematic review, we identified a considerable amount of studies regarding the treatment of antisperm antibodies (mainly associated with male infertility) using glucocorticoids. These studies reported mixed results and overall the risks associated with glucocorticoid therapy outweighed the benefits. In-depth information can be found elsewhere (134).

DISCUSSION

Summary of evidence

Sexual function, reproductive hormones and fertility

Regarding sexual function, reproductive hormones and fertility, most of the available information focuses on the effect of immunosuppressive drugs on male fertility (specifically on sperm quality). Less information was available for sexual function or reproductive hormones.

Based on the available information on the effect of immunosuppressive drugs on male sexual function, reproductive hormones and fertility the following classification is provided:

- **No negative effect:** Acitretin, azathioprine, ciclosporine, isotretinoin, TNF-α inhibitors, verdolizumab.
- **Negative effect:** Cyclophosphamide, sirolimus, sulfasalazine.
- **Unclear effect:** Chloroquine, colchicine, methotrexate, NSAID's, systemic glucocorticoids.

Worth mentioning, TNF-α plays an important role in spermatogenesis and testicular homeostasis, one of the main findings for this group of drugs is that disease activity itself might play a role in baseline sperm quality characteristics and on the subsequent effect that TNF- α inhibitors have on sperm quality. At least for patients diagnosed with ankylosing spondylitis, TNF-α inhibitors appear to have a positive effect on sperm quality. As it is the case for most of the drugs included in this systematic review, further research is needed.

Disease activity was taken into consideration in the study design of a few studies. By doing this, authors showed that disease activity can also induce sperm abnormalities (33, 70, 158). Considering that IMDs have different inflammatory phenotypes, the effect of disease activity could be an important confounder in future studies on the impact of medications on sperm quality.

Pregnancy and child outcomes

Regarding pregnancy and child outcomes, we found no clear evidence to support restriction in the prescription these drugs. Although the number of patients is low in case reports/series and in small cohorts. In some cases detailed information is available. In contrast, in population-based registries, predominantly from Denmark, larger numbers of patients have been reported. In these populations, ORs or HRs can be calculated but they lack important detailed information about the used dose, indication and co-medication use.

Findings

Sexual function, reproductive hormones and fertility.

The effect of many immunosuppressive drugs on sexual function, reproductive hormones and fertility have not been properly evaluated. Many factors can contribute to this situation, for example; sperm samples are needed to evaluate sperm quality and this may lead to many logistic problems. In addition, there is a general misconception that male contributions to pregnancy are not important, which can contribute to a lack of interest by researchers and clinicians.

Furthermore, the effect of immunosuppressive drugs on sexual function, reproductive hormones and fertility cannot be studied separately. Multiple factors are interconnected in this process and should be considered in clinical practice and in future research.

Pregnancy and child outcomes.

The possible influence of paternal exposure before conception on pregnancy and child outcomes is also a neglected topic. In the last years, the number of publications is increasing. In most cases, these studies include maternal and paternal exposures with little attention to the outcomes secondary to paternal exposure. Most of the times no in-depth details of the paternal cases were available.

Strengths and limitations

The strengths of this study are based on the design and conduction of the SR. It followed strict pre-specified and reproducible methods. A comprehensive search strategy was developed to summarize the available information on many aspects of sexual health and reproduction. We did not restrict the search to a specific disease or drug (group) but tried to compile information about all important drug (groups) used for several IMDs. Systematic reviews can also demonstrate where knowledge is lacking and we consider that this is another major strength of this SR. Major areas of opportunities for future research regarding this topic were identified.

Unfortunately, several limitations should be addressed; most of the studies included small numbers of patients and controls. In addition, studies about sexual function, reproductive hormones and fertility in men with IMDs suffer from an inconsistent methodological quality, disease activity was not evaluated as a potential confounder in many studies and relevant comorbidities that also have a direct effect on these outcomes were not reported in all studies. Results might only apply to the specific populations studied.

Importantly, our findings should be interpreted with caution since a significant proportion of our included studies are case reports and small case series that tend to overestimate the outcomes of interest.

Regarding the pregnancy and child outcomes the level of detail and specific information that is available in the publications needs to improve.

In this review no animal studies were included. Animal studies show effects on reproductive outcomes for drugs like methotrexate and thiopurines (170, 171). Outcomes of animal studies are not always predictive for humans. Based on these outcomes and in addition to the lack of well documented human paternal exposures in large studies, a restrictive wording is placed in the SmPCs by the regulatory agencies.

Research recommendations

For many immunosuppressive drugs that are prescribed to millions of men with IMD such as methotrexate or hydroxychloroquine, the possibility of reevaluating their reproductive toxicity is of major importance and should be discussed. Semen analysis is still considered to be the most valid method to evaluate testicular toxicity in humans. Ideally, RCTs, case-control well-designed prospective cohort studies should be designed to reach conclusive evidence.

While experimental studies are not ethical for assessing reproductive toxicity, observational studies such as those utilizing case control or cohort designs may be and should be considered. As a rule of thumb, if no increased incidence of malformations is observed within at least 1000 first trimester exposed prospectively collected pregnancies, a conclusion might be reached that the drug of interest is not responsible for a 2-fold or more increase of the overall incidence of malformations (172).

Several factors such as the number of exposed patients, the incidence of the outcome in the unexposed control group, the minimum relative risk to be detected, and the ratio of unexposed control to exposed study subjects can affect the power of a cohort study and should be considered during the early stages of a study design (Strom 2020).

Focusing only on the prevalence of exposure and in order to put this into perspective, for frequently used drugs (>10% of the population) such as paracetamol, smaller sample sizes are needed to detect an increased risk of congenital malformations. For such drugs, the required sample size ranges from approximately 8,140 participants in a population cohort study to 614 participants in a case-control study. This range increases drastically for less frequently used drugs such as rituximab (<1% of the population), where approximately 814,000 participants are needed in population cohort studies to 51,116 participants in case-control studies.

Based on these recommendations and following the example of the large Scandinavian cohorts here presented, collecting prospective data on current paternal exposures should be strongly recommended considered for future research on this topic. In the meantime, health care professionals should think about these potential adverse events and intervene appropriately (see table 4 with research recommendations-standardization).

Recently it has been shown that disease activity can also impair fertility in men with rheumatic diseases (33, 70, 158, 173). In consequence, it is very important to start focusing on developing well designed epidemiological studies where study design and data analysis consider how, together, diseases and drugs, can affect sexual health and reproduction.

Table 4. Research recommendations to conduct future research on these topics.

Sexual function	Use standardized screening questionnaires (IIEF). Case-control studies and well-designed prospective cohort studies are encouraged over cross-sectional studies. Consider relevant comorbidities and potential confounders (Depression, anxiety, disease activity).
Sperm quality	Use standardized methods to report sperm quality (WHO) (primary endpoint). DNA fragmentation index could provide more information regarding male fertility potential and should be considered as a secondary endpoint. Ideally, technicians should be blinded regarding the drug-exposure. RCTs are ideal but case-control and well-designed prospective cohort studies are also encouraged over cross-sectional studies. Consider disease activity, relevant co-medication, comorbidities and potential confounders (Age, smoking, varicocele)
Reproductive hormones	Use standardized methods to measure hormones. RCTs are ideal but case-control and well-designed prospective cohort studies are also encouraged over cross-sectional studies. Consider disease activity, relevant comorbidities and potential confounders (Age, co-medication)
Pregnancy and offspring outcomes	Collect data prospectively or report cases with all the relevant information. For instance: Source of the information, indication, disease activity, clear description of medication use and timing (including co medication), paternal age. Regarding pregnancy/child outcome; pregnancy outcome, gestational age, birthweight, infant health, genetic testing, follow up period, Partner's relevant medical history.

To improve the overall quality of research on this topic a call to action initiative that gets scientists from many different fields involved in the topic is needed. This could result in an organized plan to study and report future research.

Furthermore, access to information is more important than ever since effective communication has become an essential part of the treatment shared decision process between health care professionals and patients. Therefore, discussing the possible effect(s) of immunosuppressive drugs on male sexual health and reproduction should be considered for every man, irrespective of whether they have a wish to become a father or not.

CONCLUSION

There is little scientific evidence regarding the potential adverse events on male sexual function, reproductive hormones and fertility of many of the commonly used immunosuppressive drugs. Most of the included studies are heterogeneous and cannot be generalized to a wider population. With a lack of conclusive evidence, it is expected that clinicians and patients are confronted with difficult treatment decisions.

The results of this systematic review did not reveal major safety issues concerning paternal exposure to immunosuppressive drugs. Although, we have to keep in mind that the numbers are low and an increased risk cannot be excluded. Well designed and fully powered observational cohort studies with longitudinal data should be conducted to properly label these drugs. In cases where the number of patients included in a study is considered to be too low to reach adequate power, researchers should use standardized methods to measure outcomes of interest, ensure the quality of the collected variables and report their findings according to the STROBE statement (Vandenbroucke et al. 2007; von Elm et al. 2008). This will provide the scientific community with valuable information and allow it to perform meta-analyses in the future.

In cases of men with a wish to become a father, the sometimes very restrictive wording in the SmPC might not be necessary. In the meantime, in case the patient wishes to become a father, clinicians must discuss the pros and cons of stopping or changing drug treatment. The potential negative effect of the disease on reproductive outcomes and potential flares need to be weight against theoretical concerns of the drug effects.

Supplementary data

Supplementary Table 1. Search strategies.
Immunosuppressive drugs male fertility

Databases	Number of Refs	Refs after de-duplication
embase.com	2366	2332
Medline Ovid	2023	1020
Cochrane CENTRAL	163	92
Web of science	1315	760
Total	**5867**	**4204**

Adjustment of search query based on comments from LP and BW in document "aanvullende publicaties SR Drugs (003).rtf" (now the 4 missing references and the 5 new references are included in the new search):

- removed drug teriflunomide
- 2 out of the 4 missed references from the document are "letters". The "letter" restriction has been removed
- Added: ((successful*) NEAR/1 (paternit*))
- Added: paternal-drug-exposure*
- Added drug: 'bosutinib'/mj and bosutinib*
- Added wildcard in "tumo*r-necrosis-factor*" to account for spelling variation

embase.com 2366
('calcineurin inhibitor'/exp/mj OR 'disease modifying antirheumatic drug'/exp/mj OR gold/exp/mj OR '15 deoxyspergualin'/mj OR '3 aurothio 2 hydroxy 1 propanesulfonate calcium'/mj OR 'azapropazone'/mj OR 'abatacept'/mj OR 'abetimus'/mj OR 'aceclofenac'/mj OR 'acemetacin'/mj OR 'adalimumab'/mj OR 'afelimomab'/mj OR 'alclofenac'/mj OR 'alefacept'/mj OR 'alitretinoin'/mj OR 'alminoprofen'/mj OR 'anakinra'/mj OR 'apremilast'/mj OR 'auranofin'/mj OR 'aurothioglucose'/mj OR 'aurothiomalate'/mj OR 'azathioprine'/mj OR 'balsalazide'/mj OR 'baricitinib'/mj OR 'basiliximab'/mj OR 'beclometasone'/mj OR 'belatacept'/mj OR 'belimumab'/mj OR 'benoxaprofen'/mj OR 'benzydamine'/mj OR 'betamethasone'/mj OR 'bosutinib'/mj OR 'briakinumab'/mj OR 'brodalumab'/mj OR 'budesonide'/mj OR 'bufexamac'/mj OR 'bumadizone'/mj OR 'canakinumab'/mj OR 'celecoxib'/mj OR 'certolizumab pegol'/mj OR 'chloroquine'/mj OR 'clofezone'/mj OR 'cloprednol'/mj OR 'colchicine'/mj OR 'cortisone'/mj OR 'cortivazol'/mj OR 'cyclophosphamide'/mj OR 'ciclosporine'/mj OR 'deflazacort'/mj OR 'dexamethasone'/mj OR 'dexibuprofen'/mj OR 'dexketoprofen'/mj OR 'diacerein'/mj OR 'diclofenac'/mj OR 'diphenpyramide'/mj OR 'droxicam'/mj OR 'eculizumab'/mj OR 'efalizumab'/mj OR 'etanercept'/mj OR 'etodolac'/mj OR 'etoricoxib'/mj OR 'etretin'/mj OR 'everolimus'/mj OR 'fenbufen'/mj OR 'fenoprofen'/mj OR 'fentiazac'/mj OR 'feprazone'/mj OR 'flufenamic acid'/mj OR 'flunoxaprofen'/mj OR 'fluocortolone'/mj OR 'flurbiprofen'/mj OR 'glycosaminoglycan polysulfate'/mj OR 'golimumab'/mj OR 'guselkumab'/mj OR 'hydrocortisone'/mj OR 'hydroxychloroquine'/mj OR 'ibuprofen'/mj OR 'ibuproxam'/mj OR 'indometacin'/mj OR 'indoprofen'/mj OR 'infliximab'/mj OR 'isotretinoin'/mj OR 'ixekizumab'/mj OR 'kebuzone'/mj OR 'ketoprofen'/mj OR 'ketorolac'/mj OR 'leflunomide'/mj OR 'lenalidomide'/mj OR 'lonazolac'/mj OR 'lornoxicam'/mj OR 'lumiracoxib'/mj OR 'lymphocyte antibody'/mj OR 'meclofenamic acid'/mj OR 'mefenamic acid'/mj OR 'meloxicam'/mj OR 'meprednisone'/mj OR 'mercaptopurine'/mj OR 'mesalazine'/mj OR 'methotrexate'/mj OR 'methylprednisolone'/mj OR 'mofebutazone'/mj OR 'morniflumate'/mj OR 'mycophenolic acid'/mj OR 'nabumetone'/mj OR 'naproxen'/mj OR 'natalizumab'/mj OR 'nelarabine'/mj OR 'niflumic acid'/mj OR 'nimesulide'/mj OR 'OKT 3'/mj OR 'olsalazine'/mj OR 'omalizumab'/mj OR 'oxaceprol'/mj OR 'oxametacin'/mj OR 'oxaprozin'/mj OR 'oxyphenbutazone'/mj OR 'paramethasone'/mj OR 'parecoxib'/mj OR 'phenylbutazone'/mj OR 'pirfenidone'/mj OR 'piroxicam'/mj OR 'pirprofen'/mj OR 'polmacoxib'/mj OR 'pomalidomide'/mj OR 'prednisolone'/mj OR 'prednisone'/mj OR 'prednylidene'/mj OR 'proglumetacin'/mj OR 'proquazone'/mj OR 'rapamycin'/mj OR 'rilonacept'/mj OR 'rituximab'/mj OR 'rofecoxib'/mj OR 'ruxolitinib'/mj OR 'salazosulfapyridine'/mj OR 'sarilumab'/mj OR 'secukinumab'/mj OR 'siltuximab'/mj OR 'sirukumab'/mj OR 'sulindac'/

mj OR 'superoxide dismutase'/mj OR 'suprofen'/mj OR 'tacrolimus'/mj OR 'tenidap'/ mj OR 'tenoxicam'/mj OR 'thalidomide'/mj OR 'tiaprofenic acid'/mj OR 'tioguanine'/mj OR 'tixocortol'/mj OR 'tocilizumab'/mj OR 'tofacitinib'/mj OR 'tolfenamic acid'/mj OR 'tolmetin'/ mj OR 'triamcinolone'/mj OR 'ustekinumab'/mj OR 'valdecoxib'/mj OR 'vedolizumab'/ mj OR 'voclosporin'/mj OR 'zomepirac'/mj OR (((Calcineurin* OR Interleukin*) NEAR/3 inhibitor*) OR ((Glucocorticoid* OR NSAID*) NEAR/3 systemic) OR ((Non-Steroid* OR NonSteroid*) NEAR/3 (Anti-Inflammato* OR AntiInflammato*) NEAR/3 (systemic)) OR (gold NEAR/3 preparation*) OR Thiopurine* OR ((tumo*r-necrosis-factor* OR TNF) NEAR/3 inhibitor*) OR abatacept* OR abetimus* OR aceclofenac* OR acemetacin* OR acitretin* OR adalimumab* OR afelimomab* OR alclofenac* OR alefacept* OR alemtuzunab* OR alitretinoin* OR alminoprofen* OR anakinra* OR ((antilymphocyte* OR anti-lymphocyte*) NEAR/3 immunoglobulin*) OR apremilast* OR auranofin* OR aurothioglucose* OR aurotioprol* OR azapropazone* OR azathioprine* OR balsalazide* OR baricitinib* OR basiliximab* OR beclometasone* OR belatacept* OR belimumab* OR benoxaprofen* OR benzydamine* OR betamethasone* OR bosutinib* OR briakinumab* OR brodalumab* OR budesonide* OR bufexamac* OR bumadizone* OR canakinumab* OR celecoxib* OR certolizumab-pegol* OR chloroquine* OR ciclosporin* OR clofezone* OR cloprednol* OR colchicine* OR cortisone* OR cortivazol* OR cyclophosphamide* OR deflazacort* OR dexamethasone* OR dexibuprofen* OR dexketoprofen* OR diacerein* OR diclofenac* OR difenpiramide* OR droxicam* OR eculizumab* OR efalizumab* OR etanercept* OR etodolac* OR etoricoxib* OR everolimus* OR everolimus* OR fenbufen* OR fenoprofen* OR fentiazac* OR feprazone* OR flufenamic-acid* OR flunoxaprofen* OR fluocortolone* OR flurbiprofen* OR fumaric-acid-derivate* OR (glucosaminoglycan* NEAR/3 polysulfate*) OR golimumab* OR guselkumab* OR gusperimus* OR hydrocortisone* OR hydroxychloroquine* OR ibuprofen* OR ibuproxam* OR (immunoglobulin NEAR/3 intravasular*) OR indometacin* OR indoprofen* OR infliximab* OR isotretinoine* OR ixekizumab* OR kebuzone* OR ketoprofen* OR ketorolac* OR leflunomide* OR lenalidomide* OR lonazolac* OR lornoxicam* OR lumiracoxib* OR meclofenamic-acid* OR mefenamic-acid* OR meloxicam* OR meprednisone* OR mercaptopurine* OR mesalazine* OR methotrexate* OR methylprednisolone* OR mofebutazone* OR morniflumate* OR muromonab-CD3* OR mycophenolic-acid* OR nabumetone* OR naproxen* OR natalizumab* OR nelarabine* OR niflumic-acid* OR nimesulide* OR olsalazine* OR omalizumab* OR orgotein* OR oxaceprol* OR oxametacin* OR oxaprozin* OR oxyphenbutazone* OR paramethasone* OR parecoxib* OR phenylbutazone* OR pirfenidone* OR piroxicam* OR pirprofen* OR polmacoxib* OR pomalidomide* OR prednisolone* OR prednisone* OR prednylidene* OR proglumetacin* OR proquazone* OR rilonacept* OR rituximab* OR rofecoxib* OR ruxolitinib* OR sarilumab* OR secukinumab* OR siltuximab* OR sirolimus* OR sirukumab* OR (sodium NEXT/1 (aurothiomalate* OR sodium-aurotiosulfate*)) OR sulfasalazine* OR sulindac* OR suprofen* OR tacrolimus* OR tenidap* OR tenoxicam* OR thalidomide* OR tiaprofenic-acid* OR tioguanine* OR tixocortol* OR tocilizumab* OR tofacitinib* OR tolfenamic-acid* OR tolmetin* OR triamcinolone* OR ustekinumab* OR valdecoxib* OR vedolizumab* OR voclosporin* OR zomepirac* OR paternal-drug-exposure*):ab,ti) AND ('male fertility'/ exp OR 'male infertility'/exp OR 'sperm quality'/exp OR 'spermatozoon count'/de OR 'spermatozoon motility'/de OR 'spermatozoon'/exp OR spermatogenesis/exp OR sperm/ exp OR 'semen analysis'/de OR (((male OR man OR men) NEAR/6 (fertil* OR infertil* OR subfertil* OR reproducti* OR steril*)) OR aspermi* OR asthenospermi* OR azoospermi* OR oligospermi* OR ejaculat* OR ((sperm* OR semen OR seminal) NEAR/6 (count* OR motility OR abnormal* OR qualit* OR morpholog* OR dna OR characteristic* OR function* OR activit* OR damage OR analy*)) OR spermatoz* OR spermatogen* OR aspermatogen* OR ((successful*) NEAR/1 (paternit*))):ab,ti OR (('paternal exposure'/exp OR 'father'/exp OR (paternal OR father* OR ((male OR men OR man OR paternal*) NEAR/6 (exposure OR drug OR medication OR patient*))):ab,ti) AND ('pregnancy outcome'/exp OR 'sexual dysfunction'/ exp OR 'newborn disease'/exp OR 'congenital disorder'/exp OR 'pregnancy disorder'/exp OR 'labor complication'/exp OR 'placenta'/exp OR 'reproduction'/de OR Childbirth/exp OR Conception/exp OR 'prenatal development'/exp OR 'progeny'/exp OR infertility/de OR 'induced abortion'/de OR (((pregnan* OR obstetr* OR labor OR labour) NEAR/3 (outcome* OR disorder* OR complication*)) OR (sexual* NEAR/3 dysfunction*) OR (Erect* NEAR/3 Dysfunct*) OR (impoten* NEAR/3 vascul*) OR dyspareun* OR (Prematur* NEAR/3 ejaculat*) OR placenta* OR ((newborn* OR neonat* OR fetus OR fetal OR foetus OR foetal) NEAR/3

(health* OR disease OR death)) OR 'birth weight' OR birthweight OR lbw OR vlbw OR elbw OR (small NEAR/3 (date OR gestation*)) OR congenital* OR preeclamp* OR eclamp* OR miscarriag* OR abort* OR reproduct* OR Childbirth* OR Conception* OR progeny OR offspring OR (prenatal* NEAR/3 develop*)):ab,ti))) NOT ([animals]/lim NOT [humans]/lim) NOT (([Conference Abstract]/lim AND [1800-2016]/py) OR [Note]/lim OR [Editorial]/lim) AND [english]/lim NOT ([animals]/lim NOT [humans]/lim)

Medline Ovid 2023

(Abatacept/ OR Acitretin/ OR Adalimumab/ OR Antilymphocyte Serum/ OR Apazone/ OR Auranofin/ OR Aurothioglucose/ OR Azathioprine/ OR Beclomethasone/ OR Benzydamine/ OR Betamethasone/ OR Budesonide/ OR Bufexamac/ OR Celecoxib/ OR Certolizumab Pegol/ OR Chloroquine/ OR Colchicine/ OR Cortisone/ OR Cyclophosphamide/ OR Ciclosporine/ OR Cyclosporins/ OR Dexamethasone/ OR Diclofenac/ OR Etanercept/ OR Etodolac/ OR Everolimus/ OR Fenoprofen/ OR Feprazone/ OR Flufenamic Acid/ OR Fluocortolone/ OR Flurbiprofen/ OR Gold/ OR Gold Compounds/ OR Gold Sodium Thiomalate/ OR Hydrocortisone/ OR Hydroxychloroquine/ OR Ibuprofen/ OR Indomethacin/ OR Indoprofen/ OR Infliximab/ OR Interleukin 1 Receptor Antagonist Protein/ OR Isotretinoin/ OR Ketoprofen/ OR Ketorolac/ OR Meclofenamic Acid/ OR Mefenamic Acid/ OR Mercaptopurine/ OR Mesalamine/ OR Methotrexate/ OR Methylprednisolone/ OR Mycophenolic Acid/ OR Naproxen/ OR Natalizumab/ OR Niflumic Acid/ OR Omalizumab/ OR Oxyphenbutazone/ OR Paramethasone/ OR Phenylbutazone/ OR Piroxicam/ OR Prednisolone/ OR Prednisone/ OR Rituximab/ OR Sirolimus/ OR Sulfasalazine/ OR Sulindac/ OR Superoxide Dismutase/ OR Superoxide Dismutase-1/ OR Suprofen/ OR Tacrolimus/ OR Thalidomide/ OR Thioguanine/ OR Tolmetin/ OR Triamcinolone/ OR Ustekinumab/ OR (((Calcineurin* OR Interleukin*) ADJ3 inhibitor*) OR ((Glucocorticoid* OR NSAID*) ADJ3 systemic) OR ((Non-Steroid* OR NonSteroid*) ADJ3 (Anti-Inflammato* OR AntiInflammato*) ADJ3 (systemic)) OR (gold ADJ3 preparation*) OR Thiopurine* OR ((Tumo*r-necrosis-factor* OR TNF) ADJ3 inhibitor*) OR abatacept* OR abetimus* OR aceclofenac* OR acemetacin* OR acitretin* OR adalimumab* OR afelimomab* OR alclofenac* OR alefacept* OR alemtuzunab* OR alitretinoin* OR alminoprofen* OR anakinra* OR ((antilymphocyte* OR anti-lymphocyte*) ADJ3 immunoglobulin*) OR apremilast* OR auranofin* OR aurothioglucose* OR aurotioprol* OR azapropazone* OR azathioprine* OR balsalazide* OR baricitinib* OR basiliximab* OR beclometasone* OR belatacept* OR belimumab* OR benoxaprofen* OR benzydamine* OR betamethasone* OR bosutinib* OR briakinumab* OR brodalumab* OR budesonide* OR bufexamac* OR bumadizone* OR canakinumab* OR celecoxib* OR certolizumab-pegol* OR chloroquine* OR ciclosporin* OR clofezone* OR cloprednol* OR colchicine* OR cortisone* OR cortivazol* OR cyclophosphamide* OR deflazacort* OR dexamethasone* OR dexibuprofen* OR dexketoprofen* OR diacerein* OR diclofenac* OR difenpiramide* OR droxicam* OR eculizumab* OR efalizumab* OR etanercept* OR etodolac* OR etoricoxib* OR everolimus* OR everolimus* OR fenbufen* OR fenoprofen* OR fentiazac* OR feprazone* OR flufenamic-acid* OR flunoxaprofen* OR fluocortolone* OR flurbiprofen* OR fumaric-acid-derivate* OR (glucosaminoglycan* ADJ3 polysulfate*) OR golimumab* OR guselkumab* OR gusperimus* OR hydrocortisone* OR hydroxychloroquine* OR ibuprofen* OR ibuproxam* OR (immunoglobulin ADJ3 intravasular*) OR indometacin* OR indoprofen* OR infliximab* OR isotretinoine* OR ixekizumab* OR kebuzone* OR ketoprofen* OR ketorolac* OR leflunomide* OR lenalidomide* OR lonazolac* OR lornoxicam* OR lumiracoxib* OR meclofenamic-acid* OR mefenamic-acid* OR meloxicam* OR meprednisone* OR mercaptopurine* OR mesalazine* OR methotrexate* OR methylprednisolone* OR mofebutazone* OR morniflumate* OR muromonab-CD3* OR mycophenolic-acid* OR nabumetone* OR naproxen* OR natalizumab* OR nelarabine* OR niflumic-acid* OR nimesulide* OR olsalazine* OR omalizumab* OR orgotein* OR oxaceprol* OR oxametacin* OR oxaprozin* OR oxyphenbutazone* OR paramethasone* OR parecoxib* OR phenylbutazone* OR pirfenidone* OR piroxicam* OR pirprofen* OR polmacoxib* OR pomalidomide* OR prednisolone* OR prednisone* OR prednylidene* OR proglumetacin* OR proquazone* OR rilonacept* OR rituximab* OR rofecoxib* OR ruxolitinib* OR sarilumab* OR secukinumab* OR siltuximab* OR sirolimus* OR sirukumab* OR (sodium ADJ (aurothiomalate* OR sodium-aurotiosulfate*)) OR sulfasalazine* OR sulindac* OR suprofen* OR tacrolimus* OR tenidap* OR tenoxicam* OR thalidomide* OR tiaprofenic-acid* OR tioguanine* OR tixocortol* OR tocilizumab* OR tofacitinib* OR tolfenamic-acid* OR tolmetin* OR triamcinolone* OR ustekinumab* OR valdecoxib*

OR vedolizumab* OR voclosporin* OR zomepirac* OR paternal-drug-exposure*).ab,ti.) AND (exp Infertility, Male/ OR Sperm Count/ OR Sperm Motility/ OR exp Spermatozoa/ OR Spermatogenesis/ OR Semen/ OR exp Semen Analysis/ OR (((male OR man OR men) ADJ6 (fertil* OR infertil* OR subfertil* OR reproducti* OR steril*)) OR aspermi* OR asthenospermi* OR azoospermi* OR oligospermi* OR ejaculat* OR ((sperm* OR semen OR seminal) ADJ6 (count* OR motility OR abnormal* OR qualit* OR morpholog* OR dna OR characteristic* OR function* OR activit* OR damage OR analy*)) OR spermatoz* OR spermatogen* OR aspermatogen* OR ((successful*) ADJ1 (paternit*))).ab,ti. OR ((Paternal Exposure/ OR Fathers/ OR (paternal OR father* OR ((male OR men OR man OR paternal*) ADJ6 (exposure OR drug OR medication OR patient*))).ab,ti.) AND (exp Pregnancy Outcome/ OR exp Sexual Dysfunction, Physiological/ OR exp Infant, Newborn, Diseases/ OR exp "Congenital, Hereditary, and Neonatal Diseases and Abnormalities"/ OR exp Obstetric Labor Complications/ OR exp Placenta/ OR exp Reproduction/ OR exp Parturition/ OR Fertilization/ OR Embryology/ OR Infertility/ OR Abortion, Spontaneous/ OR (((pregnan* OR obstetr* OR labor OR labour) ADJ3 (outcome* OR disorder* OR complication*)) OR (Sexual* ADJ3 Dysfunction*) OR (Erect* ADJ3 Dysfunct*) OR (impoten* ADJ3 vascul*) OR dyspareun* OR (Prematur* ADJ3 ejaculat*) OR placenta* OR ((newborn* OR neonat* OR fetus OR fetal OR foetus OR foetal) ADJ3 (health* OR disease OR death)) OR birth weight OR birthweight OR lbw OR vlbw OR elbw OR (small ADJ3 (date OR gestation*)) OR congenital* OR preeclamp* OR eclamp* OR miscarriag* OR abort* OR reproduct* OR Childbirth* OR Conception* OR progeny OR offspring OR (prenatal* ADJ3 develop*)).ab,ti.))) NOT (exp animals/ NOT humans/) NOT (news OR comment* OR editorial* OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. AND english.la. NOT (exp animals/ NOT humans/)

Cochrane CENTRAL 163

((((Calcineurin* OR Interleukin*) NEAR/3 inhibitor*) OR ((Glucocorticoid* OR NSAID*) NEAR/3 systemic) OR ((Non-Steroid* OR NonSteroid*) NEAR/3 (Anti-Inflammato* OR AntiInflammato*) NEAR/3 (systemic)) OR (gold NEAR/3 preparation*) OR Thiopurine* OR ((Tumo*r-necrosis-factor* OR TNF) NEAR/3 inhibitor*) OR abatacept* OR abetimus* OR aceclofenac* OR acemetacin* OR acitretin* OR adalimumab* OR afelimomab* OR alclofenac* OR alefacept* OR alemtuzunab* OR alitretinoin* OR alminoprofen* OR anakinra* OR ((antilymphocyte* OR anti-lymphocyte*) NEAR/3 immunoglobulin*) OR apremilast* OR auranofin* OR aurothioglucose* OR aurotioprol* OR azapropazone* OR azathioprine* OR balsalazide* OR baricitinib* OR basiliximab* OR beclometasone* OR belatacept* OR belimumab* OR benoxaprofen* OR benzydamine* OR betamethasone* OR bosutinib* OR briakinumab* OR brodalumab* OR budesonide* OR bufexamac* OR bumadizone* OR canakinumab* OR celecoxib* OR certolizumab-pegol* OR chloroquine* OR ciclosporin* OR clofezone* OR cloprednol* OR colchicine* OR cortisone* OR cortivazol* OR cyclophosphamide* OR deflazacort* OR dexamethasone* OR dexibuprofen* OR dexketoprofen* OR diacerein* OR diclofenac* OR difenpiramide* OR droxicam* OR eculizumab* OR efalizumab* OR etanercept* OR etodolac* OR etoricoxib* OR everolimus* OR everolimus* OR fenbufen* OR fenoprofen* OR fentiazac* OR feprazone* OR flufenamic-acid* OR flunoxaprofen* OR fluocortolone* OR flurbiprofen* OR fumaric-acid-derivate* OR (glucosaminoglycan* NEAR/3 polysulfate*) OR golimumab* OR guselkumab* OR gusperimus* OR hydrocortisone* OR hydroxychloroquine* OR ibuprofen* OR ibuproxam* OR (immunoglobulin NEAR/3 intravasular*) OR indometacin* OR indoprofen* OR infliximab* OR isotretinoine* OR ixekizumab* OR kebuzone* OR ketoprofen* OR ketorolac* OR leflunomide* OR lenalidomide* OR lonazolac* OR lornoxicam* OR lumiracoxib* OR meclofenamic-acid* OR mefenamic-acid* OR meloxicam* OR meprednisone* OR mercaptopurine* OR mesalazine* OR methotrexate* OR methylprednisolone* OR mofebutazone* OR morniflumate* OR muromonab-CD3* OR mycophenolic-acid* OR nabumetone* OR naproxen* OR natalizumab* OR nelarabine* OR niflumic-acid* OR nimesulide* OR olsalazine* OR omalizumab* OR orgotein* OR oxaceprol* OR oxametacin* OR oxaprozin* OR oxyphenbutazone* OR paramethasone* OR parecoxib* OR phenylbutazone* OR pirfenidone* OR piroxicam* OR pirprofen* OR polmacoxib* OR pomalidomide* OR prednisolone* OR prednisone* OR prednylidene* OR proglumetacin* OR proquazone* OR rilonacept* OR rituximab* OR rofecoxib* OR ruxolitinib* OR sarilumab* OR secukinumab* OR siltuximab* OR sirolimus* OR sirukumab* OR (sodium NEXT/1 (aurothiomalate* OR sodium-aurotiosulfate*)) OR sulfasalazine* OR sulindac* OR suprofen* OR tacrolimus* OR tenidap* OR tenoxicam* OR thalidomide* OR

tiaprofenic-acid* OR tioguanine* OR tixocortol* OR tocilizumab* OR tofacitinib* OR tolfenamic-acid* OR tolmetin* OR triamcinolone* OR ustekinumab* OR valdecoxib* OR vedolizumab* OR voclosporin* OR zomepirac* OR paternal-drug-exposure*):ab,ti) AND ((((male OR man OR men) NEAR/6 (fertil* OR infertil* OR subfertil* OR reproducti* OR steril*)) OR aspermi* OR asthenospermi* OR azoospermi* OR oligospermi* OR ejaculat* OR ((sperm* OR semen OR seminal) NEAR/6 (count* OR motility OR abnormal* OR qualit* OR morpholog* OR dna OR characteristic* OR function* OR activit* OR damage OR analy*)) OR spermatoz* OR spermatogen* OR aspermatogen* OR ((successful*) NEAR/1 (paternit*))):ab,ti OR (((paternal OR father* OR ((male OR men OR man OR paternal*) NEAR/6 (exposure OR drug OR medication OR patient*))):ab,ti) AND ((((pregnan* OR obstetr* OR labor OR labour) NEAR/3 (outcome* OR disorder* OR complication*)) OR (sexual* NEAR/3 dysfunction*) OR (Erect* NEAR/3 Dysfunct*) OR (impoten* NEAR/3 vascul*) OR dyspareun* OR (Prematur* NEAR/3 ejaculat*) OR placenta* OR ((newborn* OR neonat* OR fetus OR fetal OR foetus OR foetal) NEAR/3 (health* OR disease OR death)) OR 'birth weight' OR birthweight OR lbw OR vlbw OR elbw OR (small NEAR/3 (date OR gestation*)) OR congenital* OR preeclamp* OR eclamp* OR miscarriag* OR abort* OR reproduct* OR Childbirth* OR Conception* OR progeny OR offspring OR (prenatal* NEAR/3 develop*)):ab,ti)))

Web of science 1315

TS=(((((Calcineurin* OR Interleukin*) NEAR/2 inhibitor*) OR ((Glucocorticoid* OR NSAID*) NEAR/2 systemic) OR ((Non-Steroid* OR NonSteroid*) NEAR/2 (Anti-Inflammato* OR AntiInflammato*) NEAR/2 (systemic)) OR (gold NEAR/2 preparation*) OR Thiopurine* OR ((Tumo*r-necrosis-factor* OR TNF) NEAR/2 inhibitor*) OR abatacept* OR abetimus* OR aceclofenac* OR acemetacin* OR acitretin* OR adalimumab* OR afelimomab* OR alclofenac* OR alefacept* OR alemtuzunab* OR alitretinoin* OR alminoprofen* OR anakinra* OR ((antilymphocyte* OR anti-lymphocyte*) NEAR/2 immunoglobulin*) OR apremilast* OR auranofin* OR aurothioglucose* OR aurotioprol* OR azapropazone* OR azathioprine* OR balsalazide* OR baricitinib* OR basiliximab* OR beclometasone* OR belatacept* OR belimumab* OR benoxaprofen* OR benzydamine* OR betamethasone* OR bosutinib* OR briakinumab* OR brodalumab* OR budesonide* OR bufexamac* OR bumadizone* OR canakinumab* OR celecoxib* OR certolizumab-pegol* OR chloroquine* OR ciclosporin* OR clofezone* OR cloprednol* OR colchicine* OR cortisone* OR cortivazol* OR cyclophosphamide* OR deflazacort* OR dexamethasone* OR dexibuprofen* OR dexketoprofen* OR diacerein* OR diclofenac* OR difenpiramide* OR droxicam* OR eculizumab* OR efalizumab* OR etanercept* OR etodolac* OR etoricoxib* OR everolimus* OR everolimus* OR fenbufen* OR fenoprofen* OR fentiazac* OR feprazone* OR flufenamic-acid* OR flunoxaprofen* OR fluocortolone* OR flurbiprofen* OR fumaric-acid-derivate* OR (glucosaminoglycan* NEAR/2 polysulfate*) OR golimumab* OR guselkumab* OR gusperimus* OR hydrocortisone* OR hydroxychloroquine* OR ibuprofen* OR ibuproxam* OR (immunoglobulin NEAR/2 intravasular*) OR indometacin* OR indoprofen* OR infliximab* OR isotretinoine* OR ixekizumab* OR kebuzone* OR ketoprofen* OR ketorolac* OR leflunomide* OR lenalidomide* OR lonazolac* OR lornoxicam* OR lumiracoxib* OR meclofenamic-acid* OR mefenamic-acid* OR meloxicam* OR meprednisone* OR mercaptopurine* OR mesalazine* OR methotrexate* OR methylprednisolone* OR mofebutazone* OR morniflumate* OR muromonab-CD3* OR mycophenolic-acid* OR nabumetone* OR naproxen* OR natalizumab* OR nelarabine* OR niflumic-acid* OR nimesulide* OR olsalazine* OR omalizumab* OR orgotein* OR oxaceprol* OR oxametacin* OR oxaprozin* OR oxyphenbutazone* OR paramethasone* OR parecoxib* OR phenylbutazone* OR pirfenidone* OR piroxicam* OR pirprofen* OR polmacoxib* OR pomalidomide* OR prednisolone* OR prednisone* OR prednylidene* OR proglumetacin* OR proquazone* OR rilonacept* OR rituximab* OR rofecoxib* OR ruxolitinib* OR sarilumab* OR secukinumab* OR siltuximab* OR sirolimus* OR sirukumab* OR (sodium NEAR/1 (aurothiomalate* OR sodium-aurotiosulfate*)) OR sulfasalazine* OR sulindac* OR suprofen* OR tacrolimus* OR tenidap* OR tenoxicam* OR thalidomide* OR tiaprofenic-acid* OR tioguanine* OR tixocortol* OR tocilizumab* OR tofacitinib* OR tolfenamic-acid* OR tolmetin* OR triamcinolone* OR ustekinumab* OR valdecoxib* OR vedolizumab* OR voclosporin* OR zomepirac* OR paternal-drug-exposure*)) AND ((((male OR man OR men) NEAR/5 (fertil* OR infertil* OR subfertil* OR reproducti* OR steril*)) OR aspermi* OR asthenospermi* OR azoospermi* OR oligospermi* OR ejaculat* OR ((sperm* OR semen OR seminal) NEAR/5 (count* OR motility OR abnormal* OR qualit* OR

morpholog* OR dna OR characteristic* OR function* OR activit* OR damage OR analy*)) OR spermatoz* OR spermatogen* OR aspermatogen* OR ((successful*) NEAR/1 (paternit*))) OR (((paternal OR father* OR ((male OR men OR man OR paternal*) NEAR/5 (exposure OR drug OR medication OR patient*)))) AND ((((pregnan* O R obstetr* OR labor OR labour) NEAR/2 (outcome* OR disorder* OR complication*)) OR (sexual* NEAR/2 dysfunction*) OR (Erect* NEAR/3 Dysfunct*) OR (impoten* NEAR/3 vascul*) OR dyspareun* OR (Prematur* NEAR/3 ejaculat*) OR placenta* OR ((newborn* OR neonat* OR fetus OR fetal OR foetus OR foetal) NEAR/2 (health* OR disease OR death)) OR “birth weight” OR birthweight OR lbw OR vlbw OR elbw OR (small NEAR/2 (date OR gestation*)) OR congenital* OR preeclamp* OR eclamp* OR miscarriag* OR abort* OR reproduct* OR Childbirth* OR Conception* OR progeny OR offspring OR (prenatal* NEAR/2 develop*))))))

Supplementary Table 2 . Additional study details for pregnancy and child outcomes.

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
Calcineurin Inhibitors (CsP=ciclosporine, SIR=sirolimus, TAC=tacrolimus)							
Hospital Germany Schopf (Schopf 2017) 2017	Case report 1 male	NA	34 Psoriasis NS	4mg later 2.4 mg/kg/day 0.5	NS / NS	NA	Previous azoospermia possibly due to mumps induced autoimmune orchitis
Hospital Sweden Holmgren (Holmgren et al. 2004) 2004	Case series NS 3 children	Familial Amyloidotic Polyneuropathy (FAP Val30Met) who had a liver transplant	NS Familial Amyloidotic Polyneuropathy (FAP Val30Met) who had a liver transplant NS	1 tacrolimus 1 ciclosporine and prednisolone 1 ciclosporine and azathioprine NS	NS / NS	NA	
TC* China Xu (Xu et al. 2009) 2009	Case series 1981-2007 164 males	NS	31.14±4.1 Kidney transplantation 0-27	Ciclosporine 1.2-3mg/kg/day Azathioprine, prednisone 4.54±2.29	medical records / patient questionnaire	NA	
Hospital Turkey Ecevit (Ecevit et al. 2012) 2017	Case series 1997-2010 2 males	Pediatric male patients received transplantation	NS Liver transplantation 7 months / 4 years	NS NS NS	NS / NS	NA	Study included maternal exposure

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
TPR* USA Moritz (Moritz et al. 2017) 2017	Case series 1991-2017 29 Pregnancies	Pregnancies fathered by solid organ transplantation patients using sirolimus	NS Solid organ transplantation patients NS	NS NS NS	Patient questionnaire, telephone interview and medical records / telephone interview and medical records	NA	Annual report
PBR* Denmark Egeberg (Egeberg et al. 2017) 2017	Cohort 2004-2010 67 / 417567 children	Children with available information on biological father	33.7±6.5 / 32.8±5.6 NS NA	Ciclosporine NS NS	National Prescription Registry / Medical Birth Registry	maternal age (<25, 25-29, >29) and smoking (yes/no), parity (1,>1) and gender of the child	Study on four immunosuppressants, Included not only singletons Age for exposure at any time before conception

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
Colchicine							
Hospital Israel Levy (Levy et al. 1977) 1977	Case series 3 pregnancies	Patients with FMF	NS FMF NS	NS / NS 1-4	NS / NS	NA	
Ehrenfeld (Ehrenfeld et al. 1986) 1985	Case series 11 years 12 (8) children (fathers)	Married patients with FMF Patients with FMF and healthy wives	NS FMF NS	0,5-2mg/dag NS / NS 1mg/day	NS / NS Patient questionnaire / Patient questionnaire	NA NS	
Ben-Chetrit (Ben-Chetrit et al. 2004) 2004	Cohort 1995-2003 158 / 64 Pregnancies		NS FMF NS	NS NA			
Cyclophosphamide							
Hospital Turkey Balci (Balci et al. 1983) 1983	Case report 1 child	NA	36, Bechet's disease 0,5	150mg/day, 50mg/day dexamethasone, 3	NS / medical examination	NA	Chromosomal analysis was normal, 2 older siblings are healthy

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
Interleukin inhibitors							
TIS Germany Weber-Schoendorfer (Weber-Schoendorfer et al. 2016) 2016	Case series 2011-2014 2 pregnancies		NS NS 8 weeks after EDOD	800mg IV NS long-term	Standardized questionnaires, reported by HCP or parents / Standardized questionnaires, reported by HCP or parents	NA	Study included (mainly) maternal exposure
Disease society Younstein (Youngstein et al. 2017) 2017	Case series Until 2012 6 (5) children (fathers) 5 (3) children (fathers)	Paternal exposure at conception	NS, AOSD*, CAPS*, TRAPS* 4 weeks-8 years (range)	anakinra 25-100mg/day, canakinumab 150mg/8 weeks NS 0,25-20,7 (range)	Datasheet HCP* / Datasheet HCP*	NA	Study included (mainly) maternal exposure
MAH SD Warren (Warren et al. 2018) 2018	Case series Until 2017 54 pregnancies	Pregnancies with exposure to secukinumab	34.1 P 32 (59) , PA 9 (17), ASp7 (13) , unknown 6 (11) NS	NS NS NS	NS / NS	NA	Study included (mainly) maternal exposure no specific details for paternal exposures

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
Methotrexate (MTX)							
Hospital USA Perry (Perry 1983) 1983	Case report 1 male	NA	34 Reiter's syndrome NS	25mg/week oral NS intermittent	NS / NS	NA	
Hospital USA Griggs (Griggs et al. 2006) 2006	Case report 1 male	NA	32 CD* NS	25mg/week SC NS NS	NS / NS	NA	Earlier treatment 5-ASA, prednisone and 6MP. Due to side effects switch to MTX was made
Hospital Italy Lamboglia (Lamboglia et al. 2009) 2009	Case report 1 male	NA	44 CD NS	10mg/week SC Infliximab 5mg/kg/6 weeks NS	NS / NS	NA	
TIS France Beghin (Beghin et al. 2011) 2011	Case series 1997-2009 42 Pregnancies (40 fathers)	Pregnancies with paternal exposure	38 (range 30-52) 10 RA, 9 P, 2CD 7 ASp, 2 MS 6 leukemia, 2 adrenal tumor, 2 lymphoid papulosis, 1 Still's disease, 1 sarcoidosis 1 month after EDOD*	15mg/week median (7,5-30mg/week) 10 cases with other drugs (INF, LAM, HCQ, AZA, isotretinoin, acitretin, ETN, vincristine, prednisone, 6MP)	Questionnaire HCP / Questionnaire HCP	NA	19% cancer indications In 39 cases treatment during conception Mean gestational age at call was 10.6±5 weeks

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
JuMBO registry Germany Drenches (Drenches et al. 2018) 2018	Case series Up to 2018 9 Pregnancies	Male patients with pregnancies in partners	NS Juvenile idiopathic arthritis NS	NS NS NS	NS / NS	NA	Abstract with general DMARDs exposure.
PBR* Norway Engeland (Viktil et al. 2012) 2012	Cohort 2004-2011 5 singleton pregnancies	Singleton pregnancies where fathers were dispensed drug during the last 3 months before conception	NS NS NS	NS NS NS	Norwegian Prescription Database / Medical Birth Registry Norway		A lot of exclusions were made regarding pregnancies duration and birthweights
TIS Germany Weber-Schoendorfer (Weber-schoendorfer et al. 2014) 2014	Cohort 1995-2012 113 / 412 Pregnancies	Pregnancies with paternal MTX exposure	NS RA 57, P33 P or PA, ASp 7 CD 6 other disease 10 NS	15mg/week median 20 glucocorticoids, 15 biologics, 12 NSAIDs/COX2 inhibitors, 11 leflunomide NS	Standardized questionnaires, reported by HCP or parents / Standardized questionnaires, reported by HCP or parents	NA	3 cases only exposure during pregnancy Specialized analysis spontaneous abortions (Meister et al. 2008)

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
PBR Denmark Winter (Winter et al. 2017) 2017	Cohort 1997-2013 193 / 1013801 Live born children (singletons)	Live born singletons with filed prescriptions for paternal MTX	34.8 (20.9-38.8) median (IQR) RD 123 (63.7) DD 63 (32.6) IBD 14 (7.3) Cancer 3 (1.6) MS 1 (0.5) Unknown 33 (17.1)	NS NS NS NS NS	National Prescription Database / Medical Birth Registry, National Patient Registry	maternal and paternal age, parity, maternal smoking during first trimester	Only abstract Details for adjustment not stated
Andersen (Andersen et al. 2018) 2018	Cohort 1997-2015 520 / 1363543 fathers	Pregnancies with paternal exposure to MTX	1 year NS NS NS	NS NS NS NS	National Prescription Database / Medical Birth Registry, National	NS	
Friedman (Friedman, Larsen, Magnussen, Jølving, et al. 2017) 2017	Cohort 1997-2013 209 / 1056524 children	Live born children with filled paternal prescription of MTX	NS NS 9.9 (5.7-14.3) Median (IQR)		Hospital Registry National Prescription Database / Medical Birth Registry, National Patient Registry	NA	

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
Mycophenolate acid products (MPA)							
TPR* USA Moritz (Moritz et al. 2017) 2017	Cohort 1991-2017 295 / 1092 pregnancies	Pregnancies fathered by male solid organ transplant recipients	NS transplantation NS	NS NS NS	questionnaires, telephone interview and review of medical records / questionnaires, telephone interview and review of medical records	NA	First USA based now International
PBR* Norway Midtvedt (Midtvedt et al. 2017) 2017	Cohort 1995-2015 155 (112) / 195 (133) children (fathers)	Transplanted men alive	36.1±5.6 / 35.7±4.7 kidney transplantation NS	1.42±0.3 g/day, steroids and ciclosporine or tacrolimus NS	Norwegian Renal Registry (NRR) / Medical Birth Registry Norway (MBRN)	NS	
PBR* Denmark Egeberg (Egeberg et al. 2017) 2017	Cohort 2004-2010 6 / 417628 children	Children with available information on biological father	33.7±5.9 / 32.8±5.6 NS NA	Mycophenolate mofetil NS NS	National Prescription Registry / Medical Birth Registry	maternal age (<25, 25-29, >29) and smoking (yes/no), parity (1,>1) and gender of the child	Study on four immunosuppressants, included not only singletons. Age for exposure at any time before conception

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
Hospital Spain Lopez-Lopez (Lopez-Lopez et al. 2018) 2018	Cohort 1988-2015 28 (20) / 21 (13) children (fathers)	Kidney transplant patients who fathered children	39.6±4.6 / 34.6±5.7 Kidney transplantation 5.15±3.97	1.21±0.3gram/day MPA (18 MMF*, 10 MPS*) low dose prednisone, and tacrolimus or ciclosporine 7.9±5.3 / 6.3±4.5	Telephone survey patients / Telephone survey patients	NA	8 patients in the comparison group used azathioprine
Retinoids							
Hospital UK Katugampola (Katugampola et al. 2006) 2006	Case series 1974-2004 3 (2) children (fathers)	Patients with DOK on oral retinoid therapy	27, 32 and 24 PRP-III psoriasis, X-linked ichthyosis NS	NS NS 4, 9 and 3	Medical records and patient interview / Medical records and patient interview	NA	General follow up study
PBR Norway Engeland (Engeland et al. 2013) 2012	Cohort 2004-2011 80 singleton pregnancies	Singleton pregnancies where fathers were dispensed drug during the last 3 months before conception	NS NS NS	NS NS NS	Norwegian Prescription Database / Medical Birth Registry Norway	Maternal and paternal age	A lot of exclusions were made regarding pregnancies duration and birthweights

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
PBR Denmark Norgaard (Nørgaard et al. 2019) 2019	Cohort 1996-2016 244 pregnancies 205 children	Paternal acitretin exposure	NS NS NS	NS NS NS	National Prescription Registry / Medical Birth Registry and National Hospital Register	NS	Only abstract Details for adjustment not stated
Systemic corticosteroids							
Hospital UK McGeown (McGeown et al. 1978) 1978	Case series 8 males	NS	NS Kidney transplantation	10mg/day prednisolone, AZA	NS / NS	NA	
TC* China Xu (Xu et al. 2009) 2009	Case series 1981-2007 164 males	NS	31.14±4.1 Kidney transplantation 0-27	prednisone 5-10mg/day Azathioprine, ciclosporine 4.54±2.29	medical records / patient questionnaire	NA	
PBR* Norway Engeland (Viktil et al. 2012) 2012	Cohort 2004-2011 1477 singleton pregnancies	Singleton pregnancies where fathers were dispensed drug during the last 3 months before conception	NS NS NS	NS NS NS	Norwegian Prescription Database / Medical Birth Registry Norway	maternal and paternal age	A lot of exclusions were made regarding pregnancies duration and birthweights

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
PBR* Denmark Larsen (Larsen et al. 2018) 2018	Cohort 1997-2013 2380 (1558:1, 822:2)** / 1011614 live born children (singletons)	Fathers of live born singletons	32.8 / 31.9 median IBD 342 (14.4) RD 239 (10.0) Asthma/allergy 636 (26.7) CTD 141 95.9) Others 513 (21.6) Unknown 1067 (45.2) 1 year follow up	NS NS NS	National Prescription Database / Medical Birth Registry, National Patient Registry	maternal and paternal age at time of delivery, parity (1, >1), gender of the child, maternal smoking (yes/no) and BMI (<18.5, 18,5-24.9, 25-29.9, >30)	
Thiopurines (AZA=azathioprine, 6MP=6-mercaptopurine)							
Hospital Israel Ben-Neriah (Ben-Neriah et al. 2001) 2001	Case report 1 male	NA	31 Crohn's disease 4	1.5mg/kg, steroids, >4	NS / NS	NA	Unclear if drug was azathioprine or 6-mercaptopurine
Hospital UK McGeown (McGeown et al. 1978) 1978	Case series 8 males (13 pregnancies)	NS	NS Kidney transplantation NS	3mg/kg/day, Prednisolone 10mg/day NS	NS / NS	NA	Study included maternal and paternal exposure SB due to acute oligohydramnios

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
TC China Xu (Xu et al. 2009) 2009	Case series 1981-2007 164 males	NS	31.14±4.1 Kidney transplantation 0-27	Azathioprine 50-75 mg/day prednisone, ciclosporine 4.54±2.29	medical records / patient questionnaire	NA	
Hospital USA Rajapakse (Rajapakse et al. 2000) 2000	Cohort 1970-1997 13 / 90 pregnancies	Male patients who fathered children with 6MP prior to/ no use of 6MP prior to conception	34.0±0,9 / 31.6±1.1 15 CD, 8 UC NS	6MP mean 100mg/ day / 6 corticosteroids, 8 5-ASA	medical records / patient interview	NA	6MP users divided in two groups with or without 6MP use 3 months prior to conception
Hospital Spain Teruel (Teruel et al. 2010) 2003	Cohort 2007-2008 46 / 84 pregnancies	Pregnancies with paternal diagnosis of IBD before conception	34.2±4.2 / 32.7±5.4 38 (82.6) CD / 45 (53.6) CD, 9 median 9 (range 0-31)	37 AZA 153mg/day or 9 6MP 72mg, and 2 sulfasalazine, 7 5-ASA, 2 steroids, 5 TNF-α inhibitors 3 median (range 0-12)	structured questionnaire (sometimes medical records) / structured questionnaire (sometimes medical records	NS	Outcomes similar to general population OT in comparison group 2 ectopic pregnancies, 1 anembryonic pregnancy, one embryonic death
Hospital USA Francella (Francella et al. 2003) 2003	Cohort 1950-1997 37 / 73 pregnancies	Conceptions after paternal use of 6MP for IBD at conception	NS UC 27 (36) >1,5	6MP 70mg/day (range 12,5-175) Co medication: antibiotics, sulfasalazine, 5-ASA, corticosteroids, antidiarrheals, and antispasmodics range 0-16	patient interview and medical records / patient interview	NS	Study included maternal and paternal exposure

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
TIS* Germany Hoeltzenbein (Hoeltzenbein et al. 2012) 2012	Cohort 1988-2010 115 / 340 pregnancies	Prospective pregnancies with complete follow up after paternal exposure to AZA or 6MP	NS 49 CD, 30 UC, 5 KT, 5 MS and 26 other diseases 8 weeks after EDOD	AZA 150mg/day (range20-450) 6MP 100mg/day (range 75-100) 40 corticosteroids, 18 5-ASA, 6 ciclosporine, 4 pyridostigmine	standardized questionnaires, reported by HCP or parents / standardized questionnaires, reported by HCP or parents	NS	specialized analysis spontaneous abortions (Meister et al. 2008)
PBR* Denmark Norgard (Nørgård et al. 2017) 2017	Cohort 1997-2013 699/ /1012624 live born children (singletons)	Live born singletons with identifiable father	32±5.49 / 32±5.75 median 514 (73.5) IBD / 6037 (0.6) IBD NS	dose NS Co-medication not reported but was allowed NS	National Prescription Registry / Medical Birth Registry, National Patient Registry	maternal and paternal age at time of delivery (<25, 25-29,>29), parity (1, >1), gender child, maternal BMI (<18.5, 18,5-24.9, 25-29.9, >30) and smoking in pregnancy (yes/no), calendar year of birth (197-2001, 2002-2006, 2007-2013) NS	
Friedman# (Friedman, Larsen, Magnussen, Jølving, et al. 2017; Friedman, Larsen, Magnussen, Jolving, et al. 2017) 2017	Cohort 1997-2013 735 / 1056524 children	Live born children	NS NS 9.9 (5.7-14.3) Median (IQR)	NS NS NS	National Prescription Registry / Medical Birth Registry, National Patient Registry		

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
TNF-α inhibitors (INF=infliximab, ETN=etanercept, CZP=certolizumab Pegol, ADA=adalimumab, GOL=golalinumab)							
Hospital Italy Lamboglia (Lamboglia et al. 2009) 2009	Case report 1 male	NA	44 CD NS	5mg/kg/6weeks MTX 10 mg/week NS	NS / NS	NA	
Hospital Greece Paschou (Paschou et al. 2009) 2009	Case series 2001-2007 4 males (6 children)	Male patients with SpA	33.5±5.4 SpA NS	INF 5mg/kg/8 weeks MTX 1 male (2 children) >4	medical records / NS	NA NA	Patients in remission Patients in remission
Saougou (Saougou et al. 2013) 2013	2001-2010 11 males (14 children)	Male patients with SpA (3) or PsA (7)	34.1±4.2 SpA NS	INF /8 weeks 3 MTX 15mg/week, 1 MPRED 4mg/day*, 1 MPRED 2mg/day and CsP 100mg/day	medical records / NS		
Hospital Turkey Uyaroglu (Uyaroglu et al. 2017) 2017	Case series 2015-2016 42 males	Male patients using TNF-α inhibitors	36.4±5.2 AS 39 (92.9), RA 2 (4.8), PA 1 (2.4) NS	adalinumab 8 (19) , etanercept 12 (28,5), infliximab 1 (42,9) NS	NS / NS	NA	ET at week 37, due to oligohydramnion BW 2850, healthy newborn, ETN and MTX
Hospital Italy Hoxha (Hoxha et al. 2017) 2017	Case series 2008-2015 3 males	Patients with RA, PA or SpA	NS NS NS	Etanercept NS NS	questionnaire rheumatologist / questionnaire rheumatologist	NA	Study included (mainly) maternal exposure

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
TREAT registry USA Lichtenstein (Lichtenstein et al. 2018) 2018	Case series 1999-2012 42 pregnancies	Pregnancies with exposure to infliximab	31.0 median Crohn's disease NS	NS NS NS	Patient questionnaire / Patient questionnaire	NA	Study included (mainly) maternal exposure
MAH SD* Clowse (Clowse et al. 2015) 2015	Case series up to 2014 46 pregnancies	Paternal certolizumab pegol exposed pregnancies	NS NS NS	NS NS NS	NS / NS	NA	Study included mainly maternal exposure
PBR Denmark Larsen (Larsen et al. 2016) 2016	Cohort 2007-2013 372 / 399498 live born children (singletons)	Live born singletons with identifiable father	33.0 (30-37) median UC/CD 138 (37), R/D dis 253 (63) NS	INF 155 (41.7), ADA 136 (36.6), ETN 69 (18.5), GOL 11 (3.0), CTP 1 (0.3) 35 (25.4) also AZA/6MP, 4 (2.9) also MTX NS	National Prescription Registry / Medical Birth Registry, National Patient Registry	maternal and paternal age at time of delivery, parity (1, >1), maternal smoking (yes/no)and BMI	
Hospital Romania Micu (Micu et al. 2019) 2019	Cohort 2012-2017 33 / 12142 pregnancies	Males with SpA	34.6±5.5 / NS SpA NS	12 ADA 40mg/2weeks, 14 ETN 50mg/week, 7 INF 5mg/kg/8weeks, 14 (43.8) NSAIDs 3.6±2.2	HCP / patient interview	NS	Controls not from the same population, 26 (96.3) in remission at conception ET for personal reasons

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
Other selective immunosuppressants							
TIS Italy De Santis (De Santis et al. 2005) 2005	Case report 1 pregnancy	NA	NS NS NS	NS NS NS	NS / NS	NA	Study included (mainly) maternal exposure
MAH SD* Kumar (Kumar et al. 2015) 2015	Case series 1995-2014 10 pregnancies	Pregnancies following exposure to abatacept	NS NS NS	NS 3 MTX, 1 LEF, 1 MPA NS	NS / NS	NA	Study included (mainly) maternal exposure
MAH SD Mahadevan (Mahadevan et al. 2018) 2018	Case series Until 2017 84 pregnancies	Pregnancies with exposure to tofacitinib	NS UC 14, RA 7, P 60, PA 3 NS	5 or 10mg BID NS NS	NS / NS	NA	Study included (mainly) maternal exposure
DMARDs not specified per drug							
PBR Norway Vitkil (Viktil et al. 2009)2012	Cohort 2004-2007 First singleton pregnancies	First singleton pregnancies with exposure	NS NS NS	Etanercept 40 Adalumimab 6 Methotrexate 50 Leflunomide 1 Hydroxychloroquine12 Azathioprine 124 NSAIDs 705 Sulfasalazine 57 NS NS	Norwegian Prescription Database / Medical Birth Registry Norway	NA	Study included (mainly) maternal exposure

Supplementary Table 2 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Inclusion	Patient age case / comparison (years, mean ± SD) Disease case / comparison (n(%)) Follow up duration child case / comparison (years)	Drug dose (mean) Co-medication case / comparison Treatment duration case / comparison (years)	Assessment Exposure / Outcome	Adjusted for	Remarks
PBR Norway Wallenius (Wallenius et al. 2015) 2015	Cohort 2001-2011 110 DMARD/ Reference group children	Male patients with a diagnosis of inflammatory joint disease treated with DMARDS	35.4±5.4 / 32.7±6.2, SpA 43 (39) PA 25 (23) RA 18 (16) Unspec A. 18 (16) JIA 6 (5)	TNF-α i mono 36 TNF-α I + MTX 21 MTX mono and poly (not TNF-α I) 28 Sulfasalazine 17 Other 8	NOR-DMARD registry / Medical Birth Registry Norway	Maternal and paternal age and year of delivery	No drug specific information available
JuMBO registry Germany Drenches (Drenches et al. 2018) 2018	Case series Up to 2018 39 pregnancies (21 fathers)	Pregnancies with paternal use of DMARDS	23.2±4.2 (at first pregnancy) JIA NS	NS Number of drugs: 2.5±1.0 DMARDs 7.1±3.1	HCP questionnaire / Patient interviews	NA	Only abstract

Abbreviations: ADA – Adalimumab, AS – Ankylosing spondylitis, AOSD – Adult-onset Still's disease, AZA – Azathioprine, CAPS – Cryopyrin-associated periodic syndrome, CD – Crohn's disease, CYC – Cyclophosphamide, CZP – Certolizumab pegol, DOK – Disorders of keratinization, DMARDs – Disease-modifying anti-rheumatic drugs, EDOD – Estimated date of delivery, ETN – Etanercept, FMF – Familial mediterranean fever, GOL – Golimumab, HCP – Health care professional, IBD – Inflammatory bowel disease, IQR – Interquartile range, INF – Infliximab, MMF- Mycophenolate Mofetil, MPA - Mycophenolate acid products, KT – Klippel –Trénaunay syndrome, MS – Multiple sclerosis, MPA – Mycophenolic acid, MTX – Methotrexate, NA – Not applicable , NS – Not stated, NSAIDs – Nonsteroidal anti-inflammatory drugs, NR – Not reported, NRR Norwegian Renal Registry, P – Psoriasis, PA – Psoriatic arthritis, PBR – Population based registries , RA – Rheumatoid arthritis, SpA – Spondyloarthritis, SSZ – Sulfasalazine, TC – transplantation center, TPR – Transplant Pregnancy Registry International, TRAPS – Tumor necrosis factor receptor-associated periodic syndrome, 6MP – 6 mercaptopurine.

Supplementary Table 3 . Specification of reported birth defects.

Data source **Country** **Author** **Year of publication**	**Type of study** **Study period** **Number of cases** **Number of controls** **Unit cases**	**Birth defect cases /** ***comparison group***	**Pregnancy outcome** **Live births (LB)** **Spontaneous abortions (SA)** **ETOP* (ET)** **Stillbirths (SB)**	**Drugs**	**Disease**
PBR* Norway Engeland (Engeland et al. 2013) 2012	Cohort 2004-2011 80 singleton pregnancies	Patent ductus arteriosus and Down 's syndrome	LB	Isotretinoin	NS
Hospital Israel Ben-Neriah (Ben-Neriah et al. 2001) 2001	Case report 1 male	WAGR Syndrome, de novo aberration	LB	AZA or 6MP	Crohn's disease
Hospital UK McGeown (McGeown et al. 1978) 1978	Case series 8 males	Trisomy 21	LB	Azathioprine, prednisolone	Kidney transplant
TC* China Xu (Xu et al. 2009) 2009	Case series 1981-2007 164 males	hapalonychia in the toes	LB	Azathioprine, ciclosporine, prednisone	Kidney transplant
Hospital USA Rajapakse (Rajapakse et al. 2000) 2000	Cohort 1970-1997 13 / 90 pregnancies	missing thumb multiple anomalies	LB ET	6MP, 5-ASA prednisone, 5-ASA	Crohn's disease Crohn's disease

Supplementary Table 3 . Continued

Data source **Country** **Author** **Year of publication**	**Type of study** **Study period** **Number of cases** **Number of controls** **Unit cases**	**Birth defect cases /** ***comparison group***	**Pregnancy outcome** **Live births (LB)** **Spontaneous abortions (SA)** **ETOP* (ET)** **Stillbirths (SB)**	**Drugs**	**Disease**
Hospital Spain Teruel (Teruel et al. 2010) 2003	Cohort 2007-2008 46 / 84 pregnancies	interauricular communication with patent ductus arteriosus *comparison group* *urethral stenosis (surgery),* *progressive fibrodysplasia ossificans*	LB *LB* *LB*	NS *NS* *NS*	NS *NS* *NS*
Hospital USA Francella (Francella et al. 2003) 2003	Cohort 1950-1997 37 at conception/ 73 Pregnancies 44 stopped before conception/ 73 Pregnancies	meningomyelocele / *comparison group* *Down syndrome* *atrial septal defect and mitral valve cleft* Cardiac abnormality Double aortic arch with tracheal malacia Pyloric stenosis	ET *LB* *LB* ET LB LB	6 MP *no 6MP* *no 6MP* 6MP +? 3 years before 6MP +? 10 months before 6MP +? 4 years before	NS *NS* *NS* NS NS NS
TIS* Germany Hoeltzenbein (Hoeltzenbein et al. 2012) 2012	Cohort 1988-2010 115 / 340 pregnancies	major birth defects -small muscular ventricular septal defect (VSD), spontaneous closure within 6 month, horseshoe kidney, hemangioma on the bottom -VSD, ASD II, pulmonary stenosis -Motor retardation, dyspraxia, persistent foramen ovale (PFO) Minor birth defects -three children with umbilical hernias -two children with small hemangiomas -persistent foramen ovale	 LB LB LB LBs LBs LB LB LB	 Azathioprine Azathioprine Azathioprine Azathioprine Azathioprine Azathioprine until 3 months prior to conception) Azathioprine Azathioprine	 NS NS NS NS NS NS NS NS

Supplementary Table 3 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Birth defect cases / *comparison group*	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB)	Drugs	Disease
		-mild hip dysplasia			
		-xanthoma upper lip	*LB*	*NS*	*NS*
		Comparison group	*LB*	*NS*	*NS*
		major birth defects	*SA*	*NS*	*NS*
		-hydrocephalus	*LB*	*NS*	*NS*
		-abdominal cavernous hemangioma, pyelectasia	*LB*	*NS*	*NS*
		-hernia inguinalis with incarceration, hydrocele	*LB*	*NS*	*NS*
		-craniofacial malformation (surgery)	*LB*	*NS*	*NS*
		-single ventricle	*LBs*	*NS*	*NS*
		-severe hip dysplasia	*LBs*	*NS*	*NS*
		-pulmonary valve atresia, open ductus arteriosus	*LB*	*NS*	*NS*
		minor birth defects	*LB*	*NS*	*NS*
		three children with mild pyelectasia	*LB*	*NS*	*NS*
		three children with mild hip dysplasia	*LB*	*NS*	*NS*
		small hemangioma	*LB*	*NS*	*NS*
		benign neoplasm of skin	*LB*	*NS*	*NS*
		non descensus testis	*LB*	*NS*	*NS*
		glandular hypospadia	*SA*	*NS*	*NS*
		hernia umbilicalis	*ET*	*NS*	*NS*
		pigeon toes	*ET*	*NS*	*NS*
		persistent foramen ovale	*LB*	*NS*	*NS*
		Genetic disorders	*LB*	*NS*	*NS*
		trisomy 18 *Turner syndrome* *Klinefelter syndrome* *Fabry disease* *Cystic fibrosis*			

Supplementary Table 3 . Continued

Data source **Country** **Author** **Year of publication**	**Type of study** **Study period** **Number of cases** **Number of controls** **Unit cases**	**Birth defect cases /** ***comparison group***	**Pregnancy outcome** **Live births (LB)** **Spontaneous abortions (SA)** **ETOP* (ET)** **Stillbirths (SB)**	**Drugs**	**Disease**
PBR* Denmark Norgard (Nørgård et al. 2017) 2017	Cohort 1997-2013 699/ /1012624 live born children (singletons)	CAs within the nervous system [DQ00-DQ07] 1 (2.5) CAs within eye, ear, face and neck [DQ10-DQ18] 1 (2.5) CAs within circulation organs [DQ20-DQ28] 7 (17.5) CAs in the respiratory organs [DQ30-DQ34] 2 (5.0) Cleft lip and palate [DQ35-DQ37] 1 (2.5) Other CAs in the digestive organs [DQ38-DQ45] 7 (17.5) CAs in the genital organs [DQ50-DQ56] 1 (2.5) CAs in the urinary system [DQ60-DQ64] 4 (10.0) CAs in the bones and muscles [DQ65-DQ79] 11 (27.5) Other CAs [DQ80-DQ89] 3 (7.5) Chromosome anomalies [DQ90-DQ99] 2 (5.0)	NS NS NS NS NS NS NS NS NS NS NS	NS NS NS NS NS NS NS NS NS NS NS	NS NS NS NS NS NS NS NS NS NS NS
Hospital Greece Saougou (Saougou et al. 2013) 2013	Case series 2001-2010 11 males	Hydrocephaly	ET	Infliximab, methotrexate 15mg/week	PsA

Supplementary Table 3 . Continued

Data source **Country** **Author** **Year of publication**	**Type of study** **Study period** **Number of cases** **Number of controls** **Unit cases**	**Birth defect cases /** ***comparison group***	**Pregnancy outcome** **Live births (LB)** **Spontaneous abortions (SA)** **ETOP* (ET)** **Stillbirths (SB)**	**Drugs**	**Disease**
Hospital Turkey Uyaroglu (Uyaroglu et al. 2017) 2017	Case series 2015-2016 42 males	Angelman syndrome	LB	Adalimumab	AsP
TREAT registry USA Lichtenstein (Lichtenstein et al. 2018) 2018	Case series 1999-2012 42 pregnancies 17 pregnancies	Hemophilia (unknown in family) Laryngeal cyst and one vocal cord	LB LB	Infliximab Infliximab until, at last, 3 months before conception	Crohn's disease Crohn's disease
TPR* USA Moritz (Moritz et al. 2017) 2017	Case series 1991-2017 29 pregnancies	Ureteral stricture	LB	Sirolimus	Solid organ transplant patient
Hospital Turkey Balci (Balci et al. 1983) 1983	Case report 1 child	Acheiria	LB	Cyclophosphamide 150mg/day, dexamethasone, 50mg/day	Bechet's disease
JuMBO registry Germany Drenches (Drenches et al. 2018) 2018	Case series Up to 2018 39 pregnancies	Agenesis of the corpus callosum Club foot	LB LB	Methotrexate, certolizumab, corticosteroids, NSAIDs Leflunomide, corticosteroids, NSAIDs	JIA JIA

Supplementary Table 3 . Continued

Data source **Country** **Author** **Year of publication**	**Type of study** **Study period** **Number of cases** **Number of controls** **Unit cases**	**Birth defect cases /** ***comparison group***	**Pregnancy outcome** **Live births (LB)** **Spontaneous abortions (SA)** **ETOP* (ET)** **Stillbirths (SB)**	**Drugs**	**Disease**
TIS Germany Weber-Schoendorfer (Weber-schoendorfer et al. 2014) 2014	Cohort 1995-2012 113 / 412 pregnancies	Major birth defects -dilative cardiomyopathy with insufficiency of atrio-ventricular valves on both sides following lung hypoplasia; intrauterine growth retardation; 46 XX chromosomal aberrations, de novo -trisomy 16 minor birth defects -slight pyelectasia, persistent foramen ovale, intrauterine growth retardation -Hypospadias glandis -microcephaly (head circumference <3rd percentile below 2 SD for age and sex) -ureteral dilatation left side (7 mm), dermal sinus *Comparison group* *Major birth defects* *Limb defect (4th finger left missing; 1st & 2nd finger left with joint carpal bone)* *Frontal encephalocele* *2 club foot* *chromosomal aberrations, de novo* *2 trisomy 18*	ET ET LB LB LB LB *LB* *LB* *LBs* *ETs*	Methotrexate 7.5/week 15mg/week 15mg/week 25mg/week 15mg/week 10mg/week *NS* *NS* *NS* *NS*	SpA SpA RA Wegener's granuloma P PA *NS* *NS* *NS* *NS*
PBR Denmark Winter (Winter et al. 2017) 2017	Cohort 1997-2013 193 / 1013801 live born children (singletons)	2 CAs of the face/skull Plagiocephaly Malformation of face/neck Stenosis of the pulmonary artery Unspecified cardiac congenital anomaly Syndactyly Hypospadias Talipes equinovarus Hirschsprung's disease	LB LB LB LB LB LB LB LB LB	Methotrexate Methotrexate Methotrexate Methotrexate Methotrexate Methotrexate Methotrexate Methotrexate Methotrexate	NS NS NS NS NS NS NS NS NS

Supplementary Table 3 . Continued

Data source **Country** **Author** **Year of publication**	**Type of study** **Study period** **Number of cases** **Number of controls** **Unit cases**	**Birth defect cases /** ***comparison group***	**Pregnancy outcome** **Live births (LB)** **Spontaneous abortions (SA)** **ETOP* (ET)** **Stillbirths (SB)**	**Drugs**	**Disease**
Hospital Spain Lopez-Lopez (Lopez-Lopez et al. 2018) 2018	Cohort 1988-2015 28 (20) / 21 (13) children (fathers)	*Comparison group* *Down syndrome*	*LB*	*Non-MPA*	*Kidney transplantation*
PBR* Norway Engeland (Viktil et al. 2012) 2012	Cohort 2004-2011 1477 singleton pregnancies	Group CA — No OR (96%CI) Nervous — 1 0.88 0.12, 6.3 Eye, ear, face and neck — 4 1.6 0.61, 4.4 Heart and blood vessels — 11 0.74 0.41, 1.3 Lip/palate — 3 1.2 0.37, 3.6 Digestive system — 16 2.0 1.2, 3.3 Genitalia — 12 1.2 0.70, 2.2 Urinary organs — 6 2.1 0.94, 4.7 Musculoskeletal system — 26 1.1 0.78, 1.7 Multiple defects — 3 0.60 0.19, 1.9	LB LBs LBs LBs LBs LBs LBs LBs LBs	Prednisolone Prednisolone Prednisolone Prednisolone Prednisolone Prednisolone Prednisolone Prednisolone Prednisolone	NS NS NS NS NS NS NS NS NS
PBR* Denmark Larsen (Larsen et al. 2018) 2017	Cohort 1997-2013 2380 (1558:1, 822:2)** / 1011614 live born children (singletons)	CAs within the nervous system [Q00–Q07] 4 (0.17) CAs within eye, ear, face and neck [Q10–Q18] 3 (0.13) CAs within circulation organs [Q20–Q28] 47 (1.97) CAs in the respiratory organs [Q30–Q34] 7 (0.29) Cleft lip and palate [Q35–Q37] 10 (0.42) Other CAs in the digestive organs [Q38–Q45] 22 (0.92) CAs in the genital organs [Q50–Q56] 13 (0.54)	LBs LBs	Systemic corticosteroids Non-users and former users	NS NS

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Birth defect cases / *comparison group*	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB)	Drugs	Disease
		CAs in the urinary system [Q60–Q64] (0.25)	4		
		CAs in the bones and muscles [Q65–Q79] (2.31)	55		
		Other CAs [Q80–Q89] (0.88)	21		
		Chromosome anomalies [Q90–Q99] (0.38)	9		
		Comparison group			
		CAs within the nervous system [Q00–Q07] 2735 (0.27)			
		CAs within eye, ear, face and neck [Q10–Q18] 2837 (0.13)			
		CAs within circulation organs [Q20–Q28]) (1.81)	*18360*		
		CAs in the respiratory organs [Q30–Q34]) 2805 (0.28)			
		Cleft lip and palate [Q35–Q37] (0.37)	*3774*		
		Other CAs in the digestive organs [Q38–Q45] (0.74)	*7524*		
		CAs in the genital organs [Q50–Q56] (0.65)	*591*		
		CAs in the urinary system [Q60–Q64] (0.45)	*4528*		
		CAs in the bones and muscles [Q65–Q79] (2.18)	*22080*		
		Other CAs [Q80–Q89] (0.47)	*4732*		
		Chromosome anomalies [Q90–Q99] (0.20)	*1991*		

Data source **Country** **Author** **Year of publication**	**Type of study** **Study period** **Number of cases** **Number of controls** **Unit cases**	**Birth defect cases /** ***comparison group***	**Pregnancy outcome** **Live births (LB)** **Spontaneous abortions (SA)** **ETOP* (ET)** **Stillbirths (SB)**	**Drugs**	**Disease**
PBR Norway Vitkil (Viktil et al. 2012) 2012	Cohort 2004-2007	Septum defect (heart) and penoscrotal malformation 2 Orofacial malformations	LB LBs	Etanercept, ciclosporine and a NSAID methotrexate	NS NS
PBR Norway Wallenius (Wallenius et al. 2015) 2015	Cohort 2001-2011 110 DMARD/ Reference group children	Ventricular septum defect Pes equinovarus 2 Unspecified abdominal atresias	LB LB LBs	Methotrexate Methotrexate and TNF-α-i TNF-α-i	NS NS NS

Abbreviations in table
AS (Ankylosing spondylitis), AZA (azathioprine), CAs (congenital anomalies), JIA (juvenile idiopathic arthritis), MPA (mycophenolic acid), 6MP (6-mercaptopurine), NS (not stated), P (psoriasis), PA (psoriatic arthritis), PBR (population based registry), RA (rheumatoid arthritis), SpA (Spondyloarthritis), TC (transplantation centre), TIS (Teratology Information Service), TNF-α-I (Tumour necrosis factor alpha inhibitor)

Supplementary Table 4 . Other maternal and child outcomes.

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Other outcomes n (%)
Calcineurin Inhibitors (CsP=ciclosporine, SIR=sirolimus, TAC=tacrolimus)				
TC* China Xu (Xu et al. 2009) 2009	Case series 1981-2007 164 males	long-term	Ciclosporine	>8 respiratory infections/year 18
Methotrexate				
TIS France Beghin (Beghin et al. 2011) 2011	Case series 1997-2009 42 pregnancies (40 fathers)	3 months prior to conception	Methotrexate	Height 49.3±2.5 cm Head circumference 34.6±1.7 cm Sex ratio 1.9 APGAR score at 1 minute 9.06 (range 6-20) for 27 children APGAR score at 5 minutes 10 for 23 children Amniocenteses were performed in six pregnancies (at risk for Down syndrome due to maternal age), and no chromosomal abnormality was reported
TIS Germany Weber-Schoendorfer (Weber-schoendorfer et al. 2014) 2014	Cohort 1995-2012 113 / 412 pregnancies	3 months prior to conception	Methotrexate	Length, median (IQR), cm 51 (49-53) / 51 (49-53) Head circumference, median (IQR), cm 35 (34-36) / 35 (34-36)
Friedman (Friedman et al. 2017) 2017	Cohort 1997-2013 209 / 1056524 children	3 months prior to conception	At least one filled prescription of methotrexate within 3 months before the date of conception / no filled prescription of methotrexate within 3 months before the date of conception	Malignancies 0 / 1720 (0.17) Autism Spectrum Disorder/schizophrenia 0 / 2107 (0.20) Attention Deficit Hyperactivity Disorder 3 (1.44) / 2799 (0.26)

Supplementary Table 4 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Other outcomes n (%)
Mycophenolate acid products				
TPR* USA Mortiz (Coscia et al. 2017) 2017	Cohort 1991-2017 295 / 1092 pregnancies	long-term	MPA / No MPA	Neonatal death 0.4 / (0.6)
PBR* Norway Midtvedt (Midtvedt et al. 2017) 2017	Cohort 1995-2015 155 (112) / 195 (133) children (fathers)	long-term	MPA / No MPA	Acute caesarean section 16 (10.3) / 24 (12.3) Normal placenta 121 (78.1) / 118 (60.5) Child length (cm) 49.6 ± 3.2 / 49.9 ± 3.0 Child head circumference (cm) 34.7 ± 2.1 / 35.1 ± 2.1 APGAR score after 1 min 8.6 ± 1.5 / 8.6 ± 1.5 APGAR score after 5 min 9.3 ± 1.3 /9.3 ± 1.4 Born alive, dead within 24 h 0 (0.0 /) 1 (0.5) Respiratory distress syndrome 4 (2.6) / 2 (1.0) Icterus 11 (7.1) / 12 (6.2) Hip dysplasia 1 (0.6) / 1 (0.5) Preeclampsia 7 (4.5) / 14 (7.3)
Systemic corticosteroids				
TC* China Xu (Xu et al. 2009) 2009	Case series 1981-2007 164 males	long-term	Prednisone	>8 respiratory infections/year 18
PBR* Norway Engeland (Viktil et al. 2012) 2012	Cohort 2004-2011 1477 singleton pregnancies	3 months prior to conception	Prednisolone	Perinatal mortality 8, OR (95% CI) 1.1 (0.53-2.1)

Supplementary Table 4 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Other outcomes n (%)
Thiopurines (AZA=azathioprine, 6MP=6-mercaptopurine)				
Hospital UK McGeown (McGeown et al. 1978) 1978	Case series NS 8 males (11 children)	long-term	Azathioprine	Chromosome analysis 9 normal, 1 trisomy 21, 1 pending
TC* China Xu (Xu et al. 2009) 2009	Case series 1981-2007 164 males	long-term	Azathioprine	>8 respiratory infections/year 18
Hospital USA Francella (Francella et al. 2003) 2003	Cohort 1950-1997 37 / 73 pregnancies	at the time of conception	6MP / pregnancies prior to treatment 6MP	Major or frequent infections 0 / 0 Neoplasia 1 (Wilms tumor diagnosed at age 4 years, surgically removed)/2
PBR* Denmark Friedman (Friedman et al. 2017) 2017	Cohort 1997-2013 735 / 1056524 children	3 months prior to conception	At least one filled prescription of AZA or 6MP within 3 months before the date of conception / no filled prescription of AZA or 6MP within 3 months before the date of conception	Malignancies 1 (0.14)/ 1720 (0.17) Autism Spectrum Disorder/schizophrenia 1 (0.14) / 2107 (0.20) Attention Deficit Hyperactivity Disorder 3 (0.41) / 2799 (0.26)
TNF-α inhibitors (INF=infliximab, ETN=etanercept, CZP=certolizumab pegol, ADA=adalimumab, GOL=golalinumab)				
Hospital Romania Micu (Micu et al. 2019) 2019	Cohort 2012-2017 33 / 12142 pregnancies	long-term	TNF-α I	Preeclampsia / eclampsia 0 / 110 (1.1) Other neonatal diseases that require prolonged stay in neonatal intensive care unit 0 / 18 90.2)

Supplementary Table 4 . Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Other outcomes n (%)
DMARDs not specified per drug				
PBR Norway Wallenius (Wallenius et al. 2015) 2015	Cohort 2001-2011 110 DMARD/ Reference group children	3 months prior to conception	Male patients with a diagnosis of inflammatory joint disease using DMARDS	Transfer to NICU 11 (10.0) / 52,766 (8.8) OR (95% CI) 1.14 (0.55-2.33) Perinatal death 0 (0.0) 3,401 (0.6) Post perinatal death 0 (0.0) 850 (0.1) Maternal preeclampsia 5 (4.5) 22,247 (3.7) OR (95% CI) 1.35 (0.55-3.31)
JuMBO registry Germany Drenches (Drenches et al. 2018) 2018	Case series Up to 2018 39 pregnancies (21 fathers)	26 (66.7) at the time of conception	12 etanercept 3 adalimumab 3 infliximab 2 certolizumab 1 anakinra 9 methotrexate 2 leflunomide	Pregnancy complications in live births 22% (18% exposed, unexposed 30%) Neonatal hospitalizations (22.7) / 3 (30.0)

Abbreviations in table
ADA (adalimumab), AZA (azathioprine), CZP (certolizumab pegol), CsP (ciclosporine), DMARDs (disease modifying anti rheumatic drugs) ETN (etanercept), GOL (golimumab), IQR (interquartile range), INF (infliximab), MPA (mycophenolic acid), 6MP (6-mercaptopurine), NICU (neonatal intensive care unit), NS (not stated), P (psoriasis), PA (psoriatic arthritis), PBR (population based registry), RA (rheumatoid arthritis), SIR (sirolimus), SpA (Spondyloarthritis), TAC (tacrolimus), TPR (transplantation population registry), TC (transplantation centre), TIS (Teratology Information Service), TNF-α-I (Tumour necrosis factor alpha inhibitor)

Supplementary Table 5. Exposure any time before conception for pregnancy and child outcomes.

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects+ (BD, n(%)) Other outcomes	QA* H, L NA
Calcineurin Inhibitors (CsP=ciclosporine, SIR=sirolimus, TAC=tacrolimus)								
PBR* Denmark Egeberg (Egeberg et al. 2017) 2017	Cohort 2004-2010 247 / 417387 children	Any time prior to conception	Ciclosporine / no immunosuppressants	NA	PB 15 (6.1) / 18957 (4.5) OR (95% CI) 1.36 (0.81-2.29) Adj. OR (95% CI) 1.45 (0.86-2.44)	LBW 19 (7.7) / 22070 (5.3) OR (95% CI) 1.49 (0.93-2.38) Adj. OR (95% CI) 1.51 (0.93-2.45)	BD 16 (6.5) / 31222 (7.5) OR (95% CI) 0.86 (0.52-1.42) Adj. OR (95% CI) 0.82 (0.49-1.39)	H
Methotrexate								
PBR* Denmark Egeberg (Egeberg et al. 2017) 2017	Cohort 2004-2010 864 / 416770	Any time prior to conception	Methotrexate / no immunosuppressants	NA	PB 39 (4.5) / 18933 (4.5) OR (95% CI) 0.99 (0.72-1.37) Adj. OR (95% CI) 1.02 (0.74-1.42)	LBW 40 (4.6) / 22049 (5.3) OR (95% CI) 0.87 (0.63-1.19) Adj. OR (95% CI) 0.86 (0.62-1.19)	BD 72 (8.3) / 31166 (7.5) OR (95% CI) 1.12 (0.88-1.43) Adj. OR (95% CI) 1.12 (0.87-1.43)	H
Mycophenolate acid products								
PBR* Denmark Egeberg (Egeberg et al. 2017) 2017	Cohort 2004-2010 37 / 417597 children	Any time prior to conception	Mycophenolate mofetil/ no immunosuppressants	NA	PB 3 (8.1) / 18969 (4.5) OR (95% CI) 1.85 (0.56-6.04) Adj. OR (95% CI) 1.84 (0.56-6.01)	LBW 3 (8.1) / 22086 (5.3) OR (95% CI) 1.58 (0.49-5.14) Adj. OR (95% CI) 1.55 (0.47-5.09)	BD <3 / 31236 (7.5) OR (95% CI) 0.71 (0.17-2.94) Adj. OR (95% CI) 0.70 (0.17-2.91)	H

Supplementary Table 5. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects+ (BD, n(%)) Other outcomes	QA* H, L NA
Retinoids								
PBR* Denmark Norgaard (Nørgaard et al. 2019) 2019	Cohort 1996-2016 244 pregnancies 205 children	1 year prior to conception and during first trimester	Acitretin / NS	SA Adj. HR (95%CI) 0.71 (0.43-1.17)	NS	NS	BD Adj. OR (95%CI) 1.15 (0.57-2.34)	L
Systemic corticosteroids								
PBR* Denmark Larsen (Larsen et al. 2018) 2018	Cohort 1997-2013 4942 / 1011614 live born children (singletons)	1 year till 3 months prior to conception	Filled prescriptions for systemic corticosteroids 81% prednisone, 12% prednisolone / No filled prescriptions for systemic corticosteroids in one year prior to conception	NA	PB 292 (5.91) / 56677 (5.63) OR (95% CI) 1.04 (0.90-1.20) Adj. OR (95% CI) 1.04 (0.89-1.20)	SGA 169 (3.43) / 33987 (3.39) OR (95% CI) 1.01 (0.85-1.20) Adj. OR (95% CI) 1.02 (0.85-1.20)	BD 251 (5.08) / 50170 (4.98) OR (95% CI) 1.02 (0.89-1.16) Adj. OR (95% CI) 1.03 (0.90-1.17)	H
Thiopurines (AZA=azathioprine, 6MP=6-mercaptopurine)								
Hospital USA Rajapakse (Rajapakse et al. 2000) 2000	Cohort 1970-1997 37 / 90 pregnancies	Until 3 months prior to conception	6MP / never taken 6MP or only after conception	SA 1 (2.7) / 2 (2.2)	NS	NS	BD 1 (2.7) / 0	L

Supplementary Table 5. Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n(%))	Birthweight (BW in gram, mean ± SD) Low birth weight (LBW, n(%)) Small for gestational age (SGA, n(%))	Birth defects+ (BD, n(%)) Other outcomes	QA* H, L NA
Hospital USA Francella (Francella et al. 2003) 2003	Cohort 1950-1997 44 / 73 pregnancies	Stopped before conception	6MP / pregnancies prior to treatment 6MP	LB 33 / 62 SA 4 / 11 ET 1 / 0	PB 1 / 3	LBW 2 / 3	BD 2 / 2	L
PBR* Denmark Egeberg (Egeberg et al. 2017) 2017	Cohort 2004-2010 1246 / 416388 children	Any time prior to conception	Azathioprine/ no immunosuppressants	NA	PB 66 (5.3) / 18906 (4.5) OR (95% CI) 1.18 (0.92-1.51) Adj. OR (95% CI) 1.10 (0.84-1.43)	LBW 73 (5.9) / 22016 (5.3) OR (95% CI) 1.11 (0.88-1.41) Adj. OR (95% CI) 1.08 (0.84-1.39)	BD 94 (7.5) / 31144 (7.5) OR (95% CI) 1.01 (0.82-1.25) Adj. OR (95% CI) 0.99 (0.80-1.23)	H

Abbreviations in table
H (high), L (low), ETOP (elective termination of pregnancy), NA (not applicable), NS (not stated), PBR (population based registry), QA (quality assessment)

REFERENCES

1. Engeland A, Bjørge T, Daltveit AK, Skurtveit S, Vangen S, Vollset SE, et al. Effects of preconceptional paternal drug exposure on birth outcomes: Cohort study of 340000 pregnancies using Norwegian population-based databases. Br J Clin Pharmacol. 2013;75(4):1134-41.
2. Crijns I, Bos J, Knol M, Straus S, de Jong-van den Berg L. Paternal drug use: before and during pregnancy. Expert Opin Drug Saf. 2012;11(4):513-8.
3. Schirm E, Pedersen L, Tobi H, Nielsen GL, Sorensen HT, de Jong-van den Berg LTW. Drug use among fathers around time of conception: two register based surveys from Denmark and The Netherlands. Pharmacoepidemiology and Drug Safety. 2004;13(9):609-13.
4. Khandwala YS, Zhang CA, Lu Y, Eisenberg ML. The age of fathers in the USA is rising: an analysis of 168 867 480 births from 1972 to 2015. Human reproduction (Oxford, England). 2017;32(10):2110-6.
5. Sasaki JC, Chapin RE, Hall DG, Breslin W, Moffit J, Saldutti L, et al. Incidence and nature of testicular toxicity findings in pharmaceutical development. Birth Defects Res B Dev Reprod Toxicol. 2011;92(6):511-25.
6. EMA. ICH S5 (R3) guideline on reproductive toxicology: detection of toxicity to reproduction for medicinal products including toxicity to male fertility. 2017.
7. FDA. Testicular Toxicity: Evaluation during Drug Development Guidance for Industry, Draft Guidance. 2015.
8. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
9. Bramer WM, de Jonge GB, Rethlefsen ML, Mast F, Kleijnen J. A systematic approach to searching: an efficient and complete method to develop literature searches. J Med Libr Assoc. 2018;106(4):531-41.
10. Bramer WM, Rethlefsen ML, Mast F, Kleijnen J. Evaluation of a new method for librarian-mediated literature searches for systematic reviews. Res Synth Methods. 2018;9(4):510-20.
11. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. Journal of the Medical Library Association : JMLA. 2016;104(3):240-3.
12. Wells G SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013.
13. Modesti PA, Reboldi G, Cappuccio FP, Agyemang C, Remuzzi G, Rapi S, et al. Panethnic Differences in Blood Pressure in Europe: A Systematic Review and Meta-Analysis. PLoS One. 2016;11(1):e0147601.
14. Nørgaard M, Andersen JT. Paternal acitretin exposure and pregnancy risks. Arch Dis Child. 2019;104(6).
15. Egeberg A, Gislason GH, Nast A. Birth Outcomes in Children Fathered by Men Treated with Immunosuppressant Drugs before Conception—A Danish Population-Based Cohort Study. J Invest Dermatol. 2017;137(8):1790-2.
16. Larsen MD, Friedman S, Magnussen B, Nørgård BM. Birth Outcomes in Children Fathered by Men Treated with Anti-TNF-alpha Agents Before Conception. American Journal of Gastroenterology. 2016;111(11):1608-13.
17. Di Paolo MC, Paoluzi OA, Pica R, Iacopini F, Crispino P, Rivera M, et al. Sulphasalazine and 5-aminosalicylic acid in long-term treatment of ulcerative colitis: Report on tolerance and side-effects. Dig Liver Dis. 2001;33(7):563-9.
18. Zelissen PMJ, Van Hattum J, Poen H, Scholten P, Gerritse R, Te Velde ER. Influence of salazosulphapyridine and 5-aminosalicylic acid on seminal qualities and male sex hormones. SCAND J GASTROENTEROL. 1988;23(9):1100-4.

19. Riley SA, Lecarpentier J, Mani V. Sulphasalazine induced seminal abnormalities in ulcerative colitis: Results of mesalazine substitution. GUT. 1987;28(8):1008-12.
20. Cosentino MJ, Chey WY, Takihara H, Cockett ATK. The effects of sulfasalazine on human male fertility potential and seminal prostaglandins. J UROL. 1984;132(4):682-6.
21. Freixa R, Rosello Catafau J, Gelpi E. Comparative study of antiinflammatory drugs and sulphasalazine in relation to prostaglandin E and 19 hydroxylated prostaglandin E levels and human male fertility. Prostaglandins Leukotrienes Med. 1984;16(3):359-69.
22. O'Morain C, Smethurst P, Dore CJ, Levi AJ. Reversible male infertility due to sulphasalazine: Studies in man and rat. GUT. 1984;25(10):1078-84.
23. Ragni G, Bianchi Porro G, Ruspa M. Abnormal semen quality and low serum testosterone in men with inflammatory bowel disease treated for a long time with sulfasalazine. Andrologia 1984;16(2):162-7.
24. Hudson E, Dore C, Sowter C. Sperm size in patients with inflammatory bowel disease on sulfasalazine therapy. Fertil Steril 1982;38(1):77-84.
25. Freeman JG, Reece VAC, Venables CW. Sulphasalazine and spermatogenesis. Digestion 1982;23(1):68-71.
26. Tobias R, Coetzee T, Sapire KE, Marks IN. Male infertility due to sulphasalazine. Postgrad Med J. 1982;58(676):102-3.
27. Toovey S, Hudson E, Hendry WF, Levi AJ. Sulphasalazine and male infertility: Reversibility and possible mechanism. GUT. 1981;22(6):445-51.
28. Levi AJ, Fischer AM, Hughes L, Hendry WF. Male infertility due to sulphasalazine. Lancet. 1979;2(8137):276-8.
29. Toth A. Reversible toxic effect of salicylazosulfapyridine on semen quality. Fertil Steril 1979;31(5):538-40.
30. McIntyre PB, Lennard-Jones JE. Reversal with balsalazide of infertility caused by sulphsalazine. Br Med J (Clin Res Ed). 1984;288(6431):1652-3.
31. Iglesias-cortit JL, Paz JL, Ballesca JL, Valles A, Iglesias-guiu J, Freixa R, et al. Effects of sulphasalazine, lysine acetylsalicylate and flurbiprofen on human spermatozoa. Adv Contracept Deliv Syst. 1985(1):92-6.
32. Cann PA, Holdsworth CD. Reversal of male infertility on changing treatment from sulphasalazine to 5-aminosalicylic acid. Lancet. 1984;1(8386):1119.
33. Ganatra A, Shaikh A, Chandak S, Kalke S, Bhojani N, Bhojani K. Effect of sulfasalazine on fertility of spondyloarthropathy patients. Indian J Rheumatol. 2018;13(6):S239.
34. Shaffer JL, Kershaw A, Berrisford MH. Sulphasalazine-induced infertility reversed on transfer to 5-aminosalicylic acid. Lancet. 1984;1(8388):1240.
35. Traub AI, Thompson W, Carville J. Male infertility due to sulphasalazine. Lancet. 1979;2(8143):639-40.
36. Chatzinoff M, Guarino JM, Corson SL, Batzer FR, Friedman LS. Sulfasalazine-induced abnormal sperm penetration assay reversed on changing to 5-aminosalicylic acid enemas. Dig Dis Sci. 1988;33(1):108-10.
37. Birnie GG, McLeod TI, Watkinson G. Incidence of sulphasalazine-induced male infertility. Gut. 1981;22(6):452-5.
38. Heineman MJ, Dony JMJ, Rolland R. Salicylazosulfapyridine and male infertility. EUR J OBSTET GYNECOL REPROD BIOL. 1981;12(5):297-303.
39. Ejebe DE, Ojieh AE, Ovuakporaye SI, Odion-Obomhense HK, Adegor EC, Amadi CN, et al. Effects of anti-malarial alkaloids on the sperm properties and blood levels of reproductive hormones of adult men. Afr J Biotechnol. 2008;7(19):3395-400.
40. Hargreaves CA, Rogers S, Hills F, Rahman F, Howell RJS, Homa ST. Effects of co-trimoxazole, erythromycin, amoxycillin, tetracycline and chloroquine on sperm function in vitro. Hum Reprod. 1998;13(7):1878-86.

41. Adeeko AO, Dada OA. Chloroquine excretion in semen following antimalarial-drug administration. Andrologia 1994;26(3):165-6.
42. Ette EI, Ogonor JI, Essien EE. Passage of chloroquine into semen. Br J Clin Pharmacol. 1988;26(2):179-82.
43. Zuber J, Anglicheau D, Elie C, Bererhi L, Timsit MO, Mamzer-Bruneel MF, et al. Sirolimus may reduce fertility in male renal transplant recipients. Am J Transplant. 2008;8(7):1471-9.
44. Skrzypek J, Krause W. Azoospermia in a renal transplant recipient during sirolimus (rapamycin) treatment. Andrologia. 2007;39(5):198-9.
45. Deutsch MA, Kaczmarek I, Huber S, Schmauss D, Beiras-Fernandez A, Schmoeckel M, et al. Sirolimus-associated infertility: Case report and literature review of possible mechanisms. Am J Transplant. 2007;7(10):2414-21.
46. Kaczmarek I, Groetzner J, Adamidis I, Landwehr P, Mueller M, Vogeser M, et al. Sirolimus impairs gonadal function in heart transplant recipients. Am J Transplant. 2004;4(7):1084-8.
47. Lee S, Coco M, Greenstein SM, Schechner RS, Tellis VA, Glicklich DG. The effect of sirolimus on sex hormone levels of male renal transplant recipients. Clinical Transplantation. 2005;19(2):162-7.
48. Misro MM, Chaki SP, Srinivas M, Chaube SK. Effect of cyclosporine on human sperm motility in vitro. Arch Androl. 1999;43(3):215-20.
49. Sajad Hussain S, Farhat S, Wani I. Oligospermia secondary to sirolimus. Indian J Transplant. 2015;9(3):119-21.
50. Boobes Y, Bernieh B, Saadi H, Hakim MRA, Abouchacra S. Gonadal dysfunction and infertility in kidney transplant patients receiving sirolimus. Int Urol Nephrol. 2010;42(2):493-8.
51. Bererhi L, Flamant M, Martinez F, Karras A, Thervet E, Legendre C. Rapamycin-induced oligospermia [3]. Transplantation. 2003;76(5):885-6.
52. Fritsche L, Budde K, Dragun D, Einecke G, Diekmann F, Neumayer HH. Testosterone concentrations and sirolimus in male renal transplant patients. Am J Transplant. 2004;4(1):130-1.
53. Tondolo V, Citterio F, Panocchia N, Nanni G, Favi E, Brescia A, et al. Gonadal function and immunosuppressive therapy after renal transplantation. Transplant Proc. 2005;37(4):1915-7.
54. Kramer BK, Neumayer HH, Stahl R, Pietrzyk M, Kruger B, Pfalzer B, et al. Graft function, cardiovascular risk factors, and sex hormones in renal transplant recipients on an immunosuppressive regimen of everolimus, reduced dose of cyclosporine, and basiliximab. Transplant Proc. 2005;37(3):1601-4.
55. Haberman J, Karwa G, Greenstein SM, Soberman R, Glicklich D, Tellis V, et al. Male fertility in cyclosporine-treated renal transplant patients. J UROL. 1991;145(2):294-6.
56. Samojlik E, Kirschner MA, Ribot S, Szmal E. Changes in the hypothalamic-pituitary-gonadal axis in men after cadaver kidney transplantation and cyclosporine therapy. J ANDROL. 1992;13(4):332-6.
57. Kantarci G, Sahin S, Uras AR, Ergin H. Effects of different calcineurin inhibitors on sex hormone levels in transplanted male patients. Transplant Proc. 2004;36(1):178-9.
58. Peces R, Delatorre M, Urra JM. Pituitary Testicular Function in Cyclosporine-Treated Renal-Transplant Patients. Nephrology Dialysis Transplantation. 1994;9(10):1453-5.
59. Eid MM, Abdel-Hamid IA, Sobh MA, el-Saied MA. Assessment of sperm motion characteristics in infertile renal transplant recipients using computerized analysis. Int J Androl. 1996;19(6):338-44.
60. Moritz M, Coscia L, Armenti D, Constantinescu S. Transplant pregnancy registry international: Fathered pregnancy outcomes with exposure to mycophenolic acid products. Transplant Int. 2017;30:152.
61. Schopf R. Cyclosporine treatment for psoriasis followed by fathering of a healthy child in a previously infertile male. J Am Acad Dermatol. 2017;76(6):AB71.

62. Holmgren G, Lundgren HE, Suhr OB. Successful pregnancies and fatherhood in familial amyloidotic polyneuropathy (FAP Val30Met) patients with liver transplantation. Amyloid. 2004;11(2):125-9.
63. Ecevit C, Ünal F, Baran M, Aydoğdu S. Parenthood in pediatric liver transplant patients. Pediatr Transplant. 2012;16(4):346-9.
64. Xu L, Han S, Liu Y, Wang H, Yang Y, Qiu F, et al. The influence of immunosuppressants on the fertility of males who undergo renal transplantation and on the immune function of their offspring. Transplant Immunol. 2009;22(1-2):28-31.
65. Moskovitz B, Lin R, Nassar S, Levin DR. Effect of diclofenac sodium (Voltaren) on spermatogenesis of infertile oligospermic patients. Eur Urol 1988;14(5):395-7.
66. Kirchin VS, Southgate HJ, Beard RC. Colchicine: An unusual cause of reversible azoospermia. BJU Int. 1999;83(1):156.
67. Sarica K, Suzer O, Gurler A, Baltact S, Ozdiler E, Dincel C. Urological evaluation of Behcet patients and the effect of colchicine on fertility. Eur Urol 1995;27(1):39-42.
68. Ben-Chetrit A, Ben-Chetrit E, Nitzan R, Ron M. Colchicine inhibits spermatozoal motility in vitro. Int J Fertil 1993;38(5):301-4.
69. Merlin HE. Azoospermia caused by colchicine--a case report. Fertil Steril. 1972;23(3):180-1.
70. Kaya Aksoy G, Koyun M, Usta MF, Çomak E, Akman S. Semen analysis in adolescents with familial Mediterranean fever. J Pediatr Urol. 2019.
71. Kastrop P, Kimmel I, Bancsi L, Weima S, Giltay J. The effect of colchicine treatment on spermatozoa: A cytogenetic approach. J Assisted Reprod Genet. 1999;16(9):504-7.
72. Levy M, Eliakim M. Long-term colchicine prophylaxis in familial Mediterranean fever. Br Med J 1977;2(6090):808.
73. Bremner WJ, Paulsen CA. Colchicine and testicular function in man. New Engl J Med 1976;294(25):1384-5.
74. Ehrenfeld M, Levy M, Margalioth EJ, Eliakim M. The effects of long-term colchicine therapy on male fertility in patients with familial Mediterranean fever. Andrologia 1986;18(4):420-6.
75. Ben-Chetrit E, Berkun Y, Ben-Chetrit E, Ben-Chetrit A. The outcome of pregnancy in the wives of men with familial mediterranean fever treated with colchicine. Semin Arthritis Rheum. 2004;34(2):549-52.
76. Suehiro RM, Borba EF, Bonfa E, Okay TS, Cocuzza M, Soares PMF, et al. Testicular Sertoli cell function in male systemic lupus erythematosus. Rheumatology (UK). 2008;47(11):1692-7.
77. Soares PMF, Borba EF, Bonfa E, Hallak J, Corrêa AL, Silva CAA. Gonad evaluation in male systemic lupus erythematosus. Arthritis Rheum. 2007;56(7):2352-61.
78. Anserini P, Chiodi S, Spinelli S, Costa M, Conte N, Copello F, et al. Semen analysis following allogeneic bone marrow transplantation. Additional data for evidence-based counselling. Bone Marrow Transplant. 2002;30(7):447-51.
79. Bogdanovic R, Banicevic M, Cvoric A. Testicular function following cyclophosphamide treatment for childhood nephrotic syndrome: Long-term follow-up study. Pediatr Nephrol. 1990;4(5):451-4.
80. Perrone L, Sinisi AA, Del Gado R, Del Gaizo D, Bellastella A, Faggiano M. Late effects of cyclophosphamide on testicular function in prepubertal boys and adults. J PEDIATR ENDOCRINOL. 1989;3(2):105-8.
81. Watson AR, Rance CP, Bain J. Long term effects of cyclophosphamide on testicular function. Br Med J 1985;291(6507):1457-60.
82. Ogata H, Shibata T, Hirai Y. Effect of cyclophosphamide on the reproductive function. (Study of testicular histology in male patients with nephrotic syndrome). Nephron 1982;32(3):294.
83. Fukutani K, Ishida H, Shinohara M. Suppression of spermatogenesis in patients with Behcet's disease treated with cyclophosphamide and colchicine. Fertil Steril 1981;36(1):76-80.

84. Trompeter RS, Evans PR, Barratt TM. Gonadal function in boys with steroid-responsive nephrotic syndrome treated with cyclophosphamide for short periods. Lancet. 1981;1(8231):1177-9.
85. Marina S, Barcelo P. Permanent sterility after immunosuppressive therapy. Int J Androl 1979;2(1):6-13.
86. Hsu AC, Folami AO, Bain J, Rance CP. Gonadal function in males treated with cyclophosphamide for nephrotic syndrome. Fertil Steril 1979;31(2):173-7.
87. Etteldorf JN, West CD, Pitcock JA, Williams DL. Gonadal function, testicular histology, and meiosis following cyclophosphamide therapy in patients with nephrotic syndrome. J Pediatr. 1976;88(2):206-12.
88. Pennisi AJ, Grushkin CM, Lieberman E. Gonadal function in children with nephrosis treated with cyclophosphamide. Am J Dis Child 1975;129(3):315-8.
89. Kirkland RT, Bongiovanni AM, Cornfeld D. Gonadotropin responses to luteinizing release factor in boys treated with cyclophosphamide for nephrotic syndrome. J Pediatr. 1976;89(6):941-4.
90. Kumar R, Biggart JD, McEvoy J, McGeown MG. Cyclophosphamide and reproductive function. Lancet. 1972;1(7762):1212-4.
91. Penso J, Lippe B, Ehrlich R, Smith FG. Testicular function in prepubertal and pubertal male patients treated with cyclophosphamide for nephrotic syndrome. J Pediatr. 1974;84(6):831-6.
92. Feng PH, George CR, Evans RA, Murkin GE, Spicer E, Thomas BS, et al. Cyclophosphamide and infertility. Lancet. 1972;1(7755):840-2.
93. Masala A, Faedda R, Alagna S, Satta A, Chiarelli G, Rovasio PP, et al. Use of testosterone to prevent cyclophosphamide-induced azoospermia. ANN INTERN MED. 1997;126(4):292-5.
94. Fairley KF, Barrie JU, Johnson W. Sterility and testicular atrophy related to cyclophosphamide therapy. Lancet. 1972;1(7750):568-9.
95. Balci S, Sarikayalar F. Absence of a hand (acheiria) in a child whose father was treated with cyclophosphamide for Behcet's disease. Turk J Pediatr. 1983;25(1):55-8.
96. Weber-Schoendorfer C, Schaefer C. Pregnancy outcome after tocilizumab therapy in early pregnancy-case series from the German Embryotox Pharmacovigilance Center. Reprod Toxicol. 2016;60:29-32.
97. Youngstein T, Hoffmann P, Gül A, Lane T, Williams R, Rowczenio DM, et al. International multi-centre study of pregnancy outcomes with interleukin-1 inhibitors. Rheumatology. 2017;56(12):2102-8.
98. Warren R, Reich K, Langley R, Strober B, Gladman D, Deodhar A, et al. Secukinumab in pregnancy: Outcomes in psoriasis, psoriatic arthritis and ankylosing spondylitis from the global safety database. Acta Derm -Venereol. 2018;98:11.
99. Ley D, Jones J, Parrish J, Salih S, Caldera F, Tirado E, et al. Methotrexate Reduces DNA Integrity in Sperm From Men With Inflammatory Bowel Disease. 2018.
100. Sussman A, Leonard JM. Psoriasis, methotrexate, and oligospermia. Arch Dermatol. 1980;116(2):215-7.
101. Van Scott EJ, Reinertson RP. Morphologic and physiologic effects of chemotherapeutic agents in psoriasis. J Invest Dermatol. 1959;33:357-69.
102. Pandhi D, Gupta R, Singal A. Gynaecomastia with oligospermia: an unusual complication of low-dose methotrexate for pustular psoriasis. Clin Exp Dermatol. 2006;31(1):138-40.
103. El-Beheiry A, El-Mansy E, Kamel N, Salama N. Methotrexate and fertility in men. ARCH ANDROL. 1979;3(2):177-9.
104. Grunnet E, Nyfors A, Brogaard Hansen K. Studies on human semen in topical corticosteroid treated and in methotrexate treated psoriatics. Dermatologica. 1977;154(2):78-84.

105. Perry WH. Methotrexate and teratogenesis. Arch Dermatol. 1983;119(11):874-5.
106. Griggs LR, Schwartz DA. Successful paternity of a healthy child while taking methotrexate for Crohn's disease [13]. Am J Gastroenterol. 2006;101(12):2893-4.
107. Lamboglia F, D'Incà R, Oliva L, Bertomoro P, Sturniolo GC. Patient with severe Crohn's disease became a father while on methotrexate and infliximab therapy. Inflammatory Bowel Dis. 2009;15(5):648-9.
108. Beghin D, Cournot MP, Vauzelle C, Elefant E. Paternal exposure to methotrexate and pregnancy outcomes. J Rheumatol. 2011;38(4):628-32.
109. Drenches P, Klotsche J, Niewerth M, Horneff G, Minden K. Pregnancy outcomes in partners of DMARD exposed men with juvenile idiopathic arthritis-an observational study. Arthritis Rheum. 2018;70:1580-1.
110. Weber-schoendorfer C, Hoeltzenbein M, Wacker E, Meister R, Schaefer C. No evidence for an increased risk of adverse pregnancy outcome after paternal low-dose methotrexate: An observational cohort study. Rheumatology. 2014;53(4):757-63.
111. Winter RW, Larsen MD, Magnussen B, Friedman S, Kammerlander H, Nøgård BM. Birth outcomes after preconception paternal exposure to methotrexate: A nationwide cohort study. Reprod Toxicol. 2017;74:219-23.
112. Andersen J, Askaa B, Broedbaek K. Paternal exposure to methotrexate and the risk of miscarriage-A registerbased nationwide cohort study. Pharmacoepidemiol Drug Saf. 2018;27:231.
113. Friedman S, Larsen MD, Magnussen B, Jølving LR, de Silva P, Nørgård BM. Paternal use of azathioprine/6-mercaptopurine or methotrexate within 3 months before conception and long-term health outcomes in the offspring—A nationwide cohort study. Reprod Toxicol. 2017;73:196-200.
114. Jones A, Clary MJ, McDermott E, Coscia LA, Constantinescu S, Moritz MJ, et al. Outcomes of pregnancies fathered by solid-organ transplant recipients exposed to mycophenolic acid products. Prog Transplant. 2013;23(2):153-7.
115. Midtvedt K, Bergan S, Reisæter AV, Vikse BE, Åsberg A. Exposure to Mycophenolate and Fatherhood. Transplantation. 2017;101(7):e214-e7.
116. Åsberg A, Reisæter AV, Bergan S, Vikse BE, Midtvedt K. Exposure to mycophenolate and fatherhood-is there a risk? Transplant Int. 2017;30:152-3.
117. Lopez-Lopez I, Rodelo-Haad C, Agüera ML, Cabello-Jabalquinto R, Esquivias-Motta E, Navarro MD, et al. Administration of mycophenolic acid is not associated with malformations in descendants from kidney transplanted males. PLoS ONE. 2018;13(9).
118. Poratsoldin O, Soldin SJ. Preliminary Studies on the Invitro and Invivo Effect of Salicylate on Sperm Motility. Therapeutic Drug Monitoring. 1992;14(5):366-70.
119. Bendvold E, Gottlieb C, Svanborg K. The effect of naproxen on the concentration of prostaglandins in human seminal fluid. Fertil Steril 1985;43(6):922-6.
120. Knuth UA, Kuhne J, Crosby J, Bals-Pratsch M, Kelly RW, Nieschlag E. Indomethacin and oxaprozin lower seminal prostaglandin levels but do not influence sperm motion characteristics and serum hormones of young healthy men in a placebo-controlled double-blind trial. J Androl 1989;10(2):108-19.
121. Kristensen DM, Desdoits-Lethimonier C, Mackey AL, Dalgaard MD, De Masi F, Munkbol CH, et al. Ibuprofen alters human testicular physiology to produce a state of compensated hypogonadism. Proc Natl Acad Sci U S A. 2018;115(4):E715-E24.
122. Albert O, Desdoits-Lethimonier C, Lesné L, Legrand A, Guillé F, Bensalah K, et al. Paracetamol, aspirin and indomethacin display endocrine disrupting properties in the adult human testis in vitro. Hum Reprod. 2013;28(7):1890-8.
123. Liu H, Li J, Yu L. Effects of acitretin on semen quality and reproductive hormone levels in patients with psoriasis vulgaris. Dermatol Sin. 2017;35(2):55-8.

124. Schmitt-Hoffmann AH, Roos B, Sauer J, Brown T, Weidekamm E, Meyer I, et al. Low levels of alitretinoin in seminal fluids after repeated oral doses in healthy men. Clin Exp Dermatol. 2011;36(SUPPL. 2):12-7.
125. Rossi M, Pellegrino M. Acitretin-associated erectile dysfunction: A case report. Cases J. 2009;2(11).
126. Parsch EM, Ruzicka T, Przybilla B, Schill WB. Andrological investigation in men treated with acitretin (Ro 10-1670). Andrologia 1990;22(5):479-82.
127. Çinar L, Kartal D, Ergin C, Aksoy H, Karadag MA, Aydin T, et al. The effect of systemic isotretinoin on male fertility. Cutaneous Ocul Toxicol. 2016;35(4):296-9.
128. Torok L, Kadar L, Kasa M. Spermatological investigations in patients treated with etretinate and isotretinoin. Andrologia. 1987;19(6):629-33.
129. Coleman R, MacDonald D. Effects of isotretinoin on male reproductive system [18]. Lancet. 1994;344(8916):198.
130. Healy D, Le Noury J, Mangin D. Enduring sexual dysfunction after treatment with antidepressants, 5α-reductase inhibitors and isotretinoin: 300 cases. Int J Risk Saf Med. 2018;29(3-4):125-34.
131. Katugampola RP, Finlay AY. Oral retinoid therapy for disorders of keratinization: Single-centre retrospective 25 years' experience on 23 patients. Br J Dermatol. 2006;154(2):267-76.
132. McDonald JH, Heckel NJ. The effect of cortisone on the spermatogenic function of the human testes. J Urol. 1956;75(3):527-9.
133. Martens HF, Sheets PK, Tenover JS, Dugowson CE, Bremner WJ, Starkebaum G. Decreased testosterone levels in men with rheumatoid arthritis: effect of low dose prednisone therapy. J Rheumatol. 1994;21(8):1427-31.
134. Drobnis EZ, Nangia AK. Immunosuppressants and male reproduction. Adv Exp Med Biol. 2017;1034:179-210.
135. Larsen MD, Friedman S, Magnussen B, Norgard BM. Birth Outcome of Children Fathered by Men Treated with Systemic Corticosteroids during the Conception Period - A Cohort Study based on Nationwide Data. Basic & Clinical Pharmacology & Toxicology. 2018;122(1):133-8.
136. McGeown MG, Nevin NC. Cytogenetic analysis on children born of parents treated with immunosuppressive drugs. Proc Eur Dial Transplant Assoc. 1978;15:384-90.
137. Xu LG, Yang YR, Wang HW, Qiu F, Peng WL, Xu HM, et al. Characteristics of male fertility after renal transplantation. Andrologia. 2011;43(3):203-7.
138. Penn I, Makowski E, Droegemueller W, Halgrimson CG, Starzl TE. Parenthood in renal homograft recipients. Jama. 1971;216(11):1755-61.
139. Dejaco C, Mittermaier C, Reinisch W, Gasche C, Waldhoer T, Strohmer H, et al. Azathioprine treatment and male fertility in inflammatory bowel disease. Gastroenterology. 2001;121(5):1048-53.
140. Farthing MJG, Dawson AM. Impaired semen quality in Crohn's disease - Drugs, ill health, or undernutrition? Scand J Gastroenterol. 1983;18(1):57-60.
141. Baumgarten SR, Lindsay GK, Wise GJ. Fertility problems in the renal transplant patient. J Urol. 1977;118(6):991-3.
142. Grosen A, Nersting J, Bungum M, Christensen LA, Schmiegelow K, Spanò M, et al. Sperm DNA integrity is unaffected by thiopurine treatment in men with inflammatory bowel disease. J Crohn's Colitis. 2019;13(1):3-11.
143. Rajapakse RO, Korelitz BI, Zlatanic J, Baiocco PJ, Gleim GW. Outcome of pregnancies when fathers are treated with 6-mercaptopurine for inflammatory bowel disease. Am J Gastroenterol. 2000;95(3):684-8.
144. Francella A, Dyan A, Bodian C, Rubin P, Chapman M, Present DH. The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: A retrospective cohort study. Gastroenterology. 2003;124(1):9-17.

145. Teruel C, Román ALS, Bermejo F, Taxonera C, Pérez-Calle JL, Gisbert JP, et al. Outcomes of pregnancies fathered by inflammatory bowel disease patients exposed to thiopurines. Am J Gastroenterol. 2010;105(9):2003-8.
146. Hoeltzenbein M, Weber-Schoendorfer C, Borisch C, Allignol A, Meister R, Schaefer C. Pregnancy outcome after paternal exposure to azathioprine/6-mercaptopurine. Reprod Toxicol. 2012;34(3):364-9.
147. Nørgård BM, Magnussen B, Larsen MD, Friedman S. Reassuring results on birth outcomes in children fathered by men treated with azathioprine/6-mercaptopurine within 3 months before conception: A nationwide cohort study. Gut. 2017;66(10):1761-6.
148. Oh JS, Heo HM, Kim YG, Lee SG, Lee CK, Yoo B. The effect of anti-tumor necrosis factor agents on sexual dysfunction in male patients with ankylosing spondylitis: A pilot study. Int J Impotence Res. 2009;21(6):372-5.
149. Kreitenberg AJ, Ortiz EC, Arkfeld DG. Priapism after tumor necrosis factor alpha inhibitor use. Clin Rheumatol. 2015;34(4):801-2.
150. Perrier d'Hauterive S, Kesseler S, Ruggeri P, Timmermans M, Gaspard O, Kumke T, et al. Certolizumab PEGOL did not result in a decrease in semen quality in healthy volunteers: results from a phase 1 study. Annals of the rheumatic disease. 2012;71.
151. Heppt F, Colsman A, Maronna A, Uslu U, Heppt MV, Kiesewetter F, et al. Influence of TNF-alpha inhibitors and fumaric acid esters on male fertility in psoriasis patients. J Eur Acad Dermatol Venereol. 2017;31(11):1860-6.
152. Micu MC, Micu R, Surd S, Gîrlovanu M, Bolboac SD, Ostensen M. TNF-α inhibitors do not impair sperm quality in males with ankylosing spondylitis after short-term or long-term treatment. Rheumatology. 2014;53(7):1250-5.
153. Almeida BP, Saad CGS, Souza FHC, Moraes JCB, Nukumizu LA, Viana VST, et al. Testicular Sertoli cell function in ankylosing spondylitis. Clin Rheumatol. 2013;32(7):1075-9.
154. Grosen A, Bungum M, Christensen LA, Cordelli E, Larsen OH, Leter G, et al. Semen Quality and Sperm DNA Integrity in Patients With Severe Active Inflammatory Bowel Disease and Effects of Tumour Necrosis Factor-alpha Inhibitors. J Crohns Colitis. 2019;13(5):564-71.
155. Micu MC, Ostensen M, Bojinca V, Serban O, Mihai M, Suta C, et al. Pregnancy Outcomes in Couples with Males Exposed to Longterm Anti-tumor Necrosis Factor-alpha Inhibitor Therapies: A Prospective Study. 2019.
156. Pascarelli NA, Fioravanti A, Moretti E, Guidelli GM, Mazzi L, Collodel G. The effects in vitro of TNF-α and its antagonist 'etanercept' on ejaculated human sperm. Reprod Fertil Dev. 2017;29(6):1169-77.
157. Ramonda R, Foresta C, Ortolan A, Bertoldo A, Oliviero F, Lorenzin M, et al. Influence of tumor necrosis factor α inhibitors on testicular function and semen in spondyloarthritis patients. Fertil Steril. 2014;101(2):359-65.
158. Villiger PM, Caliezi G, Cottin V, Förger F, Senn A, Østensen M. Effects of TNF antagonists on sperm characteristics in patients with spondyloarthritis. Ann Rheum Dis. 2010;69(10):1842-4.
159. Mahadevan U, Terdiman JP, Aron J, Jacobsohn S, Turek P. Infliximab and semen quality in men with inflammatory bowel disease. Inflammatory Bowel Dis. 2005;11(4):395-9.
160. Paschou S, Voulgari PV, Vrabie IG, Saougou IG, Drosos AA. Fertility and reproduction in male patients with ankylosing spondylitis treated with infliximab. J Rheumatol. 2009;36(2):351-4.
161. Saougou I, Markatseli TE, Papagoras C, Kaltsonoudis E, Voulgari PV, Drosos AA. Fertility in male patients with seronegative spondyloarthropathies treated with infliximab. Jt Bone Spine. 2013;80(1):34-7.
162. Uyaroglu OA, Seyhoglu E, Erden A, Kilic L, Armagan B, Sari A, et al. Pregnancy outcomes in male patients using anti-tumor necrosis factor alpha patients with inflammatory arthritis; hur-bio real life experiences. Arthritis Rheum. 2017;69.

163. Hoxha A, Calligaro A, Di Poi E, Peccatori S, Favaro M, Del Ross T, et al. Pregnancy and foetal outcomes following anti-tumor necrosis factor alpha therapy: A prospective multicentre study. Jt Bone Spine. 2017;84(2):169-73.
164. Lichtenstein GR, Feagan BG, Mahadevan U, Salzberg BA, Langholff W, Morgan GJ, et al. Pregnancy Outcomes Reported During the 13-Year TREAT Registry: A Descriptive Report. Am J Gastroenterol. 2018;113(11):1678-88.
165. Clowse MEB, Wolf DC, Förger F, Cush JJ, Golembesky A, Shaughnessy L, et al. Pregnancy outcomes in subjects exposed to certolizumab pegol. J Rheumatol. 2015;42(12):2270-8.
166. Grosen A, Bungum M, Hvas CL, Julsgaard M, Cordelli E, Kelsen J. Vedolizumab Does Not Impair Sperm DNA Integrity in Men With Inflammatory Bowel Disease. Gastroenterology. 2019;156(8):2342-4.
167. De Santis M, Straface G, Cavaliere A, Carducci B, Caruso A. Paternal and maternal exposure to leflunomide: Pregnancy and neonatal outcome. Ann Rheum Dis. 2005;64(7):1096-7.
168. Kumar M, Ray L, Vemuri S, Simon T. Pregnancy outcomes following exposure to abatacept during pregnancy. Internal medicine journal Conference: 56th annual scientific meeting of the australian rheumatology association in conjunction with the rheumatology health professionals association Australia. 2015;45:31.
169. Mahadevan U, Dubinsky MC, Su C, Lawendy N, Jones TV, Marren A, et al. Outcomes of pregnancies with maternal/paternal exposure in the tofacitinib safety databases for ulcerative colitis. Inflammatory Bowel Dis. 2018;24(12):2494-500.
170. Grosen A, Kelsen J, Hvas CL, Bellaguarda E, Hanauer SB. The Influence of Methotrexate Treatment on Male Fertility and Pregnancy Outcome after Paternal Exposure. Inflammatory Bowel Dis. 2017;23(4):561-9.
171. Simsek M, Lambalk CB, Wilschut JA, Mulder CJJ, De Boer NKH. The associations of thiopurines with male fertility and paternally exposed offspring: A systematic review and meta-analysis. Hum Reprod Update. 2018;24(2):192-206.
172. EMA. Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling. . 2008. p. 1-18.
173. Perez-Garcia LF, Te Winkel B, Carrizales JP, Bramer W, Vorstenbosch S, van Puijenbroek E, et al. Sexual function and reproduction can be impaired in men with rheumatic diseases: A systematic review. Semin Arthritis Rheum. 2020.

CHAPTER 7

Is methotrexate safe for men with an immune-mediated inflammatory disease and an active desire to become a father? Results of a prospective cohort study (iFAME-MTX)

Published

Perez-Garcia LF, Röder E, Krijthe BP, Kranenburg-van Koppen LJ, van Adrichem R, Zirkzee E, Griffioen PH, Peeters K, Lin M, Struys EA, Jansen G, van Doorn MB, de Jonge R, Dohle GR, Dolhain RJ.

Ann Rheum Dis. 2023 Aug;82(8):1068-1075.

ABSTRACT

Introduction

Current scientific evidence guiding the decision whether men with an active desire to become a father should be treated with methotrexate (MTX) remains controversial. We aimed to prospectively evaluate the testicular-toxicity profile of MTX focusing on several markers of male fertility including semen parameters and sperm DNA fragmentation index (sDFI). As a secondary outcome, we aimed to evaluate if MTX-polyglutamates can be detected in spermatozoa and seminal plasma and to evaluate the enzymatic activity in spermatozoa of folylpolyglutamate synthetase (FPGS).

Methods

In a prospective cohort study, men ≥18 years who started therapy with MTX were invited to participate (MTX-starters). Participants were instructed to produce 2 semen samples (a pre-exposure and a post-exposure sample after 13 weeks). Healthy men ≥18 years were invited to participate as controls. Conventional semen analyses, male reproductive endocrine axis and sDFI were compared between groups. FPGS enzymatic activity and MTX-PG1-5 concentrations were determined by mass spectrometry analytical methods.

Results

In total 20 MTX-starters and 25 controls were included. The pre-exposure and post-exposure semen parameters of MTX-starters were not statistically significant different. Compared to healthy controls, the conventional semen parameters and the sDFI of MTX-starters were not statistically significant different. These data were corroborated by the marginal accumulation of MTX-PGs in spermatozoa, consistent with the very low FPGS enzymatic activity associated with the expression of an alternative FPGS splice-variant.

Conclusion

Treatment with MTX is not associated with testicular toxicity, consistent with the very low concentration of intracellular MTX-PG. Therefore, therapy with MTX can be safely started or continued in men and with a wish to become a father.

INTRODUCTION

Methotrexate (MTX) is one of the most frequently prescribed immunosuppressive drugs for the treatment of several immune-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and psoriasis. Remarkably, for men with an active desire to become a father, the decision of whether they should stop or continue therapy with MTX before conception remains controversial.

In this regard, the American College of Rheumatology recently updated its recommendations on paternal immunosuppressive exposure before conception (1). Concerning MTX, they recommend that MTX can be "conditionally continued" in men planning to father a child. Furthermore, the British Society for Rheumatology guideline on prescribing drugs in pregnancy considers paternal exposure to low-dose MTX (≤25mg/week) as compatible with pregnancy (2). Conversely, other federal agencies and medical associations recommend that MTX should be stopped at least 3 to 6 months before conception (3-5).

A fundamental reason for these contradictory recommendations is the scarcity of solid scientific data on the testicular toxicity profile of MTX. In its guideline to evaluate testicular toxicity, the Food and Drug Administration (FDA) considers semen analysis parameters as the main outcomes of interest (6). Furthermore, in studies evaluating testicular toxicity, the FDA recommends evaluating at least one baseline and one follow-up semen sample (at the end of the first 13 weeks).

In addition to spermatogenesis, the production of hormones is another important function of the testicles. Therefore, the evaluation of the male reproductive endocrine axis (i.e. testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH)) should also be considered an important outcome (7).

Another novel outcome of interest that reflects the integrity or damage of the sperm DNA and that can be evaluated, is the sperm DNA Fragmentation Index (sDFI) (8). Sperm DNA integrity is indispensable for the birth of healthy offspring and sperm DNA damage has been strongly associated with male infertility and a higher risk of miscarriages (9). Sperm DNA damage can be induced by either the pharmacological exposure itself or the oxidative stress and inflammation states associated with a diagnosis of IMID (10).

Lastly, it is known that the pharmacological efficacy of MTX critically depends on the intracellular bioactivation of MTX to MTX-polyglutamates (MTX-PG). This process is catalyzed by the enzyme folylpolyglutamate synthetase (FPGS). Lower FPGS activity and

subsequent inefficient polyglutamylation is a well-known phenomenon associated with a rapid efflux of MTX from cells (11). MTX-PG have been detected in several human cells such as erythrocytes or peripheral blood mononuclear cells (PBMCs) and low levels of MTX-PG have been associated with increased resistance to therapy (12, 13). In this regard, recent molecular studies have shown that a significant reduction of FPGS activity is associated with aberrant pre-mRNA splicing of this enzyme, including partial retention of intron 8 (8PR) and a higher ratio of FPGS 8PR over FPGS wild type (WT) (14). Whether intracellular MTX-PG can be detected in the spermatozoa and whether the spermatozoa have the enzymatic capabilities of forming and retaining intracellular MTX-PG has never been studied before.

To establish if MTX can be safely used by men diagnosed with an IMID and a wish to conceive, we aimed to prospectively evaluate the testicular toxicity profile of MTX focusing on several markers of male fertility such as semen parameters, the male reproductive endocrine axis and the sDFI. Furthermore, as a secondary outcome, we aimed to evaluate if MTX-PG can be detected in spermatozoa and seminal plasma and to evaluate the FPGS enzymatic activity in spermatozoa.

METHODS

Study design and patient selection

The iFAME-MTX study was a prospective cohort study conducted in the Erasmus University Medical Center, Rotterdam, The Netherlands. All participants were aged 18-55 years and were proven fertile (history of a partner's positive pregnancy test). Three groups of men were included in the study. First, men diagnosed with an IMID (RA, Spondyloarthritis (SpA), PsA, psoriasis) based on the expert opinion of their rheumatologist or dermatologist, who were not exposed to MTX in the last year and were going to start therapy with MTX, were included in the "MTX-starters" group. Second, to evaluate the effect of chronic MTX exposure, men who were exposed to MTX ($\geq$ 15 mg/week for $\geq$ 1 year) were included in the "MTX-chronic" group. Third, healthy men were included as "healthy controls".

Men who were not proven fertile, who were exposed to drugs with known testicular toxic side effects (i.e. oligospermia) were excluded. Importantly, concomitant therapy with prednisone ($\leq$7.5 mg/day), hydroxychloroquine or TNF-inhibitors was allowed (See Supplement 1, Table 1. Exclusion criteria and Table 2. Exclusion criteria, drug exposure).

Study visits

A study visit consisted of three parts. First, the demographic and medical history were obtained from an interview, followed by a concise physical evaluation. Second, a blood sample was obtained. Lastly, participants provided a semen sample. Two study visits were required from participants from the MTX-starters group, one before exposure to MTX (pre-exposure) and another one at least 13 weeks after their initial MTX exposure (post-exposure). Participants from the MTX-chronic and healthy control groups were just required to complete one study visit.

Demographic characteristics, medical history and physical evaluation

Participants answered a questionnaire that included questions concerning their demographic characteristics, medical history (including reproductive history) and their current and past medication exposure.

A physical evaluation was performed to determine height, weight and testicular volume (using an orchidometer). Disease activity was calculated using validated scores (DAS28 for RA, BASDAI for SpA, DAPSA for PsA and PASI for psoriasis).

Blood sample

Blood from all participants was obtained between 09:00 and 11:00 hours by venipuncture. The concentration of testosterone, LH, FSH, inhibin B, sex hormone binding globulin (SHBG), and C-reactive protein (CRP) were evaluated. Erythrocytes and PBMCs were isolated using the protocol previously described (12, 15).

Semen sample collection

Semen samples were delivered by masturbation. To ensure a timely analysis of the samples, participants provided the sample in the hospital. All samples were evaluated within 30 minutes of production. The fresh semen sample was analyzed for semen volume, sperm concentration and motility. Slides were prepared for the morphology analysis and sent to a specialized center (Radboud UMC, Nijmegen The Netherlands).

Thereafter, the semen samples were individually processed to prepare pellets for further analysis. First, samples were processed for future sDFI measurement following the steps previously published (16). Second, the semen samples were centrifuged and washed out three times with PBS and spermatozoa were isolated for future MTX-PG concentration, FPGS catalytic activity and mRNA expression measurements. All samples were stored at -80 °C.

Sperm DNA Fragmentation Index

Assessment of sDFI was performed using the TUNEL assay described by Mitchell et al (17). In short, the spermatozoa pellets were, after thawing, washed in phosphate buffered saline and incubated in 2 mM dithiothreitol (Sigma-Aldrich, Belgium) for 45 min. After washing, the pellets were incubated in fresh permeabilization solution (0.1% Sodium citrate, 0.1% Triton X–100, both Sigma-Aldrich, Belgium) for 5 min at 4 °C. The positive control samples were treated with 5 µl of DNase I (Qiagen, Germany) 1500 Kunitz Units for 30 min. The assay was performed using the fluorescein In Situ Cell Death Detection Kit (Roche Diagnostics, Mannheim, Germany) with an Accuri C6 flow cytometer (BD Sciences, Erembodegem, Belgium). For each sample, 5000–10000 events were recorded at a flow rate of 35 µl/min.

MTX polyglutamates quantification in erythrocytes, spermatozoa and seminal plasma.

Procedure EDTA erythrocyte cells pellets

Considering that MTX-PG have never been measured in spermatozoa, we opted to measure MTX-PG in erythrocytes as a control measure for MTX adherence. The erythrocyte cell pellets are measured accordingly to our previously described validated LC-MS/MS method using custom-made stable isotopes of MTX-pg1-7 as internal standards (12, 15). This method with minor alterations was also used to measure MTX-PG in spermatozoa and seminal fluid.

Procedure spermatozoa cell pellets

Spermatozoa cell pellets were kept at -80°C until analysis. To avoid polyglutamate deconjugation activity by γ-glutamyl hydrolase (GGH), semen cells were placed on ice and denatured immediately. A volume of 320 µL Perchloric acid (16%) was added to the pellets and mixed immediately to denature. After denaturation samples were supplemented with 200 µL Saline and 200 µL internal standards mixture (pg1-pg7). Supernatants were transferred twice into clean tubes after centrifugation (Hettich micro 220R, 10 min, 21250xg, 5°C) and used for measurements of MTX-PG.

Procedure for seminal fluid

Seminal fluid samples were kept at -80°C until analysis. To avoid GGH activity, seminal fluids were shortly thawed on ice before denaturation. A sample volume of 200 µL of previously isolated seminal fluid was used. Because of its high viscosity, samples were denatured with 320 µL acidic methanol (16% Perchloric acid in methanol) and mixed immediately to denature the seminal plasma. After denaturation 200 µL of internal standard mixture (pg1-pg7) was added. Supernatants are transferred twice into clean

tubes after centrifugation (Hettich micro 220R, 10 min, 21250xg, +5°C.) Samples were dried under nitrogen flow (Evaporex EVX-192, +50°C) and dissolved in 720 µL purified water (Millipore) and mixed (IKA MTS4, 10 min. 600 rpm, RT). Samples were filtered (Whatmann mini-uniprep, UN203NPUPP) before being used for MTX-PG measurements.

FPGS activity in PBMCs and spermatozoa.

FPGS catalytic activity in PBMCs (as positive control) and spermatozoa of healthy controls and MTX-starters was analyzed in 10 µg protein extracts and assay mixtures containing 250 mmol/L MTX, and 4 mmol/L ^{15}N-labeled L-glutamic acid as subtract concentrations as described by Muller et al (18). FPGS activity is reported as pmol MTX-PG_2-^{15}N formed/hr/mg protein. In addition, cell extracts of CCRF-CEM and CEM/R30dm leukemia cells were used a positive and negative controls for FPGS activity, respectively (19).

mRNA expression profiles of folate genes in spermatozoa.

An important mechanism of loss of FPGS activity and subsequent inefficient polyglutamylation can occur due to aberrant pre-mRNA splicing of FPGS (20). We recently identified a partial retention of FPGS intron 8 (8PR) as a prominent splice variant conferring FPGS dysfunction and decreased MTX polyglutamylation in acute lymphoblastic leukaemia and RA patients (14). To evaluate if alterations in FPGS pre-mRNA splicing levels in spermatozoa could explain our findings, an additional experiment was performed. Shortly, RNA was isolated from PBMCs and spermatozoa according to the manufacturer's protocol (BD Biosciences). RNA (250 ug) was reverse transcribed to cDNA using Moloney Murine Leukaemia Virus (M-MLV; Thermo Fisher Scientific, Waltham, MA, USA) in a reaction buffer containing random hexamer primers (Roche, Basel, Switzerland), dNTPs (Roche), and a ribonuclease inhibitor RNasin (Promega, Madison, WI, USA). Primer sequences (See supplementary figure 1) and methods used to quantify the levels of FPGS 8PR, FPGS WT are described elsewhere (14).

Statistical analysis

Comparisons between the pre- and post-exposure MTX-starters groups and healthy controls were tested. Because of the low number of participants included in the MTX-chronic group, we present their data in this article only for descriptive purposes. Categorical variables were presented as number (percentage), and continuous variables are reported as mean ±SD, or median ±IQR, as appropriate. Continuous variables were compared using a one-way analysis of variance (ANOVA), Tukey post-hoc test, paired t-test, Mann-Whitney test and Wilcoxon signed-rank. Categorical variables were compared using $\chi 2$ tests and Fisher's exact tests. For linear correlation analysis we used

the Pearson correlation coefficient. The level of significance was set as a two-tailed p≤0·05, and statistical analyses were completed using Stata V.15 (StataCorp-LP).

Ethics

This study was approved by the ethic review board of the Erasmus University Medical Center in compliance with the Declaration of Helsinki (NL64218·078·18). All participants gave their informed consent.

Patient and public involvement

Three male patients diagnosed with inflammatory arthritis and who are active members of the research advisory board from the Department of Rheumatology of the Erasmus University Medical Center were involved in the design of the questionnaire and the invitation letter. Together, we carefully assessed the burden on participating patients. We intend to share the results to participating patients and will appropriately disseminate the results.

Role of the funding source

The funder had no role in study design, data collection, data analysis, or data interpretation; writing the report; or the decision to submit this manuscript for publication.

RESULTS

Between February 2019 and January 2022, a total of 118 (46 MTX-starters, 49 healthy controls and 23 MTX-chronic) men were invited to participate in the study. In total, 50 men agreed to participate (20 MTX-starters, 25 healthy control, 5 MTX-chronic). Most men who did not participate in the study provided their reasons no to do so (no time for study visits (n=23), unwilling to provide semen samples (n=16), COVID-19 lockdown (n=12), no interest in the topic (n=8), Erasmus University Medical Center being too far away (n=2) reason not provided (n=7).The demographic and clinical characteristics of these men are presented in Table 1.

Conventional semen parameters and sperm morphology

There were no statistically significant differences in the median sperm concentration, semen volume, sperm motility and sperm morphology parameters between MTX-starters and healthy controls. Only one case of oligospermia (<15 million spermatozoa/ml) was observed in an MTX-starter (pre-exposure and post-exposure samples, Table 2).

Table 1. Demographic characteristics.

	MTX-naïve Pre-exposure (n=20)	MTX-naïve Post-exposure (n=18)	Healthy controls (n=25)	MTX chronic^ (n=5)	P value
General information					
Age years, mean (95% CI)	35.2 (31.4 – 39.1)		34.7 (32.9 – 36.7)	36.6 (32.1 – 41.1)	NS
Smoking, n (%)	4 (20)	4 (20)	6 (24)	1 (20)	NS
BMI %, mean (95% CI)	27.1 (24.8 – 29.2)	26.8 (24.5 – 29.1)	25.5 (24.2 – 26.8)	25.5 (21.4 – 29.6)	NS
Testicular volume, mean (95% CI)	22.9 (21.4 - 24.3)		22.6 (21.3 – 23.8)	22.6 (21.3 – 23.8)	NS
Inflammatory arthritis					
Diagnosis: RA, n (%) PsA, n (%) SpA, n (%) Psoriasis, n (%)	 7 (35.0) 8 (40.0) 1 (5.0) 4 (20.0)	 6 (33.3) 7 (38.9) 1 (5.6) 4 (22.2)	 - - - -	 2 (40.0) 1 (20.0) 2 (40.0) 0 (0.0)	
Age at diagnosis, mean (SD)	27.4 (22.1 – 32.6)	28.5 (24.5 – 34.5)	-	30.3 (18.5 – 42.1)	
Disease duration, mean (SD)	6.9 (2.1 – 11.8)		-	5.6 (-5.5 – 16.8)	
MTX dose (mg/week), mean (95% CI)	-	16.0 (13.6 – 18.4)	-	18.3 (15.6-21.1)	
Prednisone exposure, n (%)	2 (10.0)	6 (33.3)	--	1 (20)	NS
TNFa inhibitor exposure, n (%)	3 (15.0)	5 (27.8)	--	2 (40)	NS
C Reactive Protein mg/dL, median (IQR)	2.1 (0.6 – 5.0)	1.4 (1.0 – 3.2)	0 (0.0 – 0.9)	1.1 (0 – 1.8)	• p=0.011 • p=0.008
Disease activity scores					
VAS general health mm, mean (95% CI)	42 (19 – 67)	20 (12 – 36)	17.7 (10.5-25-5)	20.20 (0.3 – 40.1)	• p=<0.001 ◊ p=0.008
VAS pain mm, mean (IQR)	42 (5.5 - 75)	14 (4-36)	--	11 (4-34)	
VAS activity mm, mean (IQR)	68 (51-78)	27 (16-49)	--	10 (4-52)	
RA: DAS28, mean (IQR)	2.7 (2.4 – 2.9)	2.55 (1.34 – 3.40)	--	2.3 (1.4 – 2.7)	
PsA: DAPSA, mean (IQR)	24.1 (20.5 – 33.3)	17.8 (11.2 – 22.7)	--	1.1 (1.1 – 1.1)	
Psoriasis: PASI, mean (IQR)	1.9 (1.3 – 5.1)	1.1 (0.7 – 3.1)	--	0.8 (0.3 – 1.2)	

◀Statistically significant difference between pre-exposure and healthy controls.
• Statistically significant difference between post-exposure and healthy controls.
◊Statistically significant difference between pre and post-exposure.
^ Presented only for descriptive purposes, no statistical analyses were conducted.

Table 2. Conventional semen parameters and sperm morphology.

	MTX-naïve Pre-exposure (n=20)	MTX-naïve Post-exposure (n=18)	Healthy controls (n=25)	MTX chronic^ (n=5)	P value
Conventional semen parameters					
Sperm concentration x10^6/ mL, median (IQR)	57.0 (35.0 – 90.5)	54.0 (41.0 – 82.0)	60.0 (37.0-111.0)	37.0 (32.0 – 59.9)	NS
Progressive motility* %, mean (95% CI)	63.2 (55.4 - 70.9)	60.1 (49.5 - 70.6)	56.9 (51.1 - 62.8)	50.4 (34.8 - 65.9)	NS
Semen volume mL, median (IQR)	2.4 (1.6 - 3.2)	3.0 (1.5 - 3.2)	3.0 (2.0 - 4.0)	2.0 (1.6 – 2.4)	NS
Sperm morphology evaluation					
Normal morphology %, mean (95% CI)	6.4 (4.5 – 8.3)	7.1 (5.6 – 8.4)	6.3 (4.7 – 7.9)	5.9 (2.6 – 9.1)	NS
Teratozoospermia index, mean (95% CI)	1.2 (1.2 – 1.3)	1.3 (1.2 – 1.4)	1.2 (1.2 – 1.3)	1.2 (1.1 – 1.4)	NS
Excess Residual Cytoplasm, median (IQR)	2.0 (0.7 – 4.3)	2.0 (1.0 – 4.5)	2.0 (1.0 – 4.0)	2.0 (1.0 – 4.0)	NS
Abnormalities in head (%), mean (95% CI)	92.8 (90.8 – 94.7)	93.0 (91.2 – 94.6)	92.7 (91.0 – 94.3)	92.3 (88.0 – 96.5)	NS
Abnormalities in middle-piece (%), mean (95% CI)	19.2 (14.2 – 24.1)	24.5 (18.6 – 30.2)	19.9 (15.3-24.5)	22.9 (5.7 – 40.0)	NS
Abnormalities in tail (%), mean (95% CI)	7.1 (3.8 – 10.5)	7.3 (3.7 – 11.1)	6.6 (3.9 – 9.3)	4.6 (1.4 -7.7)	NS

^ Presented only for descriptive purposes, no statistical analyses were conducted.

Sperm DNA Fragmentation Index

The median sDFI was higher in the pre-exposure samples from the MTX-starters (22·0% (IQR 10·7 - 30·7) but this was not statistically significant different when compared to the post-exposure sample (13·1% (IQR 9·5 - 16·3), p=0·247) and to the healthy controls (13·5% (IQR 8·7 - 20·2), p=0·257). See Table 3.

Table 3. Sperm DNA Fragmentation index.

	MTX-naïve Pre-exposure (n=20)	MTX-naïve Post-exposure (n=18)	Healthy controls (n=25)	MTX chronic^ (n=5)	P value
Sperm DNA Fragmentation Index %, median (IQR)	24.3 (7.1 – 30.7)	13.1 (9.5 – 19.9)	13.5 (8.7 – 20.2)	13.5 (13.3 – 26.1)	NS

^ Presented only for descriptive purposes, no statistical analyses were conducted.

Male reproductive endocrine axis

The median serum concentrations of testosterone, SHBG, LH and FSH were not statistically significant different between the groups. The median serum concentration of inhibin B was statistically significant lower in the pre-exposure (132·5 ng/L (IQR 101·5 - 179·5)) and post-exposure samples of the MTX-starters group (123·0 ng/L (IQR 116·0 - 179·0)) compared to the healthy controls (189·0 ng/L (170·0 - 236·0)). See Table 4.

Table 4. Male reproductive endocrine axis

	MTX-naïve Pre-exposure (n=20)	MTX-naïve Post-exposure (n=18)	Healthy controls (n=25)	MTX chronic^ (n=5)	P value
Testosterone (nmol/L) median (IQR)	14.6 (11.3 – 16.2)	13.4 (12.0 – 15.6)	14.1 (12.8 – 16.7)	16.3 (16.3 – 17.1)	NS
SHBG (nmol/L) median (IQR)	26.6 (22.6 – 34.6)	28.8 (22.5 – 34.6)	32.6 (25.7 – 41.9)	35.4 (34.1 – 38.7)	NS
LH (U/L) median (IQR)	3.1 (2.3 – 3.9)	2.7 (2.2 – 3.2)	2.9 (2.2 – 3.4)	4.10 (4.0 – 4.1)	NS
FSH (U/L) median (IQR)	4.6 (3.5 – 5.3)	4.2 (3.2 – 5.0)	3.7 (3.0 – 4.5)	4.1 (4.0 – 4.1)	NS
Inhibin B (ng/L) median (IQR)	132.5 (101.5 – 179.5)	123.0 (116.0 – 179.0)	189.0 (170.0– 236.0)	92.2 (87.0 – 203.0)	◀ p=<0.001 • p=<0.001

◀Statistically significant difference between pre-exposure and healthy controls.
• Statistically significant difference between post-exposure and healthy controls.
^ Presented only for descriptive purposes, no statistical analyses were conducted.

MTX polyglutamates quantification

MTXpg1-5 were detected in erythrocytes from all participants (Figure 1A), consistent with MTX-pg accumulation profiles in erythrocytes of patients under MTX therapy and thus confirming their intake of MTX (12). In seminal fluid, mainly MTX-pg1 was detected with a median concentration of 184 nmol/L (IQR 39 - 265), whereas MTXpg2,3 were barely noticeable (Figure 1B). In spermatozoa, mainly MTXpg1 was detected (median 0·26 fmol/10^6 spermatozoa, IQR 0·16 - 0·69), whereas MTXpg2,3 levels were at the lower limit of detection (Figure 1C). Total MTXpg levels in spermatozoa were approximately 18-fold lower than in erythrocytes (0·32 fmol/10^6 spermatozoa vs 5·8 fmol/10^6 erythrocytes, respectively, Figure 1A/C).

FPGS activity in PBMCs and spermatozoa

To determine whether the marginal MTX-pg accumulation is related to FPGS catalytic activity, this enzyme activity was measured in PBMCs and spermatozoa from 4 healthy controls and 10 MTX-starters (post-exposure). FPGS activity (pmol MTX-PG2-^{15}N formed/h/mg protein) was statistically significant higher in PBMCs (183 pmol MTX-PG2-^{15}N formed/h/mg protein) compared to spermatozoa from healthy controls (15 pmol MTX-PG2-^{15}N formed/h/mg protein) and spermatozoa from MTX-starters (5 pmol MTX-PG2-^{15}N formed/h/mg protein) (Figure 1D). Remarkably, FPGS activity in spermatozoa is even lower than a control cell line (CEM/R30dm) with acquired resistance to MTX due to loss of FPGS activity and impairment of MTX-polyglutamylation (Figure 1D) (19).

mRNA expression profiles of folate genes in spermatozoa

To explore whether molecular alterations underlie the extremely low FPGS activity in spermatozoa, mRNA expression profiles of FPGS and other folate genes was evaluated in spermatozoa from 4 healthy controls and 6 MTX-starters (See supplementary figure 1). Of note, a relatively high FPGS/8PR and FPGS 8PR/WT ratio was observed in spermatozoa compared to PBMCs (results not shown).

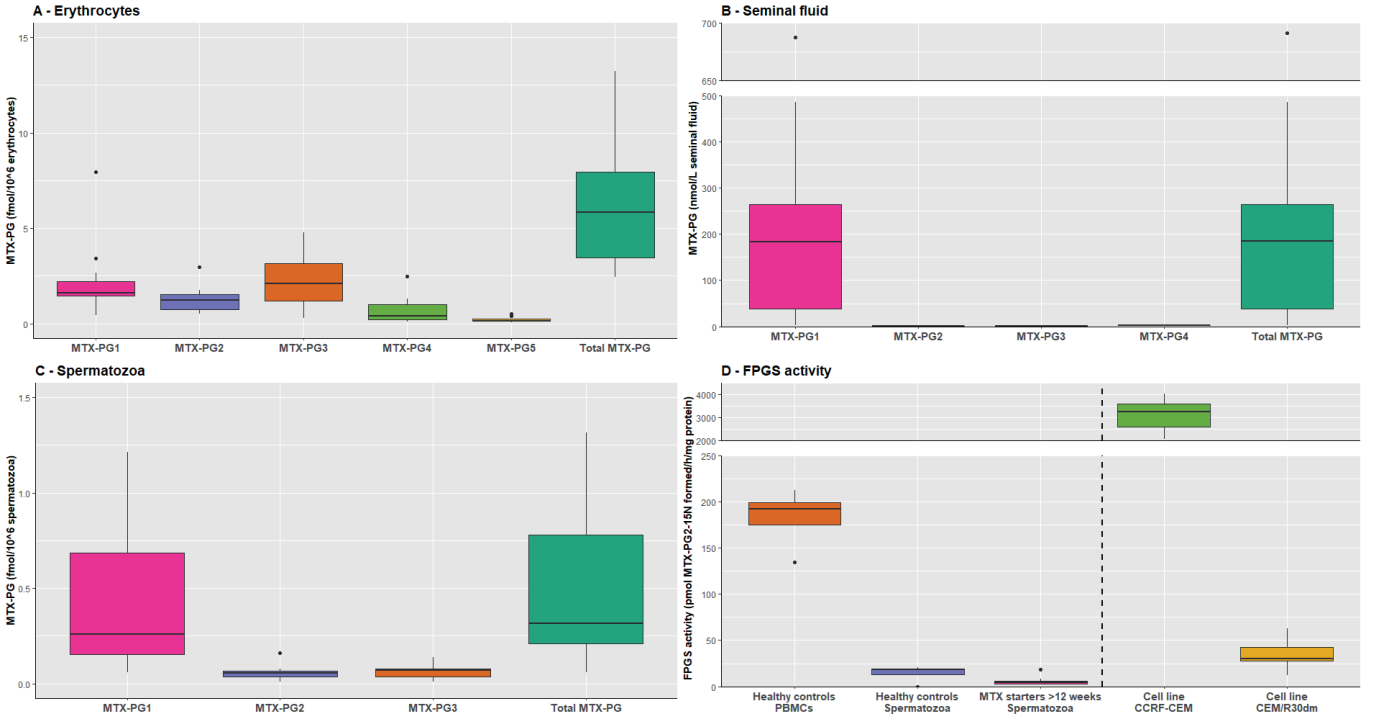


Figure 1. MTX-polyglutamate (PG) accumulation in erythrocytes, seminal fluid and spermatozoa of RA patients and FPGS activity in spermatozoa. Please note that the y axis varies between figures. (A) Individual and total MTX-PG accumulation in erythrocytes of male RA patients (n=17) on MTX therapy for >12 weeks. Data are depicted as fmol MTX-PG/106 erythrocytes and presented in box plots with the sample median and IQR. (B) MTX-PG concentrations (in nmol/L) in seminal fluid of RA patients (n=17) on MTX therapy. (C) Individual and total MTX-PG accumulation in spermatozoa of RA patients (n=17) on MTX therapy. Data are depicted as fmol MTX-PG/106 spermatozoa and presented in box plots with the sample median and IQR . (D) FPGS catalytic activity in spermatozoa of healthy donors (n=4) and RA patients (n=10) for>12 weeks on MTX therapy, and for comparison in PBMCs of healthy individuals (n=4). For comparative and analytical controls, FPGS data are shown for proliferative CCRF-CEM leukaemia cells (n=24) and CEM/R30dm cells (n=15), a subline of CCRF-CEM with 1% residual FPGS activity and with acquired resistance to MTX due to impairment of MTXPG formation. Data for FPGS catalytic activity are depicted as pmol MTX-PG2-15N formed/hr/mg protein and presented in box plots with the sample median and IQR. FPGS, folylpolyglutamate synthetase; MTX, methotrexate; MTX-PG, methotrexate polyglutamate; RA, rheumatoid arthritis.

DISCUSSION

The iFAME-MTX study is the largest study to date that prospectively evaluated the potential impact of MTX on many important markers of testicular toxicity and to evaluate the potential underlying mechanisms explaining why MTX does not impair sperm quality. It shows that MTX is not associated with conventional semen analysis abnormalities, disturbances in the male reproductive endocrine axis or with increased sperm DNA damage. Furthermore, to the best of our knowledge our study reports for the first time that the enzyme responsible for intracellular polyglutamylation and hence the bioactivation of MTX, i.e. FPGS, has an extremely low activity in spermatozoa. Ultimately resulting in very low concentrations of intracellular MTX-PG in spermatozoa.

Our results provide long-waited answers to important clinical questions. First, studies that evaluated the effect of MTX on semen parameters and/or the male reproductive endocrine axis have resulted in conflicting results (21). Most of these studies included a small number of patients, lacked prospectively collected samples, did not have a control group or did not correct for relevant confounders (i.e. disease activity or high dose glucocorticoids). Recently, Grosen et al (29) evaluated the testicular toxicity profile of MTX in a cross-sectional study that included 14 patients mainly diagnosed with Crohn's disease. Although this was not a prospective study, their findings are similar to ours, as they report that MTX therapy is not associated with abnormalities in semen parameters or the male reproductive endocrine axis.

Second, sperm DNA integrity is essential for producing normal spermatozoa and DNA damage has been associated with male infertility (22). Based on the known effects of MTX on DNA synthesis, we were concerned that MTX could result in sperm DNA damage. Reassuringly, we did not find a negative impact of MTX on sDFI. Noteworthy, the median pre-exposure sDFI of 24·3% in MTX-starters may be a reflection of a negative impact of disease activity on spermatogenesis. Albeit not statistically significant, after exposure to MTX, the sDFI decreased to 13·5%. This may be caused by a reduction of disease activity.

Third, another concern of patients and health care professionals is that it was not known whether MTX could be detected in spermatozoa. Therefore, we aimed to measure the concentration of MTXpg, the active forms of MTX in spermatozoa and in seminal fluid. Reassuringly, we detected only MTXpg1 in very low concentrations in spermatozoa and barely detected longer retained MTXpg2,3. Furthermore, the findings of our complementary experiments are reassuring, as we report a very low activity of

FPGS in spermatozoa, indicating that MTX polyglutamylation in spermatozoa is limited. Mechanistically, the low FPGS activity in spermatozoa may be associated with a higher ratio of mRNA expression of an alternatively spliced form of the FPGS gene (8PR) over the WT transcript (18). Regarding seminal fluid, similar to the recent findings of Grosen et al, we detected predominantly MTX-pg1 (29).

The iFAME-MTX study provides a strong scientific basis to consider that MTX is safe for men with an active wish to become a father. Our study showed that exposure to MTX did not result in abnormalities in semen parameters and other male fertility outcomes. Furthermore, although this study was not designed to evaluate the potential teratogenic effect of paternal MTX, three pregnancies that were exposed to paternal MTX were reported by MTX-starters (conception within 1 year after their first study visit). No negative pregnancy outcomes or congenital malformations were reported. This goes in line with our data that shows that MTX is not associated with sperm DNA damage and that polyglutamylation is inefficient in spermatozoa is reassuring. In this regard, the risk of birth defects associated to paternal MTX has been evaluated before in more than 250 men and it was concluded to that MTX was not associated with an increased risk of birth defects (21, 23).

Other secondary findings from our study warrant further discussion. Inhibin B is secreted by the Sertoli cells and is considered a marker of Sertoli cell function and spermatogenesis (24). Sertoli cells are one of the most important cells necessary for sperm production in males. Comprehensive evaluation of the reproductive axis revealed statistically significant lower serum concentrations of inhibin B in the MTX-starters before exposure to MTX. Lower serum concentrations of inhibin B have also been reported in men diagnosed with ankylosing spondylitis (25) and systemic lupus erythematosus (26). These findings further support the evidence that autoimmunity and inflammation can result in Sertoli cell dysfunction (27-29). Further research is needed to corroborate these findings.

Furthermore, both findings (higher sDFI and lower inhibin B before exposure to MTX) go in line with the conclusion of our recent study where we reported that inflammatory arthritis might impair male fertility (30). Inflammation, especially via mechanisms associated with oxidative stress, was considered as a potential contributor to these findings (10). Whether inflammation secondary to IMIDs such as IA results in an increased oxidative stress state in the testicles (or elsewhere) with the potential to disrupt the required homeostasis for normal spermatogenesis remains unknown and warrants further research. Altogether, this may imply that in men with a wish to conceive,

treating the disease with immunosuppressive drugs (without known testicular toxicity profiles) while aiming at lower disease activity states, may improve their chances of a successful pregnancy.

Our study has several strengths. It is the first prospective study that included cases and healthy controls and that was specifically designed to evaluate the impact of MTX on several markers of testicular toxicity. Our low loss to follow-up rate maximizes the validity of our data. Furthermore, our results were corroborated by the results of our complementary experiments that reported for the first time that polyglutamylation of MTX is very limited in spermatozoa leading to very low concentrations of the active forms of MTX in seminal fluid and spermatozoa. Our study has important limitations. First, our results are significant and representative for the MTX-starters group and not necessarily of the MTX-chronic group. Second, we only have one semen sample per study visit and not the ideal two (with an average value reported). Thus, the wide known variability of sperm concentration might have influenced our results.

In conclusion, treatment with MTX is not associated with testicular toxicity in men diagnosed with an IMID. It can also be concluded that the concentration of intracellular MTX-PG in seminal fluid and spermatozoa is very low. Therefore, therapy with MTX can be safely started or continued in men diagnosed with an IMID and with an active wish to become a father.

REFERENCES

1. Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. Arthritis Care Res (Hoboken). 2020;72(4):461-88.
2. Russell MD, Dey M, Flint J, Davie P, Allen A, Crossley A, et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. Rheumatology. 2023;62(4):e48-e88.
3. Menter A, Gelfand JM, Connor C, Armstrong AW, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. J Am Acad Dermatol. 2020;82(6):1445-86.
4. FDA. Methotrexate label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/040054s015,s016,s017.pdf
5. Agency EM. MTX label. https://www.ema.europa.eu/en/documents/product-information/jylamvo-epar-product-information_en.pdf
6. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. (2015). *Testicular Toxicity: Evaluation during Drug Development Guidance for Industry, Draft Guidance*. Accessed May 20, 2016.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM455102.pdf.
7. Ramaswamy S, Weinbauer GF. Endocrine control of spermatogenesis: Role of FSH and LH/testosterone. Spermatogenesis. 2014;4(2):e996025.
8. Esteves SC, Zini A, Coward RM, Evenson DP, Gosálvez J, Lewis SEM, et al. Sperm DNA fragmentation testing: Summary evidence and clinical practice recommendations. Andrologia. 2021;53(2):e13874.
9. Sakkas D, Alvarez JG. Sperm DNA fragmentation: mechanisms of origin, impact on reproductive outcome, and analysis. Fertil Steril. 2010;93(4):1027-36.
10. Vaughan DA, Tirado E, Garcia D, Datta V, Sakkas D. DNA fragmentation of sperm: a radical examination of the contribution of oxidative stress and age in 16 945 semen samples. Hum Reprod. 2020;35(10):2188-96.
11. Rots MG, Pieters R, Peters GJ, Noordhuis P, van Zantwijk CH, Kaspers GJ, et al. Role of folylpolyglutamate synthetase and folylpolyglutamate hydrolase in methotrexate accumulation and polyglutamylation in childhood leukemia. Blood. 1999;93(5):1677-83.
12. Hebing RC, Lin M, Bulatovic Calasan M, Muller IB, Mahmoud S, Heil S, et al. Pharmacokinetics of oral and subcutaneous methotrexate in red and white blood cells in patients with early rheumatoid arthritis: the methotrexate monitoring trial. Ann Rheum Dis. 2022.
13. van de Meeberg MM, Hebing RCF, Nurmohamed MT, Fidder HH, Heymans MW, Bouma G, et al. A meta-analysis of methotrexate polyglutamates in relation to efficacy and toxicity of methotrexate in inflammatory arthritis, colitis and dermatitis. Br J Clin Pharmacol. 2023;89(1):61-79.
14. Muller IB, Lin M, Lems WF, Ter Wee MM, Wojtuszkiewicz A, Nurmohamed MT, et al. Association of altered folylpolyglutamate synthetase pre-mRNA splicing with methotrexate unresponsiveness in early rheumatoid arthritis. Rheumatology (Oxford). 2021;60(3):1273-81.
15. den Boer E, Meesters RJ, van Zelst BD, Luider TM, Hazes JM, Heil SG, et al. Measuring methotrexate polyglutamates in red blood cells: a new LC-MS/MS-based method. Anal Bioanal Chem. 2013;405(5):1673-81.

16. Ribeiro S, Sharma R, Gupta S, Cakar Z, De Geyter C, Agarwal A. Inter- and intra-laboratory standardization of TUNEL assay for assessment of sperm DNA fragmentation. Andrology. 2017;5(3):477-85.
17. Mitchell LA, De Iuliis GN, Aitken RJ. The TUNEL assay consistently underestimates DNA damage in human spermatozoa and is influenced by DNA compaction and cell vitality: development of an improved methodology. Int J Androl. 2011;34(1):2-13.
18. Muller IB, Lin M, Struys EA, Heydari P, Hebing RCF, Nurmohamed MT, et al. Development and Validation of a Sensitive UHPLC-MS/MS-Based Method for the Analysis of Folylpolyglutamate Synthetase Enzymatic Activity in Peripheral Blood Mononuclear Cells: Application in Rheumatoid Arthritis and Leukemia Patients. Ther Drug Monit. 2019;41(5):598-606.
19. McCloskey DE, McGuire JJ, Russell CA, Rowan BG, Bertino JR, Pizzorno G, et al. Decreased folylpolyglutamate synthetase activity as a mechanism of methotrexate resistance in CCRF-CEM human leukemia sublines. J Biol Chem. 1991;266(10):6181-7.
20. Stark M, Wichman C, Avivi I, Assaraf YG. Aberrant splicing of folylpolyglutamate synthetase as a novel mechanism of antifolate resistance in leukemia. Blood. 2009;113(18):4362-9.
21. Perez-Garcia LF, Dolhain RJEM, Vorstenbosch S, Bramer W, van Puijenbroek E, Hazes JMW, et al. The effect of paternal exposure to immunosuppressive drugs on sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes: a systematic review. Human Reproduction Update. 2020.
22. Gunes S, Al-Sadaan M, Agarwal A. Spermatogenesis, DNA damage and DNA repair mechanisms in male infertility. Reprod Biomed Online. 2015;31(3):309-19.
23. Mouyis M, Flint JD, Giles IP. Safety of anti-rheumatic drugs in men trying to conceive: A systematic review and analysis of published evidence. Semin Arthritis Rheum. 2019;48(5):911-20.
24. Kumanov P, Nandipati K, Tomova A, Agarwal A. Inhibin B is a better marker of spermatogenesis than other hormones in the evaluation of male factor infertility. Fertil Steril. 2006;86(2):332-8.
25. Almeida BP, Saad CG, Souza FH, Moraes JC, Nukumizu LA, Viana VS, et al. Testicular Sertoli cell function in ankylosing spondylitis. Clin Rheumatol. 2013;32(7):1075-9.
26. Suehiro RM, Borba EF, Bonfa E, Okay TS, Cocuzza M, Soares PM, et al. Testicular Sertoli cell function in male systemic lupus erythematosus. Rheumatology (Oxford). 2008;47(11):1692-7.
27. Hasan H, Bhushan S, Fijak M, Meinhardt A. Mechanism of Inflammatory Associated Impairment of Sperm Function, Spermatogenesis and Steroidogenesis. Front Endocrinol (Lausanne). 2022;13:897029.
28. Hedger MP, Winnall WR. Regulation of activin and inhibin in the adult testis and the evidence for functional roles in spermatogenesis and immunoregulation. Mol Cell Endocrinol. 2012;359(1-2):30-42.
29. Kazutaka S, Winnall WR, Muir JA, Hedger MP. Regulation of Sertoli cell activin A and inhibin B by tumour necrosis factor α and interleukin 1α: interaction with follicle-stimulating hormone/adenosine 3',5'-cyclic phosphate signalling. Mol Cell Endocrinol. 2011;335(2):195-203.
30. Perez-Garcia LF, Röder E, Goekoop RJ, Hazes JMW, Kok MR, Smeele HTW, et al. Impaired fertility in men diagnosed with inflammatory arthritis: results of a large multicentre study (iFAME-Fertility). Ann Rheum Dis. 2021.

PART V

Let’s talk about sex! … in Rheumatology

CHAPTER 8

It is not just about sex: viewpoints of men with inflammatory arthritis on the overall impact of the disease on their sexual health

Published

Perez-Garcia LF, Röder E, Pastoor H, Bolt JM, van Exel J, Dolhain RJEM.

RMD Open. 2021 Sep;7(3):e001821.

ABSTRACT

Objectives

Sexual health is defined as a state of physical, emotional, mental and social well-being in relation to sexuality. The impact of Inflammatory arthritis (IA) on male sexual health has been mainly studied focusing on erectile function, one of the physical components of sexual health. Our objective was to describe the viewpoints among men with IA in the Netherlands on the overall impact of IA on their sexual health.

Methods

Q-methodology, a mixed methods approach to systematically study subjectivity was used. Adult men diagnosed with IA ranked 34 opinion statements about potential impacts of IA on their sexual health and were interviewed. By-person factor analysis was used to identify common patterns in the rankings, which were interpreted as viewpoints. Data from the interviews were used to verify and adjust the interpretations.

Results

30 men (22-77 years) with IA were included. The analysis revealed three viewpoints. Men with the viewpoint “Arthritis negatively affects my sexual health” experience a dramatic impact on all components of sexual health. In viewpoint “I am keeping up appearances”, IA negatively impacts sexual health but a distinguishing coping mechanism could mask a more serious negative impact. Men with the viewpoint “I am satisfied with my sexual health” experience no significant impact of IA on their sexual health.

Conclusion

We identified three viewpoints on the impact of IA on male sexual health, two revealed a negative influence that goes beyond the physical act of sex. IA can severely affect the emotional, mental and social components of sexual health.

INTRODUCTION

Sexual health has been defined as a state of physical, emotional, mental and social well-being in relation to sexuality (1). Despite the fact that sexual health is not merely the absence of disease, dysfunction or infirmity, the impact of inflammatory arthritis (IA) on male sexual health has mainly been studied focusing on the association of IA with erectile dysfunction (ED).

ED is a highly prevalent comorbidity in men diagnosed with IA (33-62%) (2). Several factors such as inflammation, alterations in the endocrine axis, adverse events of medication, disability secondary to disease and comorbidities are thought to be responsible for this association. Although male sexual health goes well beyond erectile function and may be impaired by factors such as fears, emotions and beliefs, the impact of IA on the emotional, mental and social components of sexual health has not yet been comprehensively studied (3, 4).

In order to be able to help men with sexual health problems due to IA, we first need to identify and understand the impact of IA, not only on the physical component but also on the emotional, mental and social components of sexual health.

These components are difficult to analyse and interpret because of their subjective nature. Questionnaires mainly generate quantitative data and can easily miss relevant subjective information. Focus groups provide qualitative data and have been used to explore sexuality (5). Q-methodology combines the strengths of qualitative and quantitative approaches and is a powerful methodology for systematically exploring and explaining patterns in subjectivities (viewpoints, opinions, beliefs) around sensitive topics and identifying consensus and contrasts between them (6). Recently, Q-methodology (7-9) has gained attention from researchers in the medical community and has been used to help us better understand complex topics in medicine such as HPV vaccination, palliative care, end-stage renal disease and organ donation (10-13). Therefore, Q-methodology can be considered as a suitable method to study the overall impact of IA on male sexual health.

Our objective is to use Q-methodology to describe the viewpoints of adult men with IA concerning the overall impact of IA on their sexual health.

METHODS

Q-methodology

Q-methodology combines qualitative and quantitative techniques to empirically study subjectivity. The whole process of a Q-methodology study can be summarized in four stages (see Figure 1) (7). Information on the use of Q-methodology in healthcare research can be found elsewhere (14). Furthermore, a checklist to include when reporting a Q-methodology study was included as supplemental table 1.

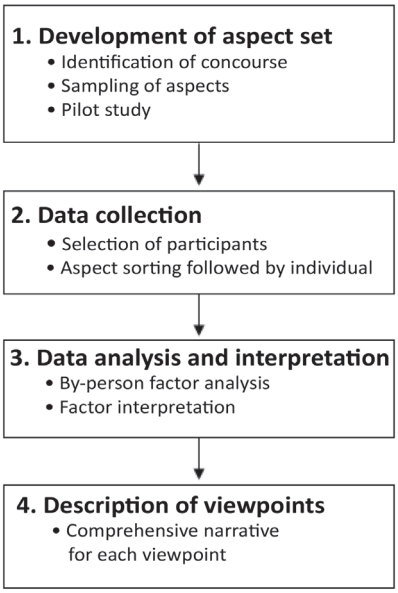


Figure 1: The stages of Q-methodology study.

Patient and public involvement

Five male patients diagnosed with IA (four were active members of the research advisory board from the Department of Rheumatology of the Erasmus University Medical Center) were involved in the design of the research question, statements, patient information leaflet and invitation letter. During a pilot study four patients evaluated the statement set and the interview materials. Three patients were involved in the interpretation of the results. We carefully assessed the burden on participating patients. We intend to share the results to participating patients and will appropriately disseminate the results.

Participants

Men of 18 years or older, diagnosed with inflammatory arthritis (IA) (rheumatoid arthritis (RA) or polyarticular juvenile idiopathic arthritis (JIA)) were invited to participate by their own rheumatologist. Because our objective was to evaluate the viewpoints of men with inflammatory arthritis and the term spondyloarthritis compromises an extensive group of diseases that are associated with a diverse range of extra-articular manifestations (i.e. low back pain and psoriatic lesions on the skin) that on their own may negatively impact sexual health (15, 16), patients diagnosed with spondyloarthritis were excluded. Therefore, in this study, when referring to IA we focus only on the diagnoses of RA and JIA. Participants were recruited between October 2019 and October 2020, mainly from the general Rheumatology and the specialized Reproductive Rheumatology outpatient clinics from the Erasmus University Medical Center, Rotterdam, the Netherlands. As the aim of the Q-methodology is to explore the variety of viewpoints, not to make claims about the percentage of people expressing them, participants were gathered purposively to ensure diversity. Therefore, recruiters were instructed to invite men with different cultural, religious and socioeconomic backgrounds as well as different sexual orientations. Furthermore, they were also instructed to invite participants of all ages ($\geq$18 year) who were either recently diagnosed with IA ($<$1 year) or had longer disease duration. To promote diversity, three researchers (LFP, ER and RD) frequently informed recruiters about the progress of inclusion of the participants. In a Q-methodology study it has been recommended to aim to include a number of participants that is smaller than the number of statements (7). Data collection proceeded until saturation was achieved. This was considered to be the case when at least five participants in each of the specified target groups of patients were interviewed and consecutive interviews revealed no significant new viewpoints as compared to earlier interviews.

Statement set development

Two researchers (LFP, ER) independently collected candidate statements on how IA can affect the various components of male sexual health (physical, emotional, mental and social factors) based on a non-systematic review of scientific (PubMed), empirical, and popular literature (e.g. online forums, blogs) on this topic. This process resulted in an initial set of 48 statements.

To evaluate its comprehensibility and comprehensiveness, the set was discussed with five male patients diagnosed with IA, one expert in the field of Reproductive Rheumatology (RD) and two experts in the field of Sexology (HP, JMB). In addition, one expert in the field

of Q-methodology (JvE) was consulted to provide methodological advice on the selection and formulation of statements. Following these discussions, a number of adjustments were made: some statements were excluded from the initial set because they covered similar topics (see supplemental table 2). and the wording of several statements was revised. At the end of this phase, a draft set of 34 statements remained for pilot testing.

To ensure the comprehensiveness and comprehensibility of the statement set and other interview materials, a pilot study involving four male patients with IA was conducted. Based on its results, no modifications to the interview materials, including the statement set were deemed necessary. Therefore, the four participants from the pilot study could be retained for the main study. The final statement set (translated into English), is presented in Table 1. The original statement set (in Dutch) can be found in supplemental table 3.

Table 1. Composite ranking of statements for each viewpoint

Statement		"Arthritis negatively affects my sex life"	"I am keeping up appearances"	"I am satisfied with my sex life"
1	**I am satisfied with my sex life** [1, 2, 3]	-2**	+3**	+4**
2	**Sex is important to my quality of life** [1]	0**	+3	+4
3	**I enjoy sex less because of my arthritis**	-1	+1	-1
4	**My sex life has changed because of my arthritis** [1, 2, 3]	0*	+2*	-1**
5	**I have sex less frequently because of my arthritis** [3]	+1	+1	-1**
6	**Pain caused by my arthritis has a negative impact on my sex life** [3]	+4	+4	+1**
7	**Fatigue has a negative impact on my sex life** [2]	+4	0**	+3
8	**Gloom has a negative impact on my sex life** [2]	+2	-1**	+3
9	**Sex has become less spontaneous due to my arthritis** [3]	+2	+1	-1**
10	**I find it difficult that fluctuations in the severity of my illness make my sex life unpredictable** [1]	+3**	-1	0
11	**My sexual problems are the same as those present in healthy men**[1, 2, 3]	-4**	0**	+3**
12	**I have fewer sexual thoughts because of my arthritis**	-3	-2	-2
13	**It is more difficult to get aroused because of my arthritis** [3]	-1	-1	-3*
14	**My sexual desire is reduced because of my arthritis^**	-2	-1	-2
15	**There are things I would like to do during sex (postures/movements) that I cannot do because of my illness** [1, 2 3]	+3**	+1**	0**

Table 1. Continued

	Statement	"Arthritis negatively affects my sex life"	"I am keeping up appearances"	"I am satisfied with my sex life"
16	**I have trouble getting and / or keeping an erection due to my arthritis** [1]	+1**	-4	-4
17	**I don't want to start having sex because I am afraid that I will have to stop halfway through my arthritis** [1]	0**	-2	-2
18	**I am having problems masturbating due to my arthritis**	-3	-3	-1
19	**I feel less masculine because of my arthritis** [3]	0	-1	-2**
20	**I feel less attractive because of my arthritis** [3]	+1	+2	-3**
21	**The physical changes make me feel less confident about sex** [3]	+2	+2	0**
22	**My sex life must be included in the choice of my treatment** [1]	0**	+2	+2
23	**I have the need to discuss the effects of my arthritis and treatment on my sex life with my healthcare provider^**	+1	0	+1
24	**I have a hard time talking about my sex life with my healthcare provider** [1]	-1**	+1	+1
25	**I prefer to search online for information about the effects of my arthritis and treatment on my sex life** [3]	-1	0	+2*
26	**I feel like I am the only one with sexual problems caused by my arthritis** [3]	-2	-2	+1**
27	**I find it difficult to discuss sexual problems with a partner** [2]	-2	0**	-3
28	**My sexual problems make it difficult to be in a relationship** [3]	-3	-3	0**
29	**I feel guilty towards my partner because of the limitations of my arthritis** [1]	+3**	0	0
30	**Intimacy has become more important than sex^**	+2	+3	+1
31	**For me, sex is only important if I want a child^**	-4	-4	-4
32	**The relationship with my partner has improved because of my arthritis** [3]	-1	-2	+2**
33	**My partner understands my sexual problems** [1, 2, 3]	+1**	+4**	+2**
34	**I sometimes have sex only because I don't want to disappoint my partner** [2]	0	-3**	0

*p < .05, **p < 0.01 vs. all other factors.
^ Consensus statement.
[1] Distinguishing statement for viewpoint 1.
[2] Distinguishing statement for viewpoint 2.
[3] Distinguishing statement for viewpoint 3.

Data collection

Participants were invited for an individual interview in the Erasmus MC, which took approximately one hour. Because of the impact of the COVID-19 pandemic, five interviews were conducted using online meeting platforms.

Each session was moderated by LFP and ER and started with instructions on the sorting of the statements and an explanation of the concept of sexual health as being a comprehensive term that goes beyond the physical act of sex.

Thereafter, participants were presented with the 34 statements printed on cards, in random order, and asked to carefully read all cards. They were asked to consider each statement in relation to the question 'How does arthritis impact your sexual health?' and sort them into three piles representing statements they agreed with, disagreed with, and found to be neutral or irrelevant. The participants were then instructed to reread the cards in each pile prior to ranking them on the sorting grid. They started with the agree pile, followed by the disagree pile and finally the neutral pile (See Figure 2).

After ranking the statements, participants were asked open-ended questions. They were asked to explain the placement of certain statements on the sorting grid and all participants elaborated on the two statements with which they most agreed and disagreed. Also, they were invited to discuss any statement they found interesting. At the end of the interview, participants were asked to briefly describe their opinion about the overall impact of IA on their sexual health in their own words. The interviews were voice recorded.

Finally, participants were asked to fill in a questionnaire, which included questions regarding their demographic characteristics, disease activity scores (HAQ-DI, RADAI, VAS-general health, VAS-disease activity, VAS-pain, VAS-fatigue) and the PHQ-9 for depression screening.

This study was reviewed by the Medical Ethics Committee of the Erasmus University Medical Center. The committee declared that the rules laid down in the Medical Research Involving Human Subjects Act do not apply to this study. Written informed consent was obtained from all participants. Participants received financial compensation for their travel and parking costs.

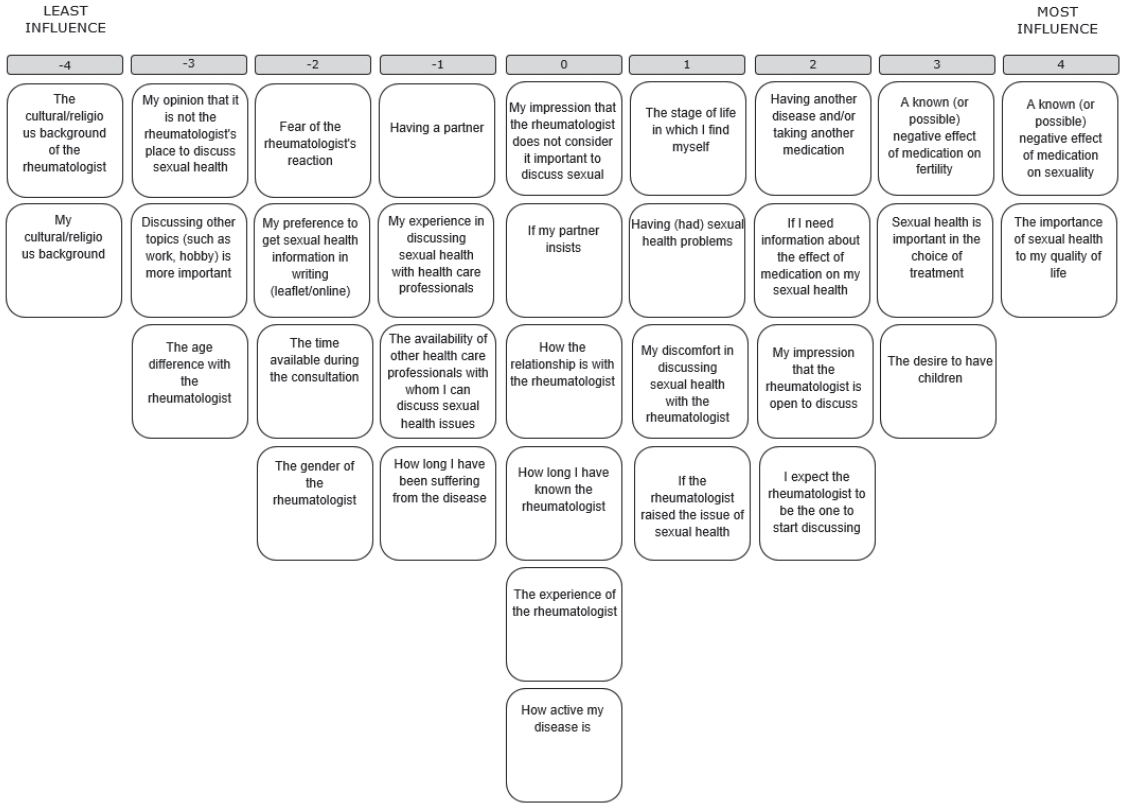


Figure 2: Sorting grid and statements, example of final result. Participants first placed statements with which they agreed with on the right side of the score sheet. They placed the two statements with which they agreed most in the two spots in the extreme right column (+4), followed by the next three statements with which they agreed most (+3), and so on. In the same manner, respondents ranked statements with which they disagreed and those that they found to be neutral on the left side and in the center of the sorting grid, respectively, until all statements were placed on the sorting grid with only one statement placed in each cell. Participants were encouraged to review the final result and, if necessary, make any changes.

Statistical analysis

Individual statement rankings were subject to by-person factor analysis (i.e., centroid factor extraction, followed by varimax rotation) using PQMethod 2.35. Identified factors, with Eigenvalue larger than one and at least two participants significantly associated ($p < 0.05$), were interpreted as viewpoints on the overall effect of IA on male sexual health. Interpretations were based on composite (i.e., weighted average) statement rankings for each factor. Inspection of statistical information (i.e. explained variance and number of defining variables per factor) and the coherence and interpretability of the factors, also consulting the qualitative materials collected during the interviews, resulted in the choice for a three-factor solution. Consensus statements (i.e., those whose rankings did not differ significantly between any pair of viewpoints) and distinguishing statements (i.e., those whose rankings in one viewpoint differed significantly from those in all other viewpoints) were identified.

The interpretation and description of each viewpoint were supplemented with the answers to the open-ended questions from participants whose rankings were associated with that viewpoint ($p < 0.05$).

RESULTS

47 men were invited to participate in the study. The final sample consisted of 30 men with IA (response rate of 64%). Their mean age was 43.2 (range 22–77) years and had a mean disease duration of 15.25 (SD 10.88) years. Most of the participants were Dutch (86.6%), sexually active during the last year (92.8%) and in a relationship (96.6%). Demographic characteristics of the study population are presented in table 2.

The analysis revealed three viewpoints. Twenty-four participants were significantly associated with one of these viewpoints ($p < 0.05$). The viewpoints explained 50% of the variance in the ranking data and table 1 shows the composite rankings of the statements for each of the three viewpoints together with the distinguishing and consensus statements.

Viewpoint 1: "Arthritis negatively affects my sexual health".

Men with this viewpoint experience a substantial impact of IA on their sexual health. In particular, pain (st.6: +4; i.e. statement 6 receives factor score +4), fatigue (st.7: +4) and gloom (st.8: +2) secondary to IA had a negative influence on their sexual health. They feel unsatisfied with their sexual health (st.1: -2) and consider that their sexual problems are not the same as those present in healthy men (st.11: -4). Due to IA, sex became less

spontaneous (st.9: +2), unpredictable (st.10: +3) and difficult (st.15: +3); "Because of pain, my sex life became more conservative than it was" (45 years, diagnosed with RA at the age of 35).

Table 2. Demographic characteristics of participants.

	All participants	"Arthritis has a negative influence on my sexual health"	"I am keeping up appearances"	"I am satisfied with my sexual health"
Participants, n (%)	30 (100.00)	6 (19.35)	5 (16.66)	13 (43.33)
Age, mean (SD)	42.76 (15.50)	36.17 (7.60)	43.80 (14.02)	43.92 (16.27)
Age at diagnosis, mean (SD)	27.66 (19.76)	15.50 (14.71)	28.60 (16.72)	31.15 (16.29)
Disease duration years, mean (SD)	15.25 (10.87)	20.67 (16.12)	15.20 (11.92)	12.77 (7.03)
Religious, n (%)	14 (46.67)	3 (50.00)	2 (40.00)	4 (30.77)
Dutch ethnicity, n (%)	26 (86.67)	6 (100.00)	5 (100.00)	10 (76.92)
Highly educated, n (%)[1]	15 (50.00)	1 (16.67)	3 (75.00)	7 (53.85)
In a relationship, n(%)	29 (96.67)	6 (100.00)	5 (100.00)	12 (92.30)
Sexual activity last 12 months[2]**, n (%)**	26 (92.86)	6 (100.00)	5 (100.00)	12 (92.31)
Number of children, mean (SD)	1.16 (1.01)	0.50 (0.87)	1.40 (0.54)	1.15 (1.21)

1. Bachelor or University.
2. All men who were sexually active reported having had sexual intercourse with women.

Although, they acknowledge that IA is associated with problems of getting and/or maintaining an erection (st.16: +1), these men strongly disagreed with the fact that IA reduces their sexual thoughts (st.12: -3), arousal (st.13: -1) and their sexual desire (st.14: -2) indicating that their sexual dysfunction is mainly due to ED and not due to impaired desire and arousal.

The effect that IA has on these men's sexual health also impacts the relationship with their partners. Guilt towards their partners (st.29: +3) and the feeling of not being completely understood by their partners (st.33: +1) could explain why these men feel that their relationship with their partners worsened because of the diagnosis of IA (st.32: -1). As one participant said "All of my relationship problems are because of my arthritis" (48 years, diagnosed with RA at the age of 44).

With regards to communication, this group of men identified themselves as "open people". They find it easy to talk about their sexual health with their partners (st.27: -2) and health care professional (st.24: -1). Nonetheless, they expressed that getting access to information regarding this topic was difficult. This was exemplified by one of the most frequently expressed comments: "My doctor is always busy and has no time for

this" (61 years, diagnosed with RA at the age of 42). Finding information online about this topic was considered as "easy", but not always adequate and therefore not their preferred method to get information (st.25: -1).

Their masculinity (st.19: 0) and attractiveness (st.20: +1) were slightly negatively influenced by IA. Notably, this was also associated with a negative effect on their confidence with regards to sex (st.21: +2): "I have never found myself attractive, I got deformities that no one else got" (48 years, diagnosed with JIA at the age of 1). During the interviews, several men also expressed a feeling of frustration and fear towards the idea of not being the partner and/or the father they would like to be. "She can get better than me" and "I'm afraid of not being able to play football with my son" (40 years, diagnosed with RA at the age of 34).

Viewpoint 1 had an eigenvalue ('characteristic value') of 2.94 and explained 10% of the variance in the ranking data. Six participants (20%) were significantly associated with this viewpoint.

Viewpoint 2: "I am keeping up appearances"

This group of men also experiences a negative effect of IA on their sexual health. The diagnosis of IA changed their sexual health (st.4: +2). This was mainly due to pain (st.6: +4), which limits their physical abilities (st.15: +1). Furthermore, sex became less frequent (st.9: +1) and they enjoy sex less (st.3: +1).

Other factors such as fatigue (st.7: 0) and gloom (st.8, -1) were not considered to have negative effects on their sexual health. In addition, IA has no negative effect on their capacity to get or maintain an erection (st.16: -4) or on their sexual desire (st.14: -1), reflecting a pure 'physical/mechanic' negative effect of pain on their sex lives. For these men, sex is considered as important contributor to their quality of life (st.2: +3) and they feel satisfied with their sexual health (st.1: +3).

A distinguishing factor of this group was that these men feel less attractive because of their IA (st.20: +2). During the interviews it became evident that for some men this was directly associated with physical deformities; "Every day I am thinking about that (his deformities)" (33 years, diagnosed with JIA at the age of 1) or "It is awkward to get naked in front of your partner when you have swollen joints"(34 years, diagnosed with JIA at the age of 12). For other men, feeling less attractive was associated with their incapacity to perform physical skills (general and during sex), which also has a negative effect on their level of self-confidence.

Another distinguishing factor associated with this group was that these men feel that their partners understand their sexual problems (st.33: +4, 34: -3) although it was not always easy for them to discuss these issues with them (st.27: 0). The impact of IA on their feelings/beliefs about being a man (masculinity) varied between these men (st.19: -1). During the interviews it became evident that their masculinity is a significant contributor to their quality of life that further defines this viewpoint; "Being a man is more than just physical, it is also mental, that is why sometimes I don't tell my wife that I am in pain, I am keeping up appearances" (36 years, diagnosed with RA at the age of 35). These men also described they had problems accepting their disease and communicating their sexual health problems to others "I want to keep everything normal, like it was before" (36 years, diagnosed with RA at the age of 35). As a result, these men tend to hide their problems.

As was the case for viewpoint 1, participants associated with this viewpoint considered that the limited time, that rheumatologists have during their regular appointments, was also the most important reason why talking about sexual health with a healthcare provider is difficult (st.24: +1). Currently, most of the participants in this group agreed with the idea that they might not feel the need to discuss this issue with health care professionals (st.23: 0). However they also indicated that it would have been helpful to receive proper information and advice earlier in their lives.

Viewpoint 2 had an eigenvalue of 1.55 and explained 5% of the variance. Five participants (17%) were significantly associated with this viewpoint.

Viewpoint 3: "I am satisfied with my sexual health"

Men with this viewpoint were satisfied with their sexual health (st.1: +4) and considered sex as an important contributor to their quality of life (st.2: +4). In addition, arthritis did not change their sexual health (st.4: -1), had no negative effect on their erectile function (st.16: -4), sexual desire (st.12: -2, st.13: -3, st.14: -2) or the frequency of sex (st.9: -1).

Gloom and fatigue had the most significant negative influence (st.7: +3, st.8: +3) on their sexual health. Notably, during the interviews, both statements were mostly defined as being associated with their 'normal life' and not specifically with IA. Pain also has a minor negative effect on their sex lives (st.6: +1). Nonetheless, the effect of pain varies between periods of high and low disease activity; "If I had filled this grid 10 years ago it would have been completely different. Back then, pain had a major effect on my sex life" (62 years, diagnosed with RA at the age of 42).

These men believe that their sexual problems are the same as those present in healthy men (st.11: +3). Furthermore, this statement was also associated with episodes of their lives where they have low disease activity or are in clinical remission; “I have no pain now and I feel like a healthy man” (31 years, diagnosed with RA at the age of 22) or with certain attitudes towards the disease itself “I want to be a healthy man” (74 years, diagnosed with RA at the age of 59). Their masculinity and feelings of attractiveness are not (or no longer) significantly impacted by the diagnosis of IA (st.19: -2, st.20: -3).

Other themes that emerged within this viewpoint were that these men believe that their relationships with their partners improved after receiving the diagnosis of IA (st.32: +2), that their partners understand their sexual problems (st.33: +2) and intimacy became more important than sex (st.30: +1).

Communication with their partners about this topic is not considered to be difficult (st.27: -3); “The diagnosis of arthritis opened the doors to us discussing other stuff” (36 years, diagnosed with RA at the age of 30). With regards to communication with health care professionals (st.24: +1), they prefer to get information about this topic online (st.25: +2).

For these men, it is important to consider their sexual health when taking decisions about their medical treatment (st.22: +2). This was of special importance when these men have an active wish to become a father.

Viewpoint 3 had an eigenvalue of 10.35 and explained 35% of the variance. Thirteen participants (43.3%) were significantly associated with this viewpoint.

Demographic and clinical differences between the viewpoints.

Although the design of this study was not intended to draw epidemiologic conclusions, the differences in the demographic and clinical characteristics of the participants across the three viewpoints are worth mentioning (See tables 2 and 3).

One of the most striking differences is that compared to men identified with viewpoints 2 and 3, men identified with viewpoint 1 received the diagnosis of IA at a younger age (28.6 vs 31.1 vs 15.5 years, respectively).

Furthermore, compared to men associated with viewpoint 3, men associated with viewpoints 1 and 2 reported higher disease activity. Noteworthy, men associated with viewpoint 1 reported more depressive symptoms while men associated with viewpoint 2 reported higher pain scores (See Table 3).

Table 3. Participants' patient reported outcomes (general health, disease activity, pain, fatigue, disability and depression)

	All participants	"Arthritis has a negative influence on my sexual health"	"I am keeping up appearances"	"I am satisfied with my sexual health"
Participants, n (%)	30 (100.00)	6 (19.35)	5 (16.66)	13 (43.33)
VAS health, median (SD)[1]	3.11 (2.32)	5.68 (1.62)	3.95 (1.92)	1.85 (1.76)
VAS activity (SD)[1]	3.32 (3.22)	4.93 (3.93)	4.55 (2.17)	2.89 (3.34)
VAS pain (SD)[1]	3.32 (3.15)	3.98 (3.00)	4.72 (1.65)	3.06 (3.60)
VAS fatigue (SD)[1]	4.72 (2.97)	6.63 (2.45)	6.20 (1.35)	3.03 (2.81)
HAQ-DI, mean (SD)[2]	0.64 (0.58)	1.30 (0.57)	0.84 (0.55)	0.41 (0.44)
RADAI (SD)[3]	2.78 (2.33)	3.72 (2.76)	3.08 (1.29)	2.56 (2.53)
PHQ-9, mean (SD)[4]	4.21 (4.56)	7.66 (5.75)	3.25 (0.50)	4.00 (4.77)

1. Score range 0-10. It is a 10 cm straight horizontal line in which the ends are defined as the extreme limits of the parameter to be measured (health, disease activity, pain, fatigue) orientated from the 0 (best) to 10 (worst).
2. Score range 0 to 3. Scores of 0 to 1 are considered to represent mild to moderate difficulty, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.

DISCUSSION

Although the WHO has indicated that sexual health goes well beyond the absence of disease (1) and others have recommended evaluating sexual health using a more holistic approach (17), so far the impact of IA on male sexual health has been mainly studied focusing on ED. Using Q-methodology, we addressed these recommendations and identified three viewpoints on the overall impact of IA on male sexual health among adult men in: "Arthritis negatively affects my sexual health", "I am keeping up appearances" and "I am satisfied with my sexual health".

A negative impact of IA on male sexual health was described in viewpoints 1 and 2. Understanding the different characteristics between these two viewpoints is an important first step towards identifying and approaching these patients.

A severe and 'full' effect of IA on sexual health was identified in viewpoint 1 ("Arthritis negatively affects my sexual health"). Not only were these men characterized by the fact that they clearly attributed their erectile problems to the diagnosis of IA but they also described how multiple characteristics of IA significantly impacted all components of sexual health: physical (pain and fatigue), emotional (feeling guilty towards their partners, lower self-confidence), mental (higher PHQ-9 scores) and social (problems with partners). These men were younger, had a longer disease duration, reported lower general health and had more depressive symptoms. Altogether this might suggest that men diagnosed with IA at an early age might be particularly vulnerable to experience

a negative effect of IA on their sexual health. Men with this viewpoint expressed their willingness to talk about and seek help concerning their sexual health problems.

In contrast, men with viewpoint 2 ("I am keeping up appearances") experience milder and mainly physical sexual problems. These problems were mainly associated with pain and were considered a difficult topic to discuss. Although they indicated that IA changed their sexual life and they enjoy sex less because of the diagnosis of IA, these men also agreed with the statement that they feel satisfied with their sexual health. A potential explanation for this discrepancy in the quantitative data was provided by the men during the interviews. These qualitative data revealed a stronger and more complex negative effect of IA on male sexual health and a distinguishing coping mechanism that these men have in relation to the diagnosis of IA and/or living with IA. Compared to women, men with RA struggle more often to accept and cope with their diagnosis (18-20). Using Q-methodology, two different coping strategies in men with RA were previously described; "acknowledge, accept and adapt" and "trying to match up to a macho ideal" (21). Men with viewpoint 2 share many distinguishing factors with the coping strategy "trying to match up to a macho ideal", which further supports the theory that some men tend to hide their feelings of vulnerability ("I am a man"). This attitude may result in difficulties for health care professionals to address the needs of their patients adequately, as they may miss important internal distress experienced by their patients. Therefore, identifying these men can be considered a challenge and requires a special approach. Instead of asking them whether they feel satisfied with their sexual health or if they have sexual health problems (i.e. erectile dysfunction), these men are more receptive to questions such as; did IA change your sexual health? or, is IA interfering with your ability to enjoy sex? .

Men with viewpoint 3 ("I am satisfied with my sexual health") indicated that they were satisfied with their sexual health and considered their sexual health problems as not being different from those of healthy men. These men associated their degree of satisfaction with their current states of clinical remission or low disease activity. Their interviews provided us with an important message about the potential dynamics of the viewpoints (See Figure 3). Participants described how ranking the statements would have been different if they participated during a period with higher disease activity. In the past, during such periods IA did impair their sexual health, which resulted in dissatisfaction. This was usually solved when low disease activity or remission was achieved. With this regard, it has been previously reported that improvement in disease activity has been associated with improved sexual function (22) and with a better quality of life (23).

Participants across the three viewpoints also pointed out that their ranking of the statements would have been different if they would have participated during a different phase of their life (i.e. adolescence/young adulthood). As an example, men who were diagnosed at a younger age described how exploring their sexuality was difficult and different compared to "other boys", how their diagnosis led to problems in their relationships during their early dating years. They also described long term consequences of the diagnosis of IA, for instance how IA interfered with their sexual development and how certain bodily malformations secondary to IA can have a long-lasting significant psychological impact on their daily lives.

In general, and similar to other chronic conditions (24-26), there was broad consensus among participants that independent of their age or health perception, sexual health is an important contributor to their quality of life. Furthermore, most participants agreed that sexual health is not only important when having an active desire to become a father. Most patients disclosed that receiving information and advice about sexual health in relation to their IA would have been helpful. They also reflected on the importance of approaching sexual health during different phases of life as well as different stages of the disease itself. This has also been reported for similar chronic musculoskeletal conditions affecting sexual health (27). They were open to discuss sexual health with their health care professionals, but this issue was hardly ever raised by health care professionals.

Several explanations for this communication gap between health care professionals and patients have been described (28). First, health care professionals generally incorrectly believe that sexual health is not as crucial as other topics or that patients do not expect them to discuss sexual concerns (29). Notwithstanding, as an important contributor to the quality of life of men with IA, and in line with recommendations (30), male sexual health should be periodically raised by health care professionals in consultations with their patients. As it has been reported in the literature, it is important to consider that the majority of patients prefers active inquiry about sexual health from their health care professionals (31). Concerning this, most participants expressed their gratitude to the research team for "starting the conversation" by inviting them to take part in the study. They described how participating in this study was a positive experience that allowed them to better understand how IA had impacted (or not) their sexual health, and lead them to discuss this topic with their partners.

Second, limited time during the consultation was described as one of the most important barriers to discuss this topic with health care professionals. Increased awareness of this problem, pre-consultation questionnaires for patients and a dedicated teamwork

effort between all health care professionals involved in the care of men with IA (GPs, rheumatologists, nurses, psychologists, sexologists, etc.) can result in an efficient method to approach this topic.

Lastly, another important barrier is that health care professionals often feel unprepared or lack the necessary knowledge to raise and discuss this topic with their patients (32). The Permission, Limited, Information, Specific Suggestions, and Intensive Therapy (PLISSIT) model can be used by health care professionals to facilitate their evaluation of sexual health (33, 34). Importantly, sexual health assessment (in the clinic and in research) should be broad and not only focus on the presence or absence of erectile dysfunction. Tailor-made educational programs about sexual health should be designed and disseminated among health care professionals in the field of Rheumatology.

Our study has several strengths. By combining qualitative and qualitative data using Q-Methodology we were able to describe the impact of IA on many components of sexual health. This allowed us to identify multiple characteristics that could have been easily missed by conventional questionnaires or screening tools and that were crucial to understand the impact of IA on male sexual health and that are relevant for the patients and their quality of life. Furthermore, to ensure a representative and relevant outcome, a multidisciplinary approach that included the input from patients and experts from several fields was used during the design, conduction and interpretation of the study.

An important limitation of this study is that the group of men included was not as diverse as the general population of men with IA. In particular, single men, of non-Dutch ethnic background, non-heterosexual and devout or very religious were difficult to recruit. In addition, the response rate of 64%, although higher than expected, does not exclude the possibility of having missed participants with communication problems or who specifically did not want to talk about sexual health. This means that additional viewpoints, particular to these groups, may have been missed. Moreover, this study was conducted in the Netherlands and the findings are thus confined to the specific socio-cultural and health care system characteristics in this country. Similar studies in other countries may reveal partly different viewpoints, with insights that are relevant in their specific patient population and clinical and social context. Replication is therefore recommended, after careful consideration of the comprehensiveness of the set of statements for local use. Although the results of this study are not generalizable to different populations, they do highlight that research into this topic and raising issues with sexual health in clinical practice may be relevant in other populations as well.

Future research should focus on identifying the prevalence of the three viewpoints in a larger population and better characterizing the clinical characteristics and predictors of impaired sexual health in men with IA. Furthermore, prospective studies on whether and to what extent these viewpoints change in association with disease activity and duration, anti-rheumatic therapy and/or the patients' age are encouraged. Ideally, such studies will provide us with enough information to elaborate questionnaires or diagnostic tools that can facilitate the identification of patients with IA and impaired sexual health. Moreover, the development of efficient intervention strategies to prevent and treat sexual health problems in men with IA are needed. To this end, multidisciplinary collaboration with fields such as Sexology, Psychology and Andrology is recommended. Establishing these research strategies will not only result in an increased awareness of this problem among the Rheumatology community but can also stimulate health care professionals to "start the conversation" and to talk about sexual health with their patients.

Our study confirms that sexual health is important for men with IA and that the overall impact of IA on their sexual health is significant and goes well beyond erectile problems.

Supplemental Table 1. Checklist to include when reporting a Q-methodological study by Churruca K et al (12) is licensed under CC BY 4.0.

Checklist	
How items/statements for the Q-set were collected	☑
How the statements were refined and reduced to produce the draft and final Q-set	☑
The number of statements in the final Q-set	☑
What, if any, piloting was done and what the results were	☑
The materials used for the Q-sorting task including the ranking scale and anchors	☑
How the Q-sorting task was administered	☑
What, if any, other methods were used in conjunction with Q-sorting, and how the data captured by these methods was used in relation to Q-data	☑
The techniques used for factor extraction and rotation	☑
The software programs used to administer and/or analyse the data	☑
The information used to decide the number of factors to extract, rotate and interpret	☑
The amount of variance explained by the factor solution	☑
The processes for interpreting the factors	☑
A rich narrative for each factor that explains the shared meaning it represents, supported by Q-set statements, and participant quotes where available	☑

Supplemental table 2. Statements that were excluded from the final statement set.

	Statement
1.	"I have not lost my interest in sex"[1]
2.	"Sex makes me feel better"[2]
3.	"I don't want to talk to other people about my sexual health problems"[1]
4.	"Sex is painful"[2]
5.	"I avoid sex because afterwards I feel more joint pain"[2]
6.	"I am (almost) always able to orgasm during sex"[2,3]
7.	"I have less self-esteem"[3]
8.	"I have received sufficient information from my rheumatologist/nurse about the (possible) effects of my disease and treatment on my sex life"[2]
9.	"I prefer to discuss my sex life with a male rheumatologist or nurse"[2]
10.	"I'd rather discuss my sex life with the nurse than with the rheumatologist" [2]
11.	"I have found other ways to be intimate" [2]
12.	"Because of my disease it is more difficult to find a partner" [2]
13.	"I am rarely in the mood for sex because of my rheumatism" [2]
14.	"I don't have enough energy for sex" [2]
15.	"My sexual problems get in the way of having children" [2]

1. Double negative: A double negative is a statement which contains two negative words. It is recommended to avoid items containing technical or complicated terminology.
2. Repetitive: It is recommended to reduce duplication of statements.
3. Confusing: These statements resulted in confusion among testers. It is recommended to avoid items containing technical or complicated terminology.

Supplemental table 3. Original statements in Dutch.

1. Ik ben tevreden met mijn seksleven
2. Seks is belangrijk voor mijn kwaliteit van leven
3. Ik geniet minder van seks door mijn reuma
4. Mijn seksleven is veranderd door mijn reuma
5. Ik heb minder vaak seks door mijn reuma
6. Pijn veroorzaakt door mijn reuma heeft een negatieve invloed op mijn seksleven
7. Vermoeidheid heeft een negatieve invloed op mijn seksleven
8. Somberheid heeft een negatieve invloed op mijn seksleven
9. Seks is minder spontaan geworden door mijn reuma
10. Ik vind het vervelend dat schommelingen in de ernst van mijn ziekte mijn seksleven onvoorspelbaar maken
11. Mijn seksuele problemen zijn hetzelfde als bij gezonde mannen
12. Ik heb minder seksuele gedachten door mijn reuma
13. Ik raak moelijker opgewonden door mijn reuma
14. Ik heb minder zin in seks door mijn reuma
15. Er zijn dingen die ik zou willen doen tijdens seks (houdingen/bewegingen), maar die ik niet kan vanwege mijn ziekte
16. Ik heb moeite een erectie te krijgen en/of vast te houden door mijn reuma
17. Ik wil niet aan seks beginnen, omdat ik bang ben halverwege te moeten stoppen door mijn reuma
18. Ik ervaar problemen bij het masturberen door mijn reuma
19. Ik voel mij minder mannelijk door mijn reuma
20. Ik voel mij minder aantrekkelijk door mijn reuma
21. Door de lichamelijke veranderingen voel ik mij minder zeker wat betreft seks
22. Mijn seksleven moet meegenomen worden in de keuze van mijn behandeling
23. Ik heb de behoefte om de effecten van mijn reuma en behandeling op mijn seksleven te bespreken met mijn zorgverlener
24. Ik vind het lastig om over mijn seksleven te praten met mijn zorgverlener
25. Ik zoek liever online naar informatie over de effecten van mijn reuma en behandeling op mijn seksleven
26. Ik heb het gevoel dat ik de enige ben met seksuele problemen veroorzaakt door mijn reuma
27. Ik vind het lastig om seksuele problemen te bespreken met een partner
28. Mijn seksuele problemen maken het hebben van een relatie moeilijk
29. Ik voel mij schuldig tegenover mijn partner door de beperkingen van mijn reuma
30. Intimiteit is belangrijker geworden dan seks
31. Voor mij is seks alleen van belang als ik een kind wil
32. De relatie met mijn partner is verbeterd door mijn reuma
33. Mijn partner heeft begrip voor mijn seksuele problemen
34. Ik heb soms seks alleen omdat ik mijn partner niet wil teleurstellen

REFERENCES

1. Organization WH. Measuring sexual health: conceptual and practical considerations and related indicators. Geneva, Switzerland: WHO publications 2010.
2. Perez-Garcia LF, Te Winkel B, Carrizales JP, Bramer W, Vorstenbosch S, van Puijenbroek E, et al. Sexual function and reproduction can be impaired in men with rheumatic diseases: A systematic review. Semin Arthritis Rheum. 2020;50(3):557-73.
3. Bay LT, Graugaard C, Nielsen DS, Möller S, Ellingsen T, Giraldi A. Sexual Health and Dysfunction in Patients With Rheumatoid Arthritis: A Cross-sectional Single-Center Study. Sex Med. 2020.
4. Hill J, Bird H, Thorpe R. Effects of rheumatoid arthritis on sexual activity and relationships. Rheumatology. 2003;42(2):280-6.
5. Frith H. Focusing on Sex: Using Focus Groups in Sex Research. Sexualities. 2000;3(3):275-97.
6. Van Exel J, De Graaf G. Q methodology: A sneak preview. Online document available from http://wwwqmethodorg. 2005.
7. Watts S, Stenner P. Doing Q Methodological Research: Theory, Method and Interpretation. London2012. Available from: https://methods.sagepub.com/book/doing-q-methodological-research.
8. Watts S, Stenner P. Doing Q methodology: theory, method and interpretation. Qualitative Research in Psychology. 2005;2(1):67-91.
9. Cross RM. Exploring attitudes: the case for Q methodology. Health Education Research. 2004;20(2):206-13.
10. Patty NJS, van Dijk HM, Wallenburg I, Bal R, Helmerhorst TJM, van Exel J, et al. To vaccinate or not to vaccinate? Perspectives on HPV vaccination among girls, boys, and parents in the Netherlands: a Q-methodological study. BMC Public Health. 2017;17(1):872.
11. Truijens D, van Exel J. Views on deceased organ donation in the Netherlands: A q-methodology study. PLOS ONE. 2019;14(5):e0216479.
12. Galekop MMJ, van Dijk HM, van Exel J, Cramm JM. Views of professionals and volunteers in palliative care on patient-centred care: a Q-methodology study in the Netherlands. BMC Palliat Care. 2019;18(1):97.
13. Cramm JM, Leensvaart L, Berghout M, van Exel J. Exploring views on what is important for patient-centred care in end-stage renal disease using Q methodology. BMC Nephrol. 2015;16:74.
14. Churruca K, Ludlow K, Wu W, Gibbons K, Nguyen HM, Ellis LA, et al. A scoping review of Q-methodology in healthcare research. BMC Medical Research Methodology. 2021;21(1):125.
15. Ferrari S, Vanti C, Giagio S, Anesi M, Youssef S, Bortolami A, et al. Low back pain and sexual disability from the patient's perspective: a qualitative study. Disabil Rehabil. 2020:1-9.
16. Perez-Garcia LF, Dolhain R, Te Winkel B, Carrizales JP, Bramer WM, Vorstenbosch S, et al. Male Sexual Health and Reproduction in Cutaneous Immune-Mediated Diseases: A Systematic Review. Sex Med Rev. 2020.
17. Douglas JM, Jr., Fenton KA. Understanding sexual health and its role in more effective prevention programs. Public Health Rep. 2013;128 Suppl 1(Suppl 1):1-4.
18. Flurey C, White A, Rodham K, Kirwan J, Noddings R, Hewlett S. 'Everyone assumes a man to be quite strong': Men, masculinity and rheumatoid arthritis: A case-study approach. Sociol Health Illn. 2018;40(1):115-29.
19. Flurey CA, Hewlett S, Rodham K, White A, Noddings R, Kirwan J. Men, rheumatoid arthritis, psychosocial impact and self-management: A narrative review. J Health Psychol. 2016;21(10):2168-82.

20. Flurey CA, Hewlett S, Rodham K, White A, Noddings R, Kirwan JR. Coping Strategies, Psychological Impact, and Support Preferences of Men With Rheumatoid Arthritis: A Multicenter Survey. Arthritis Care Res (Hoboken). 2018;70(6):851-60.
21. Flurey CA, Hewlett S, Rodham K, White A, Noddings R, Kirwan JR. Identifying different typologies of experiences and coping strategies in men with rheumatoid arthritis: a Q-methodology study. BMJ open. 2016;6(10):e012051-e.
22. L.F. P-G, Micu MC, Gheyle L, Yin Z, Tan Y, Chen K, et al. Sexual function in male and female patients with rheumatoid arthritis: a post-hoc analysis of the FINCH studies. Ann Rheum Dis. 2021;80:496.
23. Scott IC, Ibrahim F, Lewis CM, Scott DL, Strand V. Impact of intensive treatment and remission on health-related quality of life in early and established rheumatoid arthritis. RMD Open. 2016;2(2):e000270.
24. Flynn KE, Lin L, Bruner DW, Cyranowski JM, Hahn EA, Jeffery DD, et al. Sexual Satisfaction and the Importance of Sexual Health to Quality of Life Throughout the Life Course of U.S. Adults. The journal of sexual medicine. 2016;13(11):1642-50.
25. Lu Y, Fan S, Cui J, Yang Y, Song Y, Kang J, et al. The decline in sexual function, psychological disorders (anxiety and depression) and life satisfaction in older men: A cross-sectional study in a hospital-based population. Andrologia. 2020;52(5):e13559.
26. Buczak-Stec E, König HH, Hajek A. The link between sexual satisfaction and subjective well-being: a longitudinal perspective based on the German Ageing Survey. Qual Life Res. 2019;28(11):3025-35.
27. Nilsing Strid E, Ekelius-Hamping M. Experiences of sexual health in persons with hip and knee osteoarthritis: a qualitative study. BMC Musculoskelet Disord. 2020;21(1):576.
28. Dyer K, das Nair R. Why don't healthcare professionals talk about sex? A systematic review of recent qualitative studies conducted in the United kingdom. J Sex Med. 2013;10(11):2658-70.
29. Zhang X, Sherman L, Foster M. Patients' and providers' perspectives on sexual health discussion in the United States: A scoping review. Patient Education and Counseling. 2020;103(11):2205-13.
30. Matcham F, Scott IC, Rayner L, Hotopf M, Kingsley GH, Norton S, et al. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: A systematic review and meta-analysis. Seminars in Arthritis and Rheumatism. 2014;44(2):123-30.
31. Ryan KL, Arbuckle-Bernstein V, Smith G, Phillips J. Let's Talk About Sex: A Survey of Patients' Preferences When Addressing Sexual Health Concerns in a Family Medicine Residency Program Office. PRiMER. 2018;2:23.
32. Merrill JM, Laux LF, Thornby JI. Why doctors have difficulty with sex histories. South Med J. 1990;83(6):613-7.
33. Albaugh JA, Kellogg-Spadt S. Sexuality and sexual health: the nurse's role and initial approach to patients. Urol Nurs. 2003;23(3):227-8.
34. Annon JS. The PLISSIT Model: A Proposed Conceptual Scheme for the Behavioral Treatment of Sexual Problems. Journal of Sex Education and Therapy. 1976;2(1):1-15.

CHAPTER 9

Discussing male sexual and reproductive health in the rheumatology outpatient clinic: a Q-methodology study among patients and rheumatologists

Submitted

Perez-Garcia LF, Röder E, Pastoor H, Lozada-Navarro AC, Colunga-Pedraza I, Vargas-Aguirre T, van Exel J, Vargas-Guerrero A, Dolhain RJEM

ABSTRACT

Objectives

Inflammatory arthritis (IA) has been associated with various problems related to male sexual and reproductive health (SRH). However, addressing these issues in the clinic remains a challenge. In this study, we aimed to describe the viewpoints of rheumatologists and male patients with IA regarding the aspects that influence their communication about SRH.

Methods

Rheumatologists and adult men with IA were invited to participate. This study uses Q-methodology, a mixed methods approach to systematically study subjectivity. Participants ranked 32 aspects according to their degree of influence (least-most influence) in addressing SRH and were then interviewed. Factor analysis was used to identify common patterns in the rankings. These patterns were interpreted as the different viewpoints of rheumatologists and male patients, supported by the qualitative data from the interviews. To obtain more generalizable results, the study was conducted in two countries with different socio-cultural backgrounds and healthcare systems, The Netherlands and Mexico.

Results

30 rheumatologists and 30 men with IA were included in each country. The analysis revealed three viewpoints in each group. Rheumatologists are more likely to be influenced by aspects such as the patient's desire to become a father or the patients' (young) age, but patients by a much more diverse pool of aspects, such as potential side effects of medication on their sexual function.

Conclusions

This study identified different viewpoints on the aspects that influence discussing sexual and reproductive health between rheumatologists and male patients, and important differences in viewpoints between both groups. Further research is needed to reach consensus on how and when rheumatologists and male patients should discuss sexual and reproductive health.

INTRODUCTION

"Sexual and reproductive health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity, in all matters relating to the reproductive system and to its functions and processes". It also includes sexuality, "the purpose of which is the enhancement of life and personal relations, and not merely counselling and care related to reproduction and sexually transmitted diseases" (1).

More than 60% of men from the general population consider sexual and reproductive health as an important contributor to their quality of life (2) and more than 80% of patients deemed that a sexual and reproductive health history should be an integral part of medical consultations (3). Correspondingly, it is now advised that sexual and reproductive health should be part of the standard clinicians' assessment (4, 5). Nonetheless, in Rheumatology, this topic is rarely addressed with male patients (6, 7).

It is estimated that between 36-70% of individuals diagnosed with inflammatory arthritis (IA) experience some form of impaired sexual and reproductive health and most of them do not discuss these problems with their rheumatologists (8-13).

Furthermore, it is estimated that 25% of all erectile dysfunction (ED) cases are related to medication use (14). Immunosuppressive drugs used for the treatment of IA have been associated with ED (15, 16). Men experiencing symptoms from severe ED are often reluctant to disclose their symptoms to their health care professional (17) and because health care professionals rarely address this topic with their patients, the actual frequency of medication-induced ED can be higher (15).

If sexual and reproductive health can be impaired in men diagnosed with IA and it is considered as an important contributor to the patient's quality of life, the question is: why is this topic rarely discussed between patients diagnosed with IA and rheumatologists?

Answering this question is a scientific challenge. The reasons for discussing or not discussing this topic are difficult to analyse and interpret because of their subjective nature (e.g., being afraid of invading privacy, not feeling confident, not considering it relevant, assumptions, etc.). Furthermore, culture is considered to be one of the most important subjective factors that influence sexual health across the world (18).

In this study we use Q-methodology, which combines characteristics of qualitative and quantitative approaches for systematically exploring and explaining patterns in subjectivities (e.g., viewpoints, opinions, beliefs) around sensitive topics and identifying consensus and contrasts between them (19). This method has been used to study views

on complex subjective topics like organ donation (20), treatment adherence (21) and egg freezing (22), but also to describe the impact of IA on male sexual health before and helped identify communication barriers between health care professionals and patients as unmet needs that warrant further research (13, 23).

Our objective is to explore and describe the viewpoints of rheumatologists and male patients diagnosed with IA concerning the factors that influence the discussion about sexual and reproductive health with each other in a multi-cultural setting.

METHODS

Q-methodology

Q-methodology combines qualitative and quantitative techniques to empirically study subjectivity. The whole process of a Q-methodology study can be summarized in four stages (see Figure 1) (24). Information on the use of Q-methodology in healthcare research can be found elsewhere (25). Furthermore, a checklist on how to report a Q-methodology study is included as supplemental Table 1 (25).

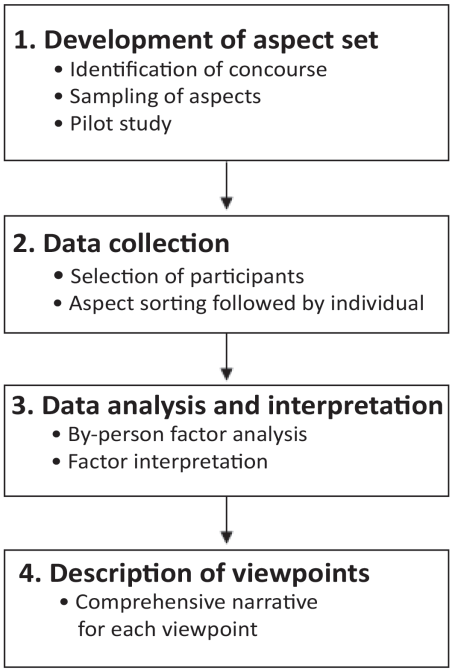


Figure 1: The stages of Q-methodology study.

Development of aspect set

In the initial phase of the study design, two researchers (LFP, ER) collected candidate statements, i.e., aspects that influence the discussion of sexual and reproductive health between rheumatologists (and other HCPs) and male patients. This was based on a non-systematic review of scientific (PubMed), empirical, and popular literature (e.g., online forums, blogs) on this topic. This process resulted in an initial set of 68 aspects.

Furthermore, to attain a comprehensive list of potentially relevant aspects, 38 patients and 51 rheumatologists from The Netherlands (NL) and Mexico (MX) completed a questionnaire that included multiple 'free text' questions about this topic. Their responses contributed a total of 38 additional aspects from the experiences of the population that was going to be studied.

The total list of potential aspects was translated into Spanish and Dutch by professional translators with experience in translations for scientific publications. To evaluate the comprehensibility and comprehensiveness of this list, it was discussed with five rheumatologists and four patients (NL/MX). In addition, one expert in the field of Q-methodology (JvE) was consulted to provide methodological advice on the selection and formulation of aspects. Following these discussions, several adjustments were made: some aspects were excluded from the initial list because they covered similar topics, and the wording of several aspects was revised. At the end of this phase, a draft set of 34 aspects for rheumatologists and 32 aspects for patients, representative for the original long list, remained for pilot testing.

To further test the comprehensiveness and comprehensibility of these two sets of aspects and the other interview materials, a pilot study involving ten rheumatologists and four patients was conducted (NL/MX). Based on the results, no modifications to the materials, including the set of aspects, were deemed necessary. Therefore, the fourteen participants from the pilot study were retained for the main study. The sets of aspects used in the main study (in Dutch and Spanish) can be found in supplemental Table 2.

Data collection

Participants were invited for an individual interview in their local hospital, which took approximately one hour. Each session was moderated by LFP (bilingual, Spanish native speaker) and ER (bilingual, Dutch native speaker) and started with instructions for the study and an explanation of the concept of sexual and reproductive health as being a comprehensive term that goes beyond the physical act of sex.

Thereafter, participants were presented with the aspects printed on cards, in random order, and asked to carefully read all cards. They were asked to consider each aspect in relation to the question 'What aspects influence the discussion of sexual and reproductive health with your rheumatologist / male patients diagnosed with IA?' and to sort them into three piles representing aspects that had the most influence, the least influence and found to be neutral or irrelevant. The participants were then instructed to read the cards in each pile once again prior to ranking them on the sorting grid. (See Figure 2). They started with the pile containing aspects that had 'most influence' according to themselves, followed by those in the pile 'least influence' pile and finally the neutral pile.

After ranking the aspects, participants were asked several open-ended questions. They were asked to explain the placement of certain aspects on the sorting grid and all participants elaborated on the two aspects that had the most and least influence according to them. Also, they were invited to discuss any aspect they found interesting or if there was an aspect that was not considered in the set. The interviews were voice recorded.

Finally, participants were asked to fill in a questionnaire, which included questions regarding their demographic characteristics and their medical history.

Data analysis and interpretation

Individual aspect rankings were subject to by-person factor analysis (i.e., centroid factor extraction, followed by varimax rotation) using KADE 2.0.0. Solutions consisting of identified factors with Eigenvalue larger than one and at least two participants significantly associated ($p < 0.05$) were interpreted as viewpoints on aspects that influence the discussion of sexual and reproductive health between rheumatologists and male patients diagnosed with IA. Interpretations were based on composite (i.e., weighted average) statement rankings for each factor and the qualitative materials of respondents associated with the factor collected during the interviews.

In addition to the characterizing aspects for each factor (i.e., those ranked in the outer two columns of the grid for each of the viewpoints according to the composite sort for the factor), distinguishing aspects per factor (i.e., those whose rankings in one viewpoint differed significantly from those in the other viewpoints) and consensus aspects across factors (i.e., those whose rankings did not differ significantly between any pair of viewpoints) were identified.

Figure 2: Sorting grid and aspects, example of final result. Participants first placed aspects which for them have an influence on discussing SRH on the right side of the score sheet. They placed the two aspects which have the most influence in the two spots in the extreme right column (+4), followed by the next three aspects which have the most influence (+3), and so on. In the same manner, respondents ranked aspects which for them have the least or no influence and those that they found to be neutral on the left side and in the center of the sorting grid, respectively, until all aspects were placed on the sorting grid with only one aspect placed in each cell. Participants were encouraged to review the final result and, if necessary, make any changes.

Description of viewpoints

The interpretation and description of each factor as a viewpoint was based on the ranking of the aspects and the qualitative data collected during the interviews from participants whose rankings were associated with that viewpoint ($p < 0.05$) explaining their ranking of the aspects. Description of the viewpoints involves developing narratives for each viewpoint based on the ranking of the aspects within a factor and relative to their ranking in other factors, also drawing on (and citing) the qualitative data of participants who fall under the viewpoint (25).

Patient and public involvement

Six male patients diagnosed with IA (four were active members of the research advisory board from the Department of Rheumatology of the Erasmus University Medical Center, NL) and five rheumatologists (NL/MX) were involved in the design of the research question and the development of the statement set, the patient information leaflet and the invitation letter. In a pilot study, four patients and ten rheumatologists evaluated the statement set and the other interview materials. We also assessed the feasibility of the study in terms of the burden of the interview on participants.

Participants

Participants were recruited between February 2022 and June 2023. Men with IA who are 18 years or older and rheumatologists who regularly treat male patients diagnosed with IA were invited. Participants had to be proficient in either Dutch or Spanish. As the aim of a Q-methodology study is to explore the variety of viewpoints that exist on a topic, not to make claims about the percentage of people holding them, participants were gathered purposively to ensure diversity. Therefore, recruiters were instructed to invite participants with different cultural and religious backgrounds as well as different health care/working environment settings (public vs private sector). To promote diversity, four researchers (LFP, ER, AV and RD) frequently informed recruiters about the progress of inclusion of participants. Data collection in each country proceeded until saturation was achieved, which was considered to be attained when around 30 interviews per group consecutive interviews had revealed no significant new viewpoints as compared to earlier interviews.

Ethics

This study was reviewed by the Medical Ethics Committee of the Erasmus University Medical Center (MEC-2021-0385) and Instituto Nacional de Cardiologia Ignacio Chavez

(NCAR-DG-DI-CI-EVAL-O63-2021). Written informed consent was obtained from all participants. All participants received financial compensation for their travel and parking costs and a gift card with a value of 20-30 euro.

RESULTS

120 participants were included (i.e., 60 patients and 60 rheumatologists). Demographic characteristics of the study population, are presented in Table 1.

Table 1. Demographic characteristics of participants.

	Patients		
	All patients	**The Netherlands**	**Mexico**
Participants, n (%)	60	30	30
Age, mean (SD)	44.7 (15.1)	44.1 (13.1)	45.4 (17.2)
Age at diagnosis, mean (SD)	33.8 (16.2)	33.0 (16.9)	34.6 (15.9)
Religious, n (%)	40 (66.0)	13 (46.5)	27 (93.1)
Disease duration years, mean (SD)	10.9 (10.2)	11.1 (10.1)	10.9 (10.6)
Diagnosis, n (%)			
Rheumatoid Arthritis	24 (41.3)	13 (44.8)	11 (37.9)
Spondyloarthropathy	15 (25.6)	6 (20.6)	9 (31.1)
Psoriatic Arthritis	9 (15.5)	5 (17.2)	4 (13.8)
Currently in a relationship, n (%)	37 (64.9)	19 (67.8)	18 (62.1)
Number of children, mean (SD)	1.5 (1.5)	1.13 (1.3)	1.86 (1.70)
Active desire to have children, n (%)	13 (22.4)	9 (31.1)	4 (13.8)
Effect of RD on sexual health, n (%)	22 (37.9)	12 (41.9)	10 (34.5)
Erection problems, n (%)	20 (34.5)	9 (31.1)	11 (37.9)
	Rheumatologists		
	All rheumatologists	**The Netherlands**	**Mexico**
Participants, n	60	30	30
Age, n (%)			
<25	0	0	0
25-34	12 (20.0)	3 (10.0)	9 (30.0)
35-44	24 (40.0)	13 (43.3)	11 (36.7)
45-54	15 (25.0)	11 (36.7)	4 (13.3)
55-64	7 (11.6)	3 (10)	4 (13.3)
>65	2 (3.3)	0	2 (6.7)
Female , n (%)	31 (51.7)	16 (53.3)	15 (50.0)
Experience, n (%)			
In training	8 (13.3)	4 (13.3)	4 (13.3)
< 5 years	13 (21.6)	7 (23.3)	6 (20.0)
5-15 years	23 (38.8)	13 (43.3)	10 (33.3)
> 15 years	16 (26.6)	6 (20.0)	10 (33.3)
Professional environment, n (%)			
University hospital	20 (33.3)	10 (33.3)	10 (33.3)
General hospital	18 (30.0)	18 (60.0)	9 (30.0)
Other/combination	22 (36.7)	2 (6.7)	11 (36.7)
Religious, n (%)	36 (60)	10 (33.3)	26 (86.6)

Description of viewpoints – Patients

The analysis revealed three viewpoints among patients diagnosed with IA. Fifty-two of the 60 patients were significantly associated with one of these viewpoints ($p < 0.05$). The viewpoints explained 44% of the variance in the ranking data and table 2 shows the composite rankings of the aspects for each of the three viewpoints.

Separate analysis (data not shown) per country revealed the same trend towards three viewpoints with similar distinguishing and consensus statements. Therefore, the data was pooled and presented as a whole.

Table 2. Composite ranking of aspects for each viewpoint - Patients.

Statement		"Let's talk about my wish to become a father"	"Let's talk about sex"	"Let's talk about my joints"
1	The gender of the rheumatologist	-3	-3	-4
2	The age difference with the rheumatologist	-3	-3	-4
3	The stage of life in which I find myself	0**	-1**	2**
4	The desire to have children	4**	-3**	-1**
5	Having a partner	1*	-2**	1*
6	My cultural/religious background	-4	-4	-2**
7	The cultural/religious background of the rheumatologist	-4*	-4*	-3*
8	The experience of the rheumatologist	-1	0	4**
9	How long I have known the rheumatologist	-2**	1	1
10	How the relationship is with the rheumatologist	0**	3	2
11	Having (had) sexual health problems	2**	-1	0
12	How active my disease is	2	2	4**
13	How long I have been suffering from the disease	0**	-2**	2**
14	Having another disease and/or taking another medication	0	0	3**
15	The time available during the consultation	-1	0**	0
16	Discussing other topics (such as work, hobby) is more important	-1	0**	-2
17	I expect the rheumatologist to be the one to start discussing the topic	0	0	0
18	If the rheumatologist raised the issue of sexual health during a previous consultation	1*	2*	-2**
19	My impression that the rheumatologist is open to discuss sexual health	1**	2**	0**
20	My impression that the rheumatologist does not consider it important to discuss sexual health	-2	1**	-2
21	Fear of the rheumatologist's reaction	-3	-1**	-3
22	My discomfort in discussing sexual health with the rheumatologist	-2**	2**	-3**

Table 2. Continued

Statement		"Let's talk about my wish to become a father"	"Let's talk about sex"	"Let's talk about my joints"
23	My opinion that it is not the rheumatologist's place to discuss sexual health	-2	-2	-1**
24	My experience in discussing sexual health with health care professionals	0	1	-1**
25	The availability of other health care professionals with whom I can discuss sexual health issues	1	1	0**
26	My preference to get sexual health information in writing (leaflet/online)	-1	-1	-1
27	If my partner insists	2**	-2**	1**
28	The importance of sexual health to my quality of life	3*	4	3
29	If I need information about the effect of medication on my sexual health	3	3*	2
30	Sexual health is important in the choice of treatment	2*	3**	1*
31	A known (or possible) negative effect of medication on fertility	4**	0	0
32	A known (or possible) negative effect of medication on sexuality	3	4*	3

*p<0.05, **p<0.01 versus all other factors.
Range -4 (least influence) to +4 (most influence)

Viewpoint 1: "Let's talk about my wish to become a father"

Three characteristic aspects distinguish patients with this viewpoint. First, having a desire to have children (aspect 4: rank score +4) and, consequently, a known (or potential) negative effect of medication on fertility (as. 31: +4) and sexuality (as. 32: +3, see table 2) were considered as the most important aspects that influence discussing sexual and reproductive health with their rheumatologists; "*If the medication could impact my desire to have children, I want to discuss other alternatives, it is an obligation of the rheumatologist*." Furthermore, they considered that sexual health is important to their quality of life (as. 28: +3), *"Sexual health is part of your life",* and that it should be considered in the decision making process (as. 30: +2). Lastly, two additional aspects of influence were having the need for information on this regard (as. 29: +3) or that their partner insists (as. 27: +2); "*Fertility means having a baby… (pause)… and that is what scares me the most, to be less afraid I need more information on this*".

Regarding communication issues, they were less likely to feel uncomfortable when discussing this topic with their rheumatologist (as. 22: -2); "*If you have a problem you have to discuss it and my discomfort has to be put aside*". Furthermore, another aspect that facilitates discussing this topic is if patients have or have had problems related to

sexual health (as. 11: +2); "*It is easier to talk about it if you already have experience with it"*.

With regards to the characteristics of their rheumatologist, two important aspects were of influence according to these patients; their impression that the rheumatologist is open to discuss the topic (as. 19: +1) and if the rheumatologist talked about this topic before (as. 18: +1). *"It is easier to talk about it because we already discussed sexual health".* On the contrary, the rheumatologist's age, gender, cultural or religious backgrounds and the kind of relationship they have with them were considered to have no influence (as. 2: -3, as. 1: -3, as. 7: -4, as. 10: 0). Furthermore, they were also open to discuss this topic with other health care professionals such as a specialized nurse (as. 25: +1).

Viewpoint 1 had an eigenvalue of 16.62 and explained 28% of the variance. Eighteen participants (30%) were significantly associated with this viewpoint. Within the total sample of patients recruited for the study, patients statistically significantly associated with this viewpoint were younger (27.4 years), and a higher proportion had an active wish to become a father (38.9%) and to express that the IA had/has an effect on their family planning (44.4%).

Viewpoint 2: "Let's talk about sex"

Sexual and reproductive health is important to their quality of life and should be considered during the decision-making process (as. 28: +4 and as. 30: +3); "*A side effect of medication that can negatively affect sexuality can also directly or indirectly impact your relationship*". A significant difference compared to viewpoint 1 is that patients with this viewpoint were more likely to be influenced by a known or potential negative effect of their disease or treatment on their sexuality (as. 32: +4) than on their fertility (as. 31: 0) "*You don't have to have an active desire to have children to be able to enjoy sex*". This can be explained by the fact that having an active desire to have children was not relevant for them (as. 4: -3).

Regarding communication, patients with this viewpoint might feel motivated to start the conversation if they need information regarding the effect of medication on their sexuality (as. 29: +3). Nonetheless, this is mostly not a straightforward action as they were more likely to feel "uncomfortable" discussing this topic with their rheumatologists (as. 22: +2); "*I have had sexual health problems that might be related to my medication, but I didn't dare to bring it up with my rheumatologist*". On the contrary, some aspects can

facilitate the conversation, such as having a good relationship with their rheumatologist (as. 10: +3); "*If the relationship is good, it does not matter (the uncomfortable feeling*)". Also, having the impression that the rheumatologist value this topic as important (as. 20: +1) and is open to discuss the topic (as. 19:+2); "*If you are a sensitive person it is relatively easy to get the feeling that someone is open to discuss this topic*" or "*When he asked me about my sexuality I got the feeling that he was not comfortable talking about this topic with me*".

Viewpoint 2 had an eigenvalue of 4.14 and explained 7% of the variance. Seventeen participants (28.3%) were significantly associated with this viewpoint. A higher proportion of the patients defining this viewpoint were single (53.3%) or had no active wish for having children (81.3%).

Viewpoint 3: "Let's talk about my joints"

Patients with this viewpoint considered that having a discussion about sexual and reproductive health depends almost exclusively on how active the disease is (as. 12: +4); "*Before I came to the rheumatologist my quality of life was super bad, I couldn't do anything, thinking about sex is then impossible*" or "*I use my medication to feel better and be able to care for my children even though the medication can negatively affect some things*" . Being diagnosed with another disease or using other medication (as. 14:+3) was also an important aspect of influence.

Contrary to the other viewpoints, some aspects related to the relation with their rheumatologist were seen to have influence on discussing sexual and reproductive health. Having an experienced rheumatologist (as. 8: +4), having a good relationship with him/her (as. 10: +2) and having known each other for some time (as. 13: +2) came forward as aspects that facilitate the discussion. "*The rheumatologist knows what is important for me, I trust him to inform me about important issues*". Furthermore, "*The good relationship I have with my rheumatologist makes having a discussion about sex easier*".

On a personal level, patients with this viewpoint were more likely to be influenced by the phase of the life they are currently in (as. 3:+2) and by their partners (as. 5: +1; as. 27: +1); "*I am 66 years old but fortunately I still have a good time with my partner*" or "*Not everybody has a partner and sometimes you need a partner to stimulate you to get the help you need*". A desire to have children (as. 4:-1) and a known negative (or potential) negative effect on fertility (as. 31:0) were not relevant in this viewpoint;

"*That would have been an interesting conversation to have… 30 years ago, but it never happened. This should be discussed with all young patients, it is so important, I really regret that I never asked about this before*".

Receiving information regarding known (or potential) negative effects on sexuality (as. 32:+3) was considered important as sexual health is valued for their quality of life (as. 28: +3); "*I would really appreciate if my rheumatologist informs me about potential sexuality side effects, then I would really have to think about it, this is information I really want to have*".

Regarding communication, patients with this viewpoint were less likely to feel discomfort (as. 22, -3) when discussing sexual and reproductive health.

Viewpoint 3 had an eigenvalue of 5.25 and explained 9% of the variance. Seventeen participants (28.3%) were significantly associated with this viewpoint. Within the total group of included patients, these men were older (53.2 years), diagnosed at an older age (40.2 years, thus after reproductive age), more likely religious (81.2%), and had more children (2.6) and more erection problems (50%).

Consensus aspects

Across viewpoints there was agreement that the gender of the rheumatologist (as. 1: -3, -4, -3) and the age difference with the rheumatologist (as. 2: -3, -4, -3) had little influence on discussing sexual and reproductive health, and that this is a topic that can be discussed with the rheumatologist (as. 23: -2, -1, -2).

Description of viewpoints - Rheumatologists.

The analysis revealed three viewpoints among rheumatologists in NL and MX. Forty-seven of the 60 rheumatologists were significantly associated with one of these viewpoints ($p < 0.05$). The viewpoints explained 55% of the variance in the ranking data and table 3 shows the composite rankings of the aspects for each of the three viewpoints together with the distinguishing and consensus aspects.

Separate analysis (data not shown) per country revealed the same trend towards three viewpoints with similar distinguishing and consensus statements. Therefore, the data was pooled and presented as a whole.

Table 3. Composite ranking of aspects for each viewpoint - Rheumatologists.

Statement		"Let's talk about side effects"	"Let's talk about your desire to have children "	"Let's talk about your joints"
1	The age difference with the patient	-1**	-3*	-4*
2	The patient's stage in life	1	1	3**
3	The patient's desire to have children	3	4	3
4	Whether the patient has a partner	-1**	1	1
5	My cultural/religious background	-4	-4	-4
6	The patient's cultural/religious background	-1	-1	1**
7	The patient's socioeconomic level/ education level	-3**	0**	0**
8	How long I have known the patient	-1*	-2*	0*
9	How the relationship is with the patient	1	0**	2
10	Personal experiences with sexual health	-3	-1*	-2
11	The patient's sexual health issues	2	2	2
12	How active the disease is	-2**	1**	4**
13	The duration of the disease	-3**	1	0
14	Comorbidity and/or medication	-2**	2	1
15	The time available during the consultation	2	-1**	3
16	Discussing other topics (such as work, hobby) is more important	-1**	-2	-2
17	I expect the patient to be the one to start discussing the topic	0	-3**	-1
18	If the patient raised the issue of sexual health during a previous consultation	4**	1	1
19	My impression that the patient is open to discuss sexual health	3**	0	0
20	My impression that the patient does not consider it important to discuss sexual health	1**	-2	-2
21	My fear of violating the patient's privacy	0**	-1*	-3*
22	My discomfort in discussing sexual health with patients	0**	-3	-3
23	My opinion that it is not the rheumatologist's place to discuss sexual health	-4	-4	-3
24	My experience in discussing sexual health with patients	0	0	-1
25	My ability to engage in sexual health conversations	0	0	-1
26	The availability of other health care professionals with whom the patient can discuss sexual health	0	-1	-1
27	My preference to provide sexual health information in writing (leaflet/online)	-2	-2	-2

Table 3. Continued

Statement		"Let's talk about side effects"	"Let's talk about your desire to have children "	"Let's talk about your joints"
28	The importance of sexual health to the patient's quality of life	2**	3	4
29	The available information on the effect of the medication on sexual health	2	2	0**
30	A known (or possible) negative effect of the medication on fertility	4	4	2**
31	A known (or possible) negative effect of the medication on sexuality	3	3	2**
32	Sexual health is important in the choice of treatment	1**	3**	-1**
33	The effect of the medication on sexual health is important for adherence to treatment	1	2**	1
34	My interest in the topic of sexual health	-2**	0	0

*p<0.05, **p<0.01versus all other factors.
Range -4 (least influence) to +4 (most influence)

Viewpoint 1: "Let's talk about side effects"

The known or potential negative side effects of medication on fertility (as. 30: +4) and sexual health (as. 31: +3) were the most influential aspects that trigger rheumatologists with this viewpoint to discuss male sexual and reproductive health (See table 3). They feel responsible for informing their patients about these side effects, especially their young patients, and more specifically those with an active wish to become a father (as. 3: +3); "*I often talk about this topic with my young patients, specifically when I start new medication that I know that may cause fertility or sexuality side effects*".

To discuss this topic, an important distinguishing characteristic of this viewpoint is that patient-related aspects can be considered as "conditioning aspects". The most important being the fact that a patient approached this topic earlier (as. 18: +4); "*The patient has to come to me with a very specific question about this topic*".

Furthermore, this viewpoint is highly influenced by the impressions of rheumatologists that the patient does not consider discussing sexual health as important (as. 20: +1) or that they are (not) open to discuss the topic (as. 19: +3) "*Sometimes I feel that the patient is a bit restless about something but does not dare to say it. If you ask them "is there anything else you want to discuss with me?" …it is almost always something about sexuality*". Limited time during consultations (as. 15: +2) and considering that

other topics might be more relevant (as. 16: -1) were frequently mentioned as limiting aspects to address this topic with their patients.

These conditions and limitations can be partially explained by the fact that these rheumatologists with this viewpoint were more likely to feel discomfort (as. 22: 0) or fear of invading the patient's privacy when discussing this topic (as. 21: 0); "*It is not a topic I am looking forward to discuss with my patients*".

During the interviews it became evident that rheumatologists with this viewpoint don't really discuss this topic with their patients but rather "inform" them about the side effects. In this regard, they are more likely to have less interest in this topic (as. 34: -2), they give less relevance to the importance of sexual health to quality of life (as. 28: +2) and were less likely to consider sexual health as an important aspect during the decision-making process (as. 28: +2); "*It does not matter if I like to talk about it or not, but a few times you have to talk about it with your patients*".

Viewpoint 1 had an eigenvalue of 25.6 and explained 43% of the variance. Twenty-six participants (43.3%) were significantly associated with this viewpoint. Within the recruited population of rheumatologists, those statistically significantly associated with this viewpoint more often worked in an academic hospital (42.3%).

Viewpoint 2: "Let's talk about your desire to have children"

Having an active wish to become a father (as. 3: +4) was the "automatic" trigger to discuss male sexual and reproductive health for rheumatologists with this viewpoint; "*I ask all my patients between 18 – 40 years if they have an active desire to have children*".

Subsequently, they feel obligated to inform their patients about known or potential negative side effects of medication on fertility (as. 30: +4) and in lesser degree, on sexuality (as. 31: +3); "*If you intervene with medication that can affect fertility you have the responsibility to provide your patients with all the available information*".

Rheumatologists with this viewpoint also believe that patients' desire to have children has a profound effect on the therapeutic decision-making process (as. 32: +3) and therapy compliance (as. 33: +2). "*A patient asked me once; you are prescribing me a new medication, but my question is how would this affect what I really want (having a baby)?"* . Furthermore, they highly value the importance of sexual health on their patients' quality of life (as. 28:+3).

Independent from the desire to have children, disease activity (as. 12: +1) is also a frequent triggering aspect that "opens the door" for discussing sexual and reproductive health. This is related to the fact that rheumatologists might adjust treatment and this in turn leads to prescribing new medication with potential side effects; "*If the disease is active and I need to start new medication with potential side effects on fertility, I will tell them about it*".

Furthermore, they don't feel discomfort (as. 22 -3) or fear of invading patient's privacy (as. 21: -1) when discussing sexual and reproductive health, or limited by the available time for consultations (as. 15: -1). In short, they are more likely to spontaneously start these kinds of conversations with patients *with an active wish to become a father*.

Viewpoint 2 had an eigenvalue of 4.07 and explained 7% of the variance. Thirteen participants (21.6%) were significantly associated with this viewpoint. Within the recruited population of rheumatologists, those statistically significantly associated with this viewpoint more often were female rheumatologists (83%).

Viewpoint 3: "Let's talk about your joints"

Although they considered sexual health as an important contributor to their patient's quality of life (as. 28: +4), controlling the disease activity was the most important aspect for rheumatologists with this viewpoint, essentially dictating when to discuss reproductive and sexual health with their male patients (as. 12: +4); *"I am a rheumatologist, I am there for the patient and the disease has to be treated, otherwise they will have all kind of problems, including fertility problems" or "First treat the disease, then the rest…".*

They rarely discuss this topic with their patients, with the exemption of men with an active wish to become a father (as. 3: +3) or young men (as. 2: +3) *"I don't think of this automatically, there must be a trigger that is initiated by the patient (e.g patient informing them of their active desire to have children)".* They acknowledge that time was also a limiting aspect to approach this topic (as. 15: +3).

Furthermore, known or potential side effects of medication on fertility or sexuality were not considered an automatic trigger to initiate the discussion (as. 30:+2 and as. 31: +2); *"Sometimes I decide not to mention a lot of "potential" side effects because I am afraid that the patient will get scared and won't take his medication".*

One distinguishing characteristic of this viewpoint is that demographic characteristics of their patients were considered more influential, in particular the religious, cultural and

socioeconomic background of patients (as. 6; 1 and as. 7;0); **"***Why should I talk about this topic with some of my patients, they would probably do not understand what I say*" or "*Maybe with some of these patients (low socioeconomic status) we do not talk about it*".

Rheumatologists with this viewpoint were not afraid they will be invading their patient's privacy or don't feel uncomfortable when discussing this topic with them (as. 21; -3, as. 22; -3). During the interviews it became evident that this applied when focusing the discussion on fertility, not necessarily on sexual health.

Viewpoint 3 had an eigenvalue of 5.25 and explained 9% of the variance. Seventeen participants (28.3%) were significantly associated with this viewpoint. Within the total group of included rheumatologists, this group was more likely to work in non-academic hospitals (100%) and be a male rheumatologist (77.8%).

Consensus aspects

Participating rheumatologists largely disagreed that it is not their place to discuss sexual and reproductive health with their patients (as. 23: -4, -3, -4). They agreed that an active wish to become a father (as. 3: +3, +4, +3) was an influential aspect to discuss sexual and reproductive health with their male patients, and that their own cultural and religious background (as. 5: -4, -4, -4) had no influence on discussing this topic.; *"I am a professional, my personal background should not influence how I treat my patients*".

DISCUSSION

This study describes viewpoints on the aspects that influence discussing sexual and reproductive health between rheumatologists and male patients with IA in two countries with distinct cultures and healthcare systems. Three viewpoints were identified and described per group, with no major differences between countries observed. Rheumatologists are mostly influenced by patients having an active wish to become a father and discussing potential side effects of medication (fertility > sexuality), while patients are influenced by a much more diverse pool of aspects. In other words, when raising this topic, rheumatologists mostly focus on fertility and reproduction, while patients' needs and interests around this topic can be much broader. The potential mismatch in viewpoint between rheumatologists and patients on the aspects that trigger them to discuss sexual and reproductive health can help to explain why this topic remains a "neglected" and perhaps also somewhat controversial topic in Rheumatology**.**

Several "historical" factors may partially explain this mismatch between rheumatologists and patients. The lack of formal sexual health curricula in medical schools (26, 27) and the predominance of research focused on potential side effects of medication on fertility (16, 28-30) may have contributed to the stronger focus of rheumatologists on aspects related to male fertility. Another potential mismatch is that both parties may expect the other to initiate the discussion about sexual and reproductive health, resulting in silence about this important topic (31).

The rheumatologist's "automatic" trigger to discuss sexual and reproductive health is the patient's active wish to become a father. Nonetheless, this is only relevant for a specific group of mainly young patients. In addition, young patients might require information on sexual and reproductive health, including family planning, years before their wish to conceive becomes active. Lastly, this study shows that patients want to discuss sexual and reproductive health with their rheumatologists, also when their family planning is fulfilled. Therefore, rheumatologists are encouraged to approach this topic early, often and in a proactive way.

Independent of the active desire to become a father, rheumatologists and patients agree that discussing known or potential side effects of medication on fertility and sexuality is important. However, in this regard rheumatologists are more comfortable talking about potential side effects related to fertility and reproduction (e.g. sperm quality or testosterone levels), than about side effects related to sexuality (e.g. erectile dysfunction (ED)). On the other side, patients, especially those without an active wish to become a father, are more interested in discussing side effects related to sexuality.

Modern Rheumatology is characterized by being a patient-centered specialty where patients are actively involved in the decision making process. It is known that patients need to be confident and well-informed about their care to be fully engaged with their care (32). In this regard, the American College of Rheumatology recommends discussing sexual and reproductive health with patients "early and often" but lack specific recommendations on how to succeed in this.

To facilitate the "early and often" discussion of sexual and reproductive health, we encourage rheumatologists to inform their patients early in the course of their disease that the disease itself or medication can impact their sexual and reproductive health. Acknowledging this association should be considered as one of the most important steps to efficiently approach this topic; not only do patients become aware of this association, but more importantly, rheumatologists let the patient know that they are open to

discuss sexual and reproductive health issues. Consequently, when patients experience sexual and reproductive health problems or have questions regarding this matter, these two important actions (inform and acknowledge) may facilitate the conversation in the outpatient clinic.

During follow-up consultations, the use of other facilitators such as specific pre-consultation questionnaires that include sexual and reproductive health questions and the involvement of other health-care professionals such as specialized nurses may facilitate the discussion of sexual and reproductive health problems (33, 34). The implementation of this approach in our Reproductive Rheumatology outpatient clinic has resulted in a high patient satisfaction rates and improved clinical outcomes (35).

The qualitative data obtained during the interviews exposed a significant "hidden" aspect of influence for some rheumatologist when discussing (or not) sexual and reproductive health; the assumptions they make about the patient. This is a known form of bias (implicit bias), defined as "a negative attitude, of which one is not consciously aware, against a specific social group" (36). Regarding male sexual and reproductive health, rheumatologists often assumed that older patients (>55 years) or patients with specific religious or cultural backgrounds may have no interest in discussing sexuality.

Our study has several strengths. By combining qualitative and quantitative data using Q-methodology we were able to describe how the same topic can be very differently perceived by two parties. On the one side, the study describes how in patients, very personal aspects influence the discussion of this sensitive topic (having a wish to become a father, having (or not) a partner, having ED symptoms). On the other side, it describes how for rheumatologists, the topic is more "legal" or "corporate" (e.g. feeling obligated to discuss side effects of medications). Furthermore, the study describes multiple characteristics that could have been easily missed by conventional questionnaires and that were crucial to understand the described viewpoints.

Moreover, this study was conducted in two countries that have very different cultural backgrounds and health-care systems. In general, the aspects triggering the discussion of sexual and reproductive health were similar in both countries. Lastly, although a Q-methodology study is not designed to answer epidemiological questions our samples are quite large (n=60 and n=60) for a Q-methodology study.

An important limitation of this study is that its results are not generalizable to different populations. Another limitation is that because the Q-sets were slightly different for

both groups (patients and rheumatologists) no direct comparisons between both groups can be made. Furthermore, since there was no know relation between the participating patients and rheumatologists, nothing can be said about 'match in patient-doctor' communication'

For future research, important research recommendations can be made. First, epidemiological research is needed to establish the prevalence of these viewpoints in the general population. Second, studies evaluating the impact of educating health care professionals regarding communication in sexual health are encouraged. The results of these future studies can be used to design evidence-based clinical pathways that can be implemented in daily practice (37). Altogether, it can be expected that these actions result in an much needed new approach of this currently neglected topic in Rheumatology.

In conclusion**,** our study describes the different viewpoints on the aspects that influence discussing sexual and reproductive health between rheumatologists and male patients with IA. Rheumatologists are more likely to initiate the discussion about this topic if their patients are young and have an active wish to have children. On the other hand, patients are influenced by more aspects that go beyond reproduction. Patients should be informed about the potential impact of sexual and reproductive health of IA early during the course of their disease and provided with "facilitators" to discuss this topic throughout the course of their disease.

Supplemental Table 1. *Checklist to include when reporting a Q-methodological study by Churruca K et al (12) is licensed under CC BY 4.0.*

Checklist	
How items/statements for the Q-set were collected	☑
How the statements were refined and reduced to produce the draft and final Q-set	☑
The number of statements in the final Q-set	☑
What, if any, piloting was done and what the results were	☑
The materials used for the Q-sorting task including the ranking scale and anchors	☑
How the Q-sorting task was administered	☑
What, if any, other methods were used in conjunction with Q-sorting, and how the data captured by these methods was used in relation to Q-data	☑
The techniques used for factor extraction and rotation	☑
The software programs used to administer and/or analyse the data	☑
The information used to decide the number of factors to extract, rotate and interpret	☑
The amount of variance explained by the factor solution	☑
The processes for interpreting the factors	☑
A rich narrative for each factor that explains the shared meaning it represents, supported by Q-set statements, and participant quotes where available	☑

Supplemental table 2. Original Statements (Dutch and Spanish)

2a. Patients.

Dutch	Spanish
Welke aspecten hebben invloed op het bespreken van uw seksuele gezondheid met uw reumatoloog?	**¿Qué aspectos influyen al hablar acerca de la salud sexual con el reumatólog@?**
Het geslacht van de reumatoloog	El género del reumatólog@
Het leeftijdsverschil met de reumatoloog	La diferencia de edad con el reumatólog@
De levensfase waarin ik mij bevind	La etapa de la vida en la que me encuentro
Het hebben van een kinderwens	El deseo de tener hijos
Het hebben van een partner	El hecho de tener pareja
Mijn culturele/religieuze achtergrond	Mi cultura/religión
De culturele/religieuze achtergrond van de reumatoloog	La cultura/religión del reumatólog@
De ervaring van de reumatoloog	La experiencia del reumatólog@
Hoe lang ik de reumatoloog ken	Cuánto tiempo hace que conozco al reumatólog@
Hoe de relatie is met de reumatoloog	Cómo es la relación que tengo con el reumatólog@
Het hebben (gehad) van problemen op het gebied van seksuele gezondheid	El hecho de tener (haber tenido) problemas de salud sexual
Hoe actief mijn ziekte is	Qué tan activa está mi enfermedad
Hoe lang ik de ziekte heb	Cuánto tiempo llevo padeciendo la enfermedad
Het hebben van een andere ziekte en/of gebruik van andere medicatie	El hecho de padecer otra enfermedad y/o de tomar otro medicamento
De beschikbare tijd tijdens het consult	El tiempo disponible durante la consulta
Het bespreken van andere onderwerpen (zoals werk, hobby) is belangrijker	Hablar sobre otros temas (como el trabajo, las aficiones) es más importante
Ik verwacht dat de reumatoloog erover begint	Espero que sea el reumatólog@ quien empiece a hablar sobre el tema
Of de reumatoloog tijdens een eerder consult naar mijn seksuele gezondheid heeft geïnformeerd	Si el reumatólog@ me preguntó sobre mi salud sexual en una consulta anterior
Mijn indruk dat de reumatoloog open staat voor het bespreken van seksuele gezondheid	Mi impresión de que el reumatólog@ está abierto a hablar sobre la salud sexual
Mijn indruk dat de reumatoloog het bespreken van seksuele gezondheid niet belangrijk vindt	Mi impresión de que el reumatólog@ no considera importante hablar de la salud sexual
Angst voor de reactie van de reumatoloog	El temor ante la reacción del reumatólog@
Ongemak om over seksuele gezondheid te praten met de reumatoloog	La incomodidad que me produce hablar sobre la salud sexual con el reumatólog@
Mijn mening dat het bespreken van seksuele gezondheid niet thuis hoort bij de reumatoloog	La opinión que tengo de que no es competencia del reumatólog@ hablar sobre la salud sexual
Mijn ervaring met het bespreken van seksuele gezondheid met zorgverleners	Mi experiencia abordando el tema de la salud sexual con los profesionales de la salud
De beschikbaarheid van andere zorgverleners waarmee ik seksuele gezondheid kan bespreken	La disponibilidad de otros profesionales de la salud con los que puedo hablar sobre la salud sexual

Supplemental table 2. Continued

Dutch	Spanish
Mijn voorkeur om informatie over seksuele gezondheid schriftelijk te krijgen (folder/ online)	El hecho de que prefiero recibir información sobre la salud sexual por escrito (folleto/en línea)
Als mijn partner erop aandringt	Si mi pareja insiste
Het belang van seksuele gezondheid voor mijn kwaliteit van leven	La importancia de la salud sexual para mi calidad de vida
Als ik behoefte heb aan informatie over het effect van medicatie op mijn seksuele gezondheid	Si necesito información sobre el efecto del medicamento en mi salud sexual
Seksuele gezondheid is van belang bij de keuze van de behandeling	La salud sexual es importante para la elección del tratamiento
Een bekend (of mogelijk) negatief effect van de medicatie op de vruchtbaarheid	Un efecto negativo conocido (o posible) del medicamento en la fertilidad
Een bekend (of mogelijk) negatief effect van de medicatie op de seksualiteit	Un efecto negativo conocido (o posible) del medicamento en la sexualidad

** Translation: Bureau voor Spaanstalige Dienstverlening*

Supplemental table 2. Continued

2b. Rheumatologists

Dutch	Spanish
Welke aspecten hebben invloed op het bespreken van uw seksuele gezondheid met uw reumatoloog?	**¿Qué aspectos influyen al hablar acerca de la salud sexual con el reumatólog@?**
Het geslacht van de reumatoloog	El género del reumatólog@
Het leeftijdsverschil met de reumatoloog	La diferencia de edad con el reumatólog@
De levensfase waarin ik mij bevind	La etapa de la vida en la que me encuentro
Het hebben van een kinderwens	El deseo de tener hijos
Het hebben van een partner	El hecho de tener pareja
Mijn culturele/religieuze achtergrond	Mi cultura/religión
De culturele/religieuze achtergrond van de reumatoloog	La cultura/religión del reumatólog@
De ervaring van de reumatoloog	La experiencia del reumatólog@
Hoe lang ik de reumatoloog ken	Cuánto tiempo hace que conozco al reumatólog@
Hoe de relatie is met de reumatoloog	Cómo es la relación que tengo con el reumatólog@
Het hebben (gehad) van problemen op het gebied van seksuele gezondheid	El hecho de tener (haber tenido) problemas de salud sexual
Hoe actief mijn ziekte is	Qué tan activa está mi enfermedad
Hoe lang ik de ziekte heb	Cuánto tiempo llevo padeciendo la enfermedad
Het hebben van een andere ziekte en/of gebruik van andere medicatie	El hecho de padecer otra enfermedad y/o de tomar otro medicamento
De beschikbare tijd tijdens het consult	El tiempo disponible durante la consulta
Het bespreken van andere onderwerpen (zoals werk, hobby) is belangrijker	Hablar sobre otros temas (como el trabajo, las aficiones) es más importante
Ik verwacht dat de reumatoloog erover begint	Espero que sea el reumatólog@ quien empiece a hablar sobre el tema
Of de reumatoloog tijdens een eerder consult naar mijn seksuele gezondheid heeft geïnformeerd	Si el reumatólog@ me preguntó sobre mi salud sexual en una consulta anterior
Mijn indruk dat de reumatoloog open staat voor het bespreken van seksuele gezondheid	Mi impresión de que el reumatólog@ está abierto a hablar sobre la salud sexual
Mijn indruk dat de reumatoloog het bespreken van seksuele gezondheid niet belangrijk vindt	Mi impresión de que el reumatólog@ no considera importante hablar de la salud sexual
Angst voor de reactie van de reumatoloog	El temor ante la reacción del reumatólog@
Ongemak om over seksuele gezondheid te praten met de reumatoloog	La incomodidad que me produce hablar sobre la salud sexual con el reumatólog@
Mijn mening dat het bespreken van seksuele gezondheid niet thuis hoort bij de reumatoloog	La opinión que tengo de que no es competencia del reumatólog@ hablar sobre la salud sexual
Mijn ervaring met het bespreken van seksuele gezondheid met zorgverleners	Mi experiencia abordando el tema de la salud sexual con los profesionales de la salud
De beschikbaarheid van andere zorgverleners waarmee ik seksuele gezondheid kan bespreken	La disponibilidad de otros profesionales de la salud con los que puedo hablar sobre la salud sexual

Dutch	Spanish
Mijn voorkeur om informatie over seksuele gezondheid schriftelijk te krijgen (folder/ online)	El hecho de que prefiero recibir información sobre la salud sexual por escrito (folleto/en línea)
Als mijn partner erop aandringt	Si mi pareja insiste
Het belang van seksuele gezondheid voor mijn kwaliteit van leven	La importancia de la salud sexual para mi calidad de vida
Als ik behoefte heb aan informatie over het effect van medicatie op mijn seksuele gezondheid	Si necesito información sobre el efecto del medicamento en mi salud sexual
Seksuele gezondheid is van belang bij de keuze van de behandeling	La salud sexual es importante para la elección del tratamiento
Een bekend (of mogelijk) negatief effect van de medicatie op de vruchtbaarheid	Un efecto negativo conocido (o posible) del medicamento en la fertilidad
Een bekend (of mogelijk) negatief effect van de medicatie op de seksualiteit	Un efecto negativo conocido (o posible) del medicamento en la sexualidad

** Translation: Bureau voor Spaanstalige Dienstverlening*

REFERENCES

1. Glasier A, Gülmezoglu AM, Schmid GP, Moreno CG, Van Look PFA. Sexual and reproductive health: a matter of life and death. The Lancet. 2006;368(9547):1595-607.
2. Flynn KE, Lin L, Bruner DW, Cyranowski JM, Hahn EA, Jeffery DD, et al. Sexual Satisfaction and the Importance of Sexual Health to Quality of Life Throughout the Life Course of U.S. Adults. The journal of sexual medicine. 2016;13(11):1642-50.
3. Zéler A, Troadec C. Doctors Talking About Sexuality: What Are the Patients' Feelings? Sex Med. 2020;8(4):599-607.
4. Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. Arthritis Care Res (Hoboken). 2020;72(4):461-88.
5. Savoy M, O'Gurek D, Brown-James A. Sexual Health History: Techniques and Tips. Am Fam Physician. 2020;101(5):286-93.
6. Flurey CA. Let's talk about sex, rheumatology! Nat Rev Rheumatol. 2022;18(2):65-6.
7. Bay LT, Graugaard C, Nielsen DS, Möller S, Ellingsen T, Giraldi A. Sexual Health and Dysfunction in Patients With Rheumatoid Arthritis: A Cross-sectional Single-Center Study. Sex Med. 2020.
8. Restoux LJ, Dasariraju SR, Ackerman IN, Van Doornum S, Romero L, Briggs AM. Systematic Review of the Impact of Inflammatory Arthritis on Intimate Relationships and Sexual Function. Arthritis Care Res (Hoboken). 2020;72(1):41-62.
9. Josefsson KA, Gard G. Sexual health in patients with rheumatoid arthritis: experiences, needs and communication with health care professionals. Musculoskeletal Care. 2012;10(2):76-89.
10. Perez-Garcia LF, Röder E, Goekoop RJ, Hazes JMW, Kok MR, Smeele HTW, et al. Impaired fertility in men diagnosed with inflammatory arthritis: results of a large multicentre study (iFAME-Fertility). Ann Rheum Dis. 2021.
11. Perez-Garcia LF, Röder E, Smeele HTW, Goekoop R, Hazes JMW, Kok MR, et al. Paternal inflammatory arthritis is associated with a higher risk of miscarriage: results of a large multicenter study (iFAME-Fertility). Rheumatology (Oxford). 2021.
12. Stransky O, Hunt N, Richards JS, Talabi MB. Exploring Family Planning, Parenting, and Sexual and Reproductive Health Care Experiences of Men With Rheumatic Diseases. J Rheumatol. 2022;49(3):251-5.
13. Perez-Garcia LF, Röder E, Pastoor H, Bolt JM, van Exel J, Dolhain R. It is not just about sex: viewpoints of men with inflammatory arthritis on the overall impact of the disease on their sexual health. RMD Open. 2021;7(3).
14. Keene LC, Davies PH. Drug-related erectile dysfunction. Adverse Drug React Toxicol Rev. 1999;18(1):5-24.
15. Kaplan-Marans E, Sandozi A, Martinez M, Lee J, Schulman A, Khurgin J. Medications Most Commonly Associated With Erectile Dysfunction: Evaluation of the Food and Drug Administration National Pharmacovigilance Database. Sexual Medicine. 2022;10(5):100543.
16. Perez-Garcia LF, Dolhain RJEM, Vorstenbosch S, Bramer W, van Puijenbroek E, Hazes JMW, et al. The effect of paternal exposure to immunosuppressive drugs on sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes: a systematic review. Human Reproduction Update. 2020.
17. Mak R, DeBacker G, Kornitzer M, Kittel F, Vander Stichele C. The relation between the international index of erectile function (IIEF) and the intention to seek medical care in the ADAM-Study. Int J Impot Res. 2001;13(suppl 1):S54.
18. Atallah S, Redón AM. Relevant (Sexual) Aspects of Cultural Differences. In: Geuens S, Polona Mivšek A, Gianotten WL, editors. Midwifery and Sexuality. Cham: Springer International Publishing; 2023. p. 271-81.

19. Van Exel J, De Graaf G. Q methodology: A sneak preview. Online document available from http://wwwqmethodorg. 2005.
20. Truijens D, van Exel J. Views on deceased organ donation in the Netherlands: A q-methodology study. PLOS ONE. 2019;14(5):e0216479.
21. Tielen M, van Exel J, Laging M, Beck DK, Khemai R, van Gelder T, et al. Attitudes to medication after kidney transplantation and their association with medication adherence and graft survival: a 2-year follow-up study. J Transplant. 2014;2014:675301.
22. Kostenzer J, Bos AME, Bont A, Exel JV. Unveiling the controversy on egg freezing in The Netherlands: A Q-methodology study on women's viewpoints. Reprod Biomed Soc Online. 2021;12:32-43.
23. Perz J, Ussher JM, Gilbert E. Constructions of sex and intimacy after cancer: Q methodology study of people with cancer, their partners, and health professionals. BMC Cancer. 2013;13:270.
24. Watts S, Stenner P. Doing Q Methodological Research: Theory, Method and Interpretation. London2012. Available from: https://methods.sagepub.com/book/doing-q-methodological-research.
25. Churruca K, Ludlow K, Wu W, Gibbons K, Nguyen HM, Ellis LA, et al. A scoping review of Q-methodology in healthcare research. BMC Medical Research Methodology. 2021;21(1):125.
26. Beebe S, Payne N, Posid T, Diab D, Horning P, Scimeca A, et al. The Lack of Sexual Health Education in Medical Training Leaves Students and Residents Feeling Unprepared. J Sex Med. 2021;18(12):1998-2004.
27. Cappiello J, Coplon L, Carpenter H. Systematic Review of Sexual and Reproductive Health Care Content in Nursing Curricula. J Obstet Gynecol Neonatal Nurs. 2017;46(5):e157-e67.
28. Perez-Garcia LF, Te Winkel B, Carrizales JP, Bramer W, Vorstenbosch S, van Puijenbroek E, et al. Sexual function and reproduction can be impaired in men with rheumatic diseases: A systematic review. Semin Arthritis Rheum. 2020;50(3):557-73.
29. Levi AJ, Fisher AM, Hughes L, Hendry WF. Male infertility due to sulphasalazine. Lancet. 1979;2(8137):276-8.
30. Ostensen M. Sexual and reproductive health in rheumatic disease. Nat Rev Rheumatol. 2017;13(8):485-93.
31. Ryan KL, Arbuckle-Bernstein V, Smith G, Phillips J. Let's Talk About Sex: A Survey of Patients' Preferences When Addressing Sexual Health Concerns in a Family Medicine Residency Program Office. PRiMER. 2018;2:23.
32. Doyle C, Lennox L, Bell D. A systematic review of evidence on the links between patient experience and clinical safety and effectiveness. BMJ Open. 2013;3(1).
33. Shamloul R, Ghanem H. Erectile dysfunction. Lancet. 2013;381(9861):153-65.
34. Hartmann U, Burkart M. Erectile dysfunctions in patient-physician communication: optimized strategies for addressing sexual issues and the benefit of using a patient questionnaire. J Sex Med. 2007;4(1):38-46.
35. Kemper E, Ghalandari N, Wintjes H, Van Steensel-Boon A, Kranenburg L, Mulders A, et al. Active counselling and well-controlled disease result in a higher percentage of women with rheumatoid arthritis that breast feed: results from the PreCARA study. RMD Open. 2022;8(2).
36. FitzGerald C, Hurst S. Implicit bias in healthcare professionals: a systematic review. BMC Medical Ethics. 2017;18(1):19.
37. Lawal AK, Rotter T, Kinsman L, Machotta A, Ronellenfitsch U, Scott SD, et al. What is a clinical pathway? Refinement of an operational definition to identify clinical pathway studies for a Cochrane systematic review. BMC Medicine. 2016;14(1):35.

PART VI

Summary and general discussion

SUMMARY

This thesis aims to obtain insight into the impact of immune-mediated inflammatory diseases (IMID) and treatment on male sexual and reproductive health and consists of six parts.

Part I. General introduction

This part consists of the general introduction (chapter 1) and introduces the reader to several key concepts relevant to this thesis such as male sexual and reproductive health, the epidemiology of IMIDs in men and the male reproductive system. Furthermore, it briefly presents the history and current scope of 'Reproductive Rheumatology'. Lastly, it describes how in this field, the lack of knowledge on the "male perspective" and other current problems experienced by patients and health care professionals can negatively impact patient care. Altogether, this part justifies the conduction of further research in the field.

Part II. Impact of immune-mediated inflammatory diseases on male sexual and reproductive health.

This part presents the available scientific literature on the topic of male sexual and reproductive health in patients diagnosed with an IMID. For this purpose, systematic reviews on the impact of several rheumatic and cutaneous IMIDs on male sexual and reproductive health were conducted;

> ***Chapter 2.*** *Sexual function and reproduction can be impaired in men with rheumatic diseases: a systematic review.*
> ***Chapter 3.*** *Male sexual health and reproduction in cutaneous immune-mediated diseases: a systematic review.*

The results of these systematic reviews suggest that male sexual and reproductive health may be impaired in men diagnosed with IMIDs (rheumatic and cutaneous). The degree and extent of sexual and reproductive health impairment varies greatly per disease. For example, compared to healthy controls (11-41%), a higher prevalence of erectile dysfunction was reported in patients with rheumatoid arthritis (RA) (33 – 62%), systemic lupus erythematosus (SLE) (12 – 68%), psoriasis (34 - 81%) and systemic sclerosis (SSc) (60 - 100%). The evidence regarding fertility outcomes was very limited, but some studies reported a higher frequency of fertility problems (e.g. low sperm quality or higher sperm DNA fragmentation index) in patients with SLE.

Regrettably, these reviews revealed a much stronger conclusion; the overall quality of the studies included in the systematic reviews was low to moderate. Therefore, research recommendations on how to conduct future research on this topic were featured in these systematic reviews (i.e. appropriate study design, use of standardized methods to report outcomes of interest, consider relevant confounders). In conclusion, IMIDs and male sexual and reproductive health should not be considered anymore as being unrelated conditions and further research of good quality is urgently needed.

Part III. Can inflammatory arthritis impair male reproductive health?

The objective of this part was to describe the impact of inflammatory arthritis (IA) on two major outcomes of male reproductive health; fertility and pregnancy outcomes.

> ***Chapter 4****. Impaired fertility in men diagnosed with inflammatory arthritis: results of a large multicentre study (iFAME-Fertility).*

This multicenter cross-sectional study demonstrated for the first time that IA diagnosed before and during the peak of reproductive age (<30 and 31-40 years, respectively) was associated with impaired male fertility. 628 men diagnosed with IA participated in the study. Using the male fertility rate (average number of biological children per man) as the main outcome of interest, it was reported that men diagnosed before and during the peak of reproductive age (1.32 and 1.60, respectively) had statistical significantly fewer children (p=<0.005) than men diagnosed with IA after the peak of reproductive age (1.88) and the general population of the Netherlands (1.79).

Furthermore, the rate of involuntary childlessness was higher in these men and they were more likely to report reproductive health problems (e.g. infertility, low sperm quality). Whether these reproductive health problems are directly related to the disease itself, the immunosuppressive treatment often used by these patients or for other reasons remains unknown.

> ***Chapter 5.*** *Paternal inflammatory arthritis is associated with a higher risk of miscarriage: results of a large multicentre study (iFAME-Fertility).*

To further evaluate the impact of IA on male fertility, the pregnancy outcomes of partners of men diagnosed with IA during the pre-conception period were also evaluated. In total, 408 male participants diagnosed with IA reported 897 singleton pregnancies that resulted in 794 live births. Compared to pregnancies conceived before the diagnosis of IA, pregnancies conceived after the diagnosis of IA had higher rate of miscarriage (12.27 vs 7.53%, p = <0.05). This increased risk was still present after adjusting for relevant

confounders, like age [OR 2.03 (95% CI 1.12, 3.69) P = 0.015]. It was concluded that pregnancies of partners of men diagnosed with IA had a significantly higher risk of miscarriage. Albeit these findings need to be corroborated by large prospective studies, rheumatologists should be aware that paternal IA may increase the risk of miscarriage.

Part IV. Testicular toxicity of immunosuppressive agents.

This part focuses on the testicular toxicity profile of immunosuppressive drugs. Chapter 6 describes the results of a systematic review on the effect of paternal exposure to immunosuppressive drugs on several outcomes of male sexual and reproductive health. Second, chapter 7 describes the results of a study that prospectively evaluated the testicular toxicity profile of one of the most frequently prescribed immunosuppressive drugs, methotrexate.

> ***Chapter 6.*** *The effect of paternal exposure to immunosuppressive drugs on sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes: a systematic review.*

A systematic literature search was performed. The searches combined keywords regarding male sexual function and fertility, pregnancy outcomes and offspring health with a list of immunosuppressive drugs. 161 articles were identified. Amongst these articles, 50 included reproductive health outcomes and 130 included sexual health outcomes. Except for large Scandinavian cohorts, most of the identified articles included a small number of participants. While a clear negative effect on sperm quality was evident for sulfasalazine and cyclophosphamide, a dubious effect was identified for colchicine, methotrexate and sirolimus. No negative effect was observed for acitretin, azathioprine, ciclosporine, isotretinoin, tumour necrosis factor-α (TNF-α) inhibitors and verdolizumab. In three articles, exposure to TNF-α inhibitors in patients diagnosed with ankylosing spondylitis resulted in improved sperm quality. The information regarding pregnancy and offspring outcomes was scant but no large negative effect associated with paternal immunosuppressive drug exposure was reported.

In conclusion, evidence regarding the safety of immunosuppressive drugs in men with a wish to become a father is inconclusive. The small number of participants included in most of the studies and the lack of standardization on how to evaluate and report male sexual and reproductive health outcomes in men exposed to immunosuppressive drugs are important contributors to this result. Future research on this topic is needed and should be preferably done with bigger and well-powered studies that use standardized methods.

> ***Chapter 7.*** *Is methotrexate safe for men with an immune-mediated inflammatory disease and an active desire to become a father? Results of a prospective cohort study (iFAME-MTX).*

The iFAME-MTX study is the largest study to date that prospectively evaluated the potential impact of MTX focusing on many important markers of testicular toxicity and evaluating the potential underlying mechanisms explaining why MTX does not impair sperm quality. In this study, exposure to MTX was not associated with conventional semen analysis abnormalities, disturbances in the male reproductive endocrine axis or increased sperm DNA damage. Furthermore, this study reports for the first time that the enzyme responsible for intracellular polyglutamylation and hence the bioactivation of MTX, that is, folylpolyglutamate synthetase (FPGS), has extremely low activity in spermatozoa. Ultimately resulting in very low concentrations of intracellular MTX-PG in spermatozoa. It was concluded that treatment with MTX is not associated with testicular toxicity, consistent with the very low concentration of intracellular MTX-PG. Therefore, it was recommended that MTX can be started or continued in men with an active wish to become a father.

Part V. Let's talk about sex! … in Rheumatology

This part describes the impact of IA on male sexual health and the different viewpoints of male patients diagnosed with IA and rheumatologists regarding the discussion of sexual and reproductive health in the outpatient clinic.

> ***Chapter 8.*** *It is not just about sex: viewpoints of men with inflammatory arthritis on the overall impact of the disease on their sexual health.*

To understand the impact of IA on male sexual health, not only the physical component but also the emotional, mental and social components of sexual health should be described. These components are difficult to analyze and interpret because of their subjective nature. Questionnaires mainly generate quantitative data and can easily miss relevant subjective information. Although, focus groups provide solid qualitative data and have been used to explore sensitive topics, interaction between group members may have the potential to decrease the quality of disclosure obtained from the members (1). Q-methodology combines the strengths of qualitative and quantitative approaches and is a powerful methodology for systematically exploring and explaining patterns in subjectivities (viewpoints, opinions, beliefs) around sensitive topics and identifying consensus and contrasts between them.

Using Q-methodology, three viewpoints on the overall impact of IA on male sexual health among adult men were identified:

- 'Arthritis negatively affects my sexual health': Men who experience a dramatic impact of IA on all components of sexual health (physical, emotional, mental and social).
- 'I am keeping up appearances': In these men, IA negatively impacts sexual health but a distinguishing coping mechanism ("I am a man") could mask a more serious negative impact.
- 'I am satisfied with my sexual health': These men experience no significant impact of IA on their sexual health.

Two of these viewpoints revealed a negative influence that goes beyond the physical act of sex. Therefore, it can be concluded that IA can severely affect the emotional, mental and social components of sexual health.

> ***Chapter 9.*** *Discussing male sexual and reproductive health in the rheumatology outpatient clinic: A Q-methodology study among patients and rheumatologists*

Discussing men's sexual and reproductive health in the outpatient clinic remains a challenge. Chapter 9 discusses the different viewpoints of male patients diagnosed with IA and rheumatologists regarding discussing sexual and reproductive health in the outpatient clinic. This study also uses the Q-methodology. Three views of rheumatologists and three views of patients were identified:

Rheumatologists:

- 'Let's talk about your wish to have children': An active wish to become a father is the most influential aspect for this group of rheumatologists. In addition, they regularly discuss with their young patients the side effects of immunosuppressants on fertility.
- 'Let's talk about side effects': Among these rheumatologists, the side effects of immunosuppressants on fertility (and to a lesser extent, sexuality) are the most important aspects to discuss this topic.
- 'Let's talk about your joints': These rheumatologists rarely discuss this topic with their patients; their priority is to get the disease under control. This topic is only discussed with men with an active wish to become a father. Nonetheless, to discuss this topic, the patient has to take the initiative.

Patients:

- 'Let's talk about my wish to become a father': For these patients, having an active wish to become a father is the main trigger to discuss this topic. They want to get information about the side effects of immunosuppressants on fertility.
- 'Let's talk about sex': For these men, sexual and reproductive health is an important aspect for their quality of life. Thefefore, this topic should be discussed and taken into account during the shared-decision treatment process.. They want to get more information about sexuality and not necessarily fertility.
- 'Let's talk about my joints': These men find a conversation about sexual and reproductive health much less important when their disease is active. Their priority is to get the disease under control, "after that comes everything else." They rely on their rheumatologists to inform them about this when necessary.

Shortly, rheumatologists are more likely to be influenced by two aspects; the patient's wish to become a father or the patients' (young) age and discussing potential side effects of medication on fertility. Nonetheless, patients are influenced by a much more diverse pool of aspects, such as discussing potential side effects of medication on their sexuality regardless of having an active wish to become a father.

Part VI. Discussion

This part is dedicated to the general discussion of this thesis. The main findings of this thesis are further debated and compared to similar studies on the topic. Furthermore, implications for the rheumatologists, other health care professionals, patients and researchers are presented. Lastly, this part also includes practical recommendations on how to approach this topic in the outpatient clinic and how to implement this findings into clinical practice.

REFERENCES

1. Frith H. Focusing on Sex: Using Focus Groups in Sex Research. Sexualities. 2000;3(3):275-97.

DISCUSSION

For many decades, male sexual and reproductive health has been a neglected topic in Rheumatology. In view of this significant knowledge gap and inspired by the expansive definition of sexual and reproductive health provided by the World Health Organization (WHO), this thesis aimed at (holistically) evaluating the impact of immune-mediated inflammatory diseases (IMIDs) and its associated pharmacological treatment on several outcomes of male sexual and reproductive health.

This thesis demonstrates that IMIDs such as inflammatory arthritis (IA) can have a negative impact on several aspects of male sexual and reproductive health (1, 2). Importantly, the impact of IA on male sexual and reproductive health goes well beyond biological outcomes. Men testified how the diagnosis of IA directly or indirectly impaired multiple aspects of their sexual health and sexual well-being (e.g. feeling "less of a man", not feeling satisfied with their sexuality, feeling less confident). Altogether, this sexual health impairment can have a significant impact on the quality of life (3).

Regarding reproductive health outcomes, IA diagnosed before and during the reproductive years (30-40 years) was associated with having less children, a higher rate of involuntary childlessness, having more fertility health problems and with a higher risk of miscarriages (4, 5).

Respecting the impact of pharmacological treatment of IMIDs on male sexual and reproductive health, the results of a systematic review showed that the current available scientific data on the testicular toxicity profile of most of the immunosuppressive drugs used for the treatment of IMIDs is scarce and therefore non-conclusive (6). This included methotrexate (MTX), one of the most frequently prescribed immunosuppressive drugs for the treatment of IMIDs.

Concerning this lack of data, the results of the iFAME-MTX study were reassuring (7). In addition to the conventional sperm quality parameters, this study was designed taking into account several fertility and testicular toxicity outcomes (sperm DNA fragmentation index, reproductive axis). Furthermore, an additional translational study was performed that concluded that spermatozoa lacks the enzyme responsible for the MTX induced toxicity (52) spermatozoa. In short, the conduction of studies that evaluate testicular toxicity requires understanding the physiology and pharmacology behind the potential mechanisms of testicular and reproductive toxicity, careful consideration of outcomes of interest (primary and secondary), innovative study designs and extensive collaboration between many fields.

Lastly, during the course of this research project, it became evident that IMIDs had the potential to negatively impact male sexual and reproductive health. Furthermore,

patients repeatedly described “missed opportunities” were during specific phases of their lives they experienced sexual and reproductive health problems that could have been related to their IMID diagnosis or treatment but that were never discussed with their health care professionals.

The aim of holistically evaluating the impact of IMIDs on male sexual and reproductive health was not complete without trying to understand what was leading to these “missed opportunities”. Therefore, an additional study was performed with the objective of describing the different viewpoints of rheumatologists and male patients diagnosed with IA on the aspects that influence discussing (or not) sexual and reproductive health in Rheumatology.

On one side, rheumatologists tend to almost exclusively focus on one group of men, those with an active wish to become a father and on the biological aspects of reproductive health (e.g. low sperm quality or testicular toxicity). On the other side, patients described their interest and need to discuss sexual health with their rheumatologists. This significant mismatch between male patients and rheumatologists can explain those “missed opportunities” and some of the difficulties regarding the discussion of this topic.

Before comprehensively discussing the results of this thesis and its subsequent implications for health care professionals, patients and researchers, some basic concepts should be acknowledged.

First, the definition of sexual and reproductive health should be emphasized; “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity, in all matters relating to the reproductive system and its functions and processes.” Certainly, sexual and reproductive health is a complex and multifactorial component of human life that includes biological and non-biological aspects. Consequently, for research and patient-care purposes, using a holistic approach that considers not only the “classical” biological aspects of this topic is strongly recommended.

Second, sexual and reproductive health is an exceptionally dynamic aspect of human life and varies greatly depending on the different phases of life. From young to old, from having a wish to become a father to being a father, from being single to being a widower, a negative impact of IMIDs on male sexual and reproductive health can be expected in any of these phases of life. Therefore, the misconception that this topic in Rheumatology is only important for men with a wish to become a father should be considered as obsolete.

Third, generating scientific information about the impact of IMIDs on male sexual and reproductive health is fruitless if the topic is not discussed in the outpatient clinic. Two

major problems could partially explain this situation; health care professionals are not aware of this association and the topic can still be considered as a taboo topic.

Regarding communication about sexual and reproductive health, much can be written about the reasons that make discussing this topic in the outpatient clinic so difficult, but one thing is certain; talking about sexual and reproductive health is easier than usually expected.

Implications for clinical practice

Sexual and reproductive health is a central aspect of being human and it can be impaired in male patients diagnosed with an IMID (8-14). IMIDs, and more specifically IA, can negatively impact several components of male sexual and reproductive health such as fertility, family planning, sexual health and wellbeing. The message for the rheumatologists and other health care professionals is clear; male sexual and reproductive health should also be considered as a relevant topic in Rheumatology.

Awareness

Because patients might not readily associate sexual and reproductive health problems with an IMID diagnosis, early in the course of the disease, male patients should be informed that their IMID and/or medication may eventually impact their sexual and reproductive health. Acknowledging this association should be considered as one of the most important steps to efficiently approach this topic; patients become aware of this association and more importantly, the rheumatologists let the patient see that they are open to discussing sexual and reproductive health issues. Therefore, when patients experience sexual and reproductive health problems or have questions in this matter, these two important actions (*inform and acknowledge*) may help to facilitate the conversation in the outpatient clinic.

A second important step is to be mindful of the different needs of patients regarding sexual and reproductive health throughout their lifespan. Patients diagnosed during childhood or adolescence may experience a significant negative effect of the disease on their sexual development and their transition to adult life and consequently may face serious sexual health problems (3, 4, 15). On the other hand, rheumatologists should not automatically assume that older patients are not sexually active or that they do not experience sexual health problems(16, 17). Between 50-73% of men older than 55 years are sexually active and may experience sexual health problems (16).

Moreover, rheumatologists are more familiar with the idea of counseling and giving medical advice regarding reproductive health to men with an active wish to conceive (18-20) than with the idea of discussing reproductive and sexual health problems with

men without an active wish to conceive(20, 21). By waiting until the moment that the patient expresses his desire to become a father, rheumatologists might miss important sexual and reproductive health problems (3, 4). Therefore, in agreement with the recent Reproductive Rheumatology guidelines published by the American College of Rheumatology, we urge rheumatologists to approach this topic with their patients "*early and often*", and not only in patients with an active wish to become a father (18).

Noteworthy, while rheumatologists tend to focus almost exclusively on the biological aspects of reproductive health and specifically on the testicular toxicity profile of the immunosuppressive drugs (e.g. which drug is safe for a men with a wish to become a father?) (21), for patients with an active wish to become a father, non-biological aspects are as relevant as the "classic" biological aspects (4). Along with information on the potential negative effects of immunosuppressive drugs on reproductive outcomes, patients need information on the genetics of their disease ("what is the risk of my baby inheriting my disease?") or on the impact of the disease on their parenthood ("will I be able to play with my kids?"). Therefore, we encourage rheumatologists to also consider non-biological aspects that may influence male sexual and reproductive health when approaching this topic with their male patients (22).

Furthermore, rheumatologists should not be afraid to discuss this topic with their patients (21, 23-25). Most patients expect rheumatologists to start the conversation and appreciate when they are informed about any potential negative effect of their disease or medication on important aspects of their quality of life (such as sexual and reproductive health) (24, 25).

From the patient's perspective, the need to receive information or to talk about this topic was also a repetitive finding reported in this thesis (3, 4). This does not only reflect the importance of the topic for the patients but perhaps, more importantly, the responsibility of health care professionals on this matter. The lack of advice (or giving incorrect advice) was considered to be one of the most important reasons that explained why men with IA diagnosed at an early age had less children than originally desired (4). This can be considered as a life-long consequence of having a diagnosis of IA.

From the rheumatologist's perspective, they also frequently expressed their desire and need to receive additional educational training on this topic . In this regard, it has been previously reported that rheumatologists are interested in receiving additional medical training and education over this topic (21). Continuous medical education on this topic should be carefully designed by experts in the field. Additionally, these programs should be easily accessible for rheumatologists and other health care professionals.

Clinical approach

A brief overview with recommendations on how and when to approach this topic with patients is presented in table 1.

Table 1. Practical recommendations for rheumatologists on approaching the topic on male sexual and reproductive health.

When?	*"Early and often"* **(18).**
Who is at higher risk? Clinical clues that should raise the suspicion of sexual and reproductive health problems in men with IA (red flags) (3, 26).	• Young age at diagnosis of IA (<30 years). • Moderate to high disease activity. • High VAS pain scores. • Chronic physical disability. • Deformities (visible and non-visible). • Depressive symptoms.
How to initiate the conversation? Suggested strategy to approach the topic of sexual health (27, 28).	• "*Inform and acknowledge*" • "It is common for men with inflammatory arthritis to experience changes in their sexual and reproductive health or difficulties, this is why I would like to ask you some questions about this aspect of your life, is that ok?"
What to ask? Suggested specific questions to identify men with sexual health problems associated to IA and other IMIDs (27, 28).	• Did IA change your sexual health? • Is IA interfering with your ability to enjoy sex? • Is pain limiting or interfering with your sexual activity? • Do you talk about your sexual health problems with your partner? • Are you planning on having children? Do you have any specific questions regarding your family planning and your disease/treatment? • **LISTEN!**
You identified a man with sexual health problems, now what? Possible interventions that can be offered within the Rheumatology consultation.	• Inform about the effects of AI and pharmacological treatment on sexual and reproductive health. • Involve their partners in the process. • Adjust treatment if indicated. • Offer practical advice about how to deal with the changes in sexuality, e.g. take more time, adjust sexual behavior and stimulation (e.g. other position, no intercourse but manual or oral), use Phosphodiesterase type 5 inhibitors (PDE5i) in case of (erectile dysfunction) ED. • Refer to multidisciplinary care (e.g. andrologist, sexologist or psychologist) when indicated.
When and where to refer? Certain patients might benefit from a multidisciplinary approach (29).	• Specialized nurse: In-depth information and advice on how to reduce the impact of IA on male sexual and reproductive health. • Internist/Urologist: Suspicion of infertility, hypogonadism and/or ED. • Sexologist: Sexual dysfunction or difficulties that go beyond practical advice and need a longer and more complex treatment (e.g. impact on partner relationship, psychological impact (e.g. fear of failure, not feeling masculine))

*Questions can be adapted to facilitate patient's comprehension (e.g. use of local expressions or simple terms)

Wish to become a father

The influence of paternal pre-conception health on pregnancy and offspring outcomes has recently gained much attention (30, 31). It is now recognized that poor paternal pre-conception health is associated with worse pregnancy outcomes (30). Based on the results of this thesis and recent important discoveries in the field of Andrology and Reproductive Medicine that suggest that systemic inflammation may be associated with male infertility (32-36), it can be hypothesized that high (and chronic?) disease activity secondary to IMIDs could also negatively influence pregnancy and offspring outcomes (37). Similar to current recommendations for women with IMIDs, it can be expected that aiming at low disease activity in men diagnosed with IMIDs could result in better pregnancy outcomes.

Therefore, one of the most important clinical questions for rheumatologists and patients is how to treat male patients who have an active wish to conceive and who are diagnosed with an IMID?

Recommendations regarding medication use for men with rheumatic diseases who are planning to father a child have been published elsewhere (18, 38). These recommendations can simplify the decision making process but will not always deliver a straightforward answer; simply because the available scientific data for many recently prescribed immunosuppressive drugs is not conclusive.

Practical recommendations on how to holistically approach a male patient diagnosed with an IMID and an active wish to conceive are presented in Table 2.

How to implement this strategy in clinical practice

Along with all the implications of treating the IMIDs, medical specialists are encouraged to consider important components of a person's life such as work and hobbies together with relevant comorbidities such as, cardiovascular disease, kidney diseases, infections, malignancies, osteoporosis and depression (42). Furthermore, in specific groups of patients they should also consider special interventions such as vaccinations and infection prophylaxis (43).

Adding sexual and reproductive health to this long list of comorbidities and "extra-articular" tasks is clearly needed but may not be feasible without a proper strategy that breaks the many barriers associated with it (i.e. lack of time, lack of educational training, etc). Certainly, this requires a strong collaboration between specialists, other health care professionals such as a specialized nurse and patients (44).

Table 2. How to approach male patients with a wish to conceive.

Pre-conception	- Approach the topic of sexual and reproductive health "*early and often*" (18).
	- Offer specific pre-conception advice (and answer their questions), including but not limited to
	  o Promote a healthy life style:
	  • Exercise regularly.
	  • Healthy diet.
	  • No smoking.
	  • No drugs.
	  • Limit alcohol consumption.
	  • Aim at ideal body mass index.
	  • Reduce exposure to harmful chemicals in the home and workplace.
	  o Educate about basic sexual and reproductive health issues:
	  • Discuss the reproductive cycle.
	  • Anticonception.
	  • Practical tips (i.e. taking a warm shower to ease stiffness before having sex, timing pain medication so its maximum effect is during sex, pillows or rolled sheets to support joints, etc) (39).
	- Depending on the disease and its current disease activity level, recommend the use of therapeutic drugs that are considered safe for men with an active wish to become a father (See ACR and/or BSR recommendations for further guidance (18, 38)).
	- A complete medical history of the patient and partner is recommended. Emphasis on (but not limited to):
	  o Family reproductive history (infertility, congenital malformations, etc.)
	  o Reproductive history (including partner's history; time to pregnancy, pregnancy complications, etc.).
	  o Sexual and erectile function.
	- When applicable consider referral to other specialists.

During pregnancy	- In general, paternal immunosuppressive drug exposure is safe during this phase. Vaginal, rectal or oral absorption of drugs is possible but not believed to be relevant for potential teratogenic problems (40, 41). - Control disease activity. Adjust treatment accordingly. - Consider referral to physiotherapy or ergotherapy if patient has chronic or acute joint problems that can interfere with his new role as a father (hand, wrist, elbow, etc.)
After pregnancy	- Control disease activity. - Ask patients if and how their disease is interfering with their responsibilities as fathers. - Address sexual and reproductive health, including family planning "early and often"

The role of the rheumatologist and patient has been already discussed in this thesis ("inform and acknowledge" and "early and often"). Patients also expressed that they are open to discuss sexual and reproductive health with other health care professionals. Nurses and specialized nurses have also expressed that they feel comfortable when discussing sexual health problems with their patients and that it might be even easier to discuss this topic with male patients (45). Nonetheless, both medical doctors and

nurses also agree that they need additional education and knowledge on the topic of reproductive and sexual health (45-48).

Therefore, in contemplation of implementing these recommendations in general practice the following actions are needed:

- Designing proper sexual and reproductive health educational programs for patients, medical specialists, nurses, specialized nurses and other health professionals.
- Redefining the role of the different health-care professionals that work together in the care of male patients diagnosed with IMIDs. For example, giving nurses and specialized nurses a more pro-active role in the approach of male patients and their sexual and reproductive health.To approach this topic efficently, it is essential to provide them with the necessary training, tools and time avaialble with the patients.
- Implementing communication tools (e.g. goal elicitation tools, person-centered care approach) that may help facilitate the conversation about sexual and reproductive health in the outpatient clinic (what are the patient's questions and needs). Furthermore, using these tools, patients can express their wish to discuss certain topics at specific timepoints of their life and disease course.

Implications for researchers.

This thesis answered relevant research and clinical questions. Nonetheless, the process of answering these questions provided the scientific community with several unanswered questions that undoubtedly warrant further research. Some examples of these questions are:

What is the effect of inflammation on several aspects of sexual and reproductive health (e.g. sperm quality, testosterone levels, sexual function, pregnancy outcomes).

- Can the negative impact of IMIDs on male sexual and reproductive health be treated and prevented? How?
- How can rheumatologists and other health care professionals effectively counsel men diagnosed with IMIDs with regard to sexual and reproductive health?

One of the most important lessons learned during the elaboration of this thesis, is that conducting research on this topic undoubtedly requires a multidisciplinary and holistic approach. Therefore, when conducting research on this topic, collaboration that involves researchers and health care professionals from many fields relevant to the topic is strongly recommended. Furthermore, it should be noted that a mayor pitfall of

the available research on this topic is its overall low quality. This can be secondary to many reasons, ranging from difficulties to include patients to the use of non-validated methods as outcomes of interest or simply conducting studies with a poor study design. In furtherance of enhancing the current scientific knowledge on this topic, it is critical that future research on this topic becomes standardized (See Table 3).

Table 3. Research recommendations to conduct future research on the effect of IMIDs on male sexual and reproductive health.

General recommendations	• Collaboration between fields relevant to male reproductive and sexual health is encouraged (e.g. Rheumatology, Immunology, Reproductive Medicine, Sexuology, Nurses, etc.) • Select appropriate study design according to research question. Follow guidelines when available (i.e. testicular toxicity studies). • Use standardized methods and outcomes that allow the conduction of meta-analysis in the future.
Sexual function as outcome of interest	• Use standardized screening questionnaires (i.e. International Index of Erectile Function, Male Sexual Health Questionnaire or Brief Male Sexual Inventory). • Appropriate study design according to the research question and outcome of interest. Case-control studies and well-designed prospective cohort studies are encouraged over cross-sectional studies. • Consider relevant comorbidities and potential confounders (e.g. depression, anxiety, obesity, disease activity).
Sperm quality as outcome of interest	• Use standardized methods to report sperm quality (WHO). • Ideally, technicians should be blinded regarding the drug-exposure. • RCTs are ideal (49) but case-control and well-designed prospective cohort studies are also encouraged over cross-sectional studies (50). • Consider disease activity, relevant co-medication, comorbidities and potential confounders (e.g. age, smoking, varicocele, BMI). • Translational studies, when applicable, may be of additional value.
Reproductive hormones as outcome of interest	• Use standardized methods to measure hormones. • RCTs are ideal but case-control and well-designed prospective cohort studies are also encouraged over cross-sectional studies. • Consider disease activity, relevant comorbidities and potential confounders (i.e. age, co-medication)
Pregnancy and offspring outcomes as outcome of interest	• Collect data prospectively or report cases with all the relevant information. For instance: ◦ Source of the information, indication, disease activity, clear description of medication use and timing (including co medication), paternal age. • Regarding pregnancy/child outcome; pregnancy outcome, gestational age, birthweight, infant health, genetic testing, follow up period, • Partner's relevant medical history.

Although guidelines on how to design studies with the objective of evaluating testicular toxicity have been published (49, 51), conducting research on this topic remains a major scientific challenge.

Furthermore, most of the original research presented in this thesis focused on inflammatory arthritis. Biological and non-biological mechanisms were described as potential causes of the described male sexual and reproductive health impairment. It can be assumed that these mechanisms, with some similarities or differences, can also affect men diagnosed with other IMIDs. Therefore, it is recommended that in the future, original research on this topic should expand its current scope and include a more diverse group of men and outcomes (e.g. other diagnoses, sexual preferences, ages, ethnicities, etc.).

Lastly, it is important to discuss that conducting research on sexual and reproductive health cannot and should not rely only on objectivity . By doing so, extremely relevant factors that are subjective by nature, such as sexual wellbeing, family planning or the sense of manhood, will be left completely ignored. Conducting research on these (subjective) topics, will not only lead to health care professionals being able to approach their patients in a more holistic way, but it will also help the scientific community better understand how counseling and intervention strategies can be efficiently designed.

CONCLUSION

Sexual and reproductive health in men diagnosed with an IMID cannot be neglected any longer. The results of this thesis can help to unravel the *"male" aspect of the Reproductive Rheumatology*. It demonstrates that not only IMID such as IA and its associated immunosuppressive treatment can impair male fertility but can also have a direct and indirect impact on other relevant components of the male sexual and reproductive health, such as sexual function, sexual wellbeing, family planning or the patient's sense of masculinity/manhood.

REFERENCES

1. Perez-Garcia LF, Te Winkel B, Carrizales JP, Bramer W, Vorstenbosch S, van Puijenbroek E, et al. Sexual function and reproduction can be impaired in men with rheumatic diseases: A systematic review. Semin Arthritis Rheum. 2020;50(3):557-73.
2. Perez-Garcia LF, Dolhain R, Te Winkel B, Carrizales JP, Bramer WM, Vorstenbosch S, et al. Male Sexual Health and Reproduction in Cutaneous Immune-Mediated Diseases: A Systematic Review. Sex Med Rev. 2020.
3. Perez-Garcia L.F., Röder E., Pastoor H., Bolt H., van Exel J., Dolhain R. It is not just about the sex: viewpoints of Dutch adult men with inflammatory arthritis regarding the impact of the disease on their sexual health. Ann Rheum Dis. 2021;80:186.
4. Perez-Garcia LF, Röder E, Goekoop RJ, Hazes JMW, Kok MR, Smeele HTW, et al. Impaired fertility in men diagnosed with inflammatory arthritis: results of a large multicentre study (iFAME-Fertility). Ann Rheum Dis. 2021.
5. Perez-Garcia LF, Röder E, Smeele HTW, Goekoop R, Hazes JMW, Kok MR, et al. Paternal inflammatory arthritis is associated with a higher risk of miscarriage: results of a large multicenter study (iFAME-Fertility). Rheumatology (Oxford). 2021.
6. Perez-Garcia LF, Dolhain RJEM, Vorstenbosch S, Bramer W, van Puijenbroek E, Hazes JMW, et al. The effect of paternal exposure to immunosuppressive drugs on sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes: a systematic review. Human Reproduction Update. 2020.
7. Perez-Garcia LF, Röder E, Van Adrichem R, Kranenburg - van Koppen LJ, Zirkzee E, Van Doorn M, et al. What is the effect of Methotrexate on semen parameters of men diagnosed with immune-mediated diseases? Results of a prospective cohort study (iFAME-MTX). Annals of the Rheumatic Diseases. 2022;81(Suppl 1):84-.
8. Bay LT, Graugaard C, Nielsen DS, Möller S, Ellingsen T, Giraldi A. Sexual Health and Dysfunction in Patients With Rheumatoid Arthritis: A Cross-sectional Single-Center Study. Sex Med. 2020;8(4):615-30.
9. Tański W, Dudek K, Tomasiewicz A, Świątoniowska-Lonc N. Sexual Dysfunction and Quality of Life in Patients with Rheumatoid Arthritis. Int J Environ Res Public Health. 2022;19(5).
10. Campos-Guzmán J, Valdez-López M, Govea-Peláez S, Aguirre-Aguilar E, Perez-Garcia LF, van Mulligen E, et al. Determinants of sexual function in male patients with systemic lupus erythematosus. Lupus. 2022;31(10):1211-7.
11. Flurey CA, Pauling JD, Saketkoo LA, Denton CP, Galdas P, Khanna D, et al. 'I turned in my man card': a qualitative study of the experiences, coping styles and support needs of men with systemic sclerosis. Rheumatology (Oxford). 2023;62(6):2160-7.
12. Krittian SM, Saur SJ, Schloegl A, Ritzau J, Xenitidis T, Pecher AC, et al. Erectile function and connective tissue diseases. Prevalence of erectile dysfunction in German men with systemic sclerosis compared to other connective tissue diseases and healthy subjects. Clin Exp Rheumatol. 2021;39 Suppl 131(4):52-6.
13. Wilton KM, Achenbach SJ, Karmacharya P, Ernste FC, Matteson EL, Crowson CS. Erectile Dysfunction in Men With Psoriatic Arthritis: A Population-based Cohort Study. J Rheumatol. 2021;48(4):527-32.
14. Merayo-Chalico J, Barrera-Vargas A, Morales-Padilla S, la Garza RR, Vázquez-Rodríguez R, Campos-Guzmán J, et al. Epidemiologic Profile of Erectile Dysfunction in Patients with Systemic Lupus Erythematosus: The Latin American Landscape. J Rheumatol. 2019;46(4):397-404.
15. Flurey C, White A, Rodham K, Kirwan J, Noddings R, Hewlett S. 'Everyone assumes a man to be quite strong': Men, masculinity and rheumatoid arthritis: A case-study approach. Sociol Health Illn. 2018;40(1):115-29.

16. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med. 2007;357(8):762-74.
17. Östlund G, Björk M, Valtersson E, Sverker A. Lived Experiences of Sex Life Difficulties in Men and Women with Early RA - The Swedish TIRA Project. Musculoskeletal Care. 2015;13(4):248-57.
18. Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. Arthritis Care Res (Hoboken). 2020;72(4):461-88.
19. El Miedany Y, Palmer D. Rheumatology-led pregnancy clinic: men perspective. Clin Rheumatol. 2021.
20. Merrill JM, Laux LF, Thornby JI. Why doctors have difficulty with sex histories. South Med J. 1990;83(6):613-7.
21. Mitchell D, Lesoon L, Edens C, Kazmerski TM, Stransky OM, Cameron FA, et al. How to Provide Sexual and Reproductive Health Care to Patients: Focus Groups With Rheumatologists and Rheumatology Advanced Practice Providers. J Rheumatol. 2023;50(2):240-5.
22. Stransky O, Hunt N, Richards JS, Talabi MB. Exploring Family Planning, Parenting, and Sexual and Reproductive Health Care Experiences of Men With Rheumatic Diseases. J Rheumatol. 2022;49(3):251-5.
23. Helland Y, Dagfinrud H, Haugen MI, Kjeken I, Zangi H. Patients' Perspectives on Information and Communication About Sexual and Relational Issues in Rheumatology Health Care. Musculoskeletal Care. 2017;15(2):131-9.
24. Ledón LL, Contreras-Yáñez I, Guaracha-Basáñez G, Valverde-Hernández SS, González-Marín A, Ballinas-Sánchez Á J, et al. Views of Mexican outpatients with rheumatoid arthritis on sexual and reproductive health: A cross-sectional study. PLoS One. 2021;16(1):e0245538.
25. Savel C, Cherillat MS, Berland P, Tronche AM, Soubrier M, Gerbaud L, et al. French survey on the crossed needs on sexual health for chronic inflammatory rheumatism patients and healthcare professionals. Rheumatol Int. 2020;40(9):1481-91.
26. Flurey CA, Hewlett S, Rodham K, White A, Noddings R, Kirwan J. Men, rheumatoid arthritis, psychosocial impact and self-management: A narrative review. J Health Psychol. 2016;21(10):2168-82.
27. Annon JS. The PLISSIT Model: A Proposed Conceptual Scheme for the Behavioral Treatment of Sexual Problems. Journal of Sex Education and Therapy. 1976;2(1):1-15.
28. Mercer B. Interviewing people with chronic illness about sexuality: an adaptation of the PLISSIT model. J Clin Nurs. 2008;17(11c):341-51.
29. Barratt CLR, Bjorndahl L, De Jonge CJ, Lamb DJ, Osorio Martini F, McLachlan R, et al. The diagnosis of male infertility: an analysis of the evidence to support the development of global WHO guidance-challenges and future research opportunities. Hum Reprod Update. 2017;23(6):660-80.
30. Kasman AM, Zhang CA, Li S, Lu Y, Lathi RB, Stevenson DK, et al. Association between preconception paternal health and pregnancy loss in the USA: an analysis of US claims data. Hum Reprod. 2021;36(3):785-93.
31. Kasman AM, Zhang CA, Li S, Stevenson DK, Shaw GM, Eisenberg ML. Association of preconception paternal health on perinatal outcomes: analysis of U.S. claims data. Fertil Steril. 2020;113(5):947-54.
32. Glazer CH, Bonde JP, Eisenberg ML, Giwercman A, Hærvig KK, Rimborg S, et al. Male Infertility and Risk of Nonmalignant Chronic Diseases: A Systematic Review of the Epidemiological Evidence. Semin Reprod Med. 2017;35(3):282-90.
33. Eisenberg ML, Li S, Cullen MR, Baker LC. Increased risk of incident chronic medical conditions in infertile men: analysis of United States claims data. Fertil Steril. 2016;105(3):629-36.
34. Brubaker WD, Li S, Baker LC, Eisenberg ML. Increased risk of autoimmune disorders in infertile men: analysis of US claims data. Andrology. 2018;6(1):94-8.

35. Hasan H, Bhushan S, Fijak M, Meinhardt A. Mechanism of Inflammatory Associated Impairment of Sperm Function, Spermatogenesis and Steroidogenesis. Front Endocrinol (Lausanne). 2022;13:897029.
36. Dutta S, Sengupta P, Slama P, Roychoudhury S. Oxidative Stress, Testicular Inflammatory Pathways, and Male Reproduction. Int J Mol Sci. 2021;22(18).
37. Wdowiak A, Gujski M, Bojar I, Raczkiewicz D, Bartosińska J, Wdowiak-Filip A, et al. Chronic Inflammation Impairs Male Fertility-A Case-Control Study in Ulcerative Colitis Patients. J Clin Med. 2021;10(7).
38. Russell MD, Dey M, Flint J, Davie P, Allen A, Crossley A, et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. Rheumatology. 2023;62(4):e48-e88.
39. Rheumatology ACo. Sex & Arthritis: ACR; 2023 [updated 04-2023. Available from: https://rheumatology.org/sex-and-arthritis.
40. Klemmt L, Scialli AR. The transport of chemicals in semen. Birth Defects Res B Dev Reprod Toxicol. 2005;74(2):119-31.
41. Crijns I, Bos J, Knol M, Straus S, de Jong-van den Berg L. Paternal drug use: before and during pregnancy. Expert Opin Drug Saf. 2012;11(4):513-8.
42. Baillet A, Gossec L, Carmona L, Wit Md, van Eijk-Hustings Y, Bertheussen H, et al. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. Annals of the Rheumatic Diseases. 2016;75(6):965-73.
43. George EF, Elena N, Mrinalini D, Sizheng Steven Z, Delphine Sophie C, Laurent A, et al. 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases. Annals of the Rheumatic Diseases. 2023;82(6):742-53.
44. Cornelissen LE, van der Mark EJ, Pennings P, Maat B, Foekens T, Willemsen-de Mey G, et al. What Matters to Patients with Rheumatoid Arthritis When Facing Medical or Non-Medical Treatment Decisions? Patient Prefer Adherence. 2021;15:1827-41.
45. Klaeson K, Hovlin L, Guvå H, Kjellsdotter A. Sexual health in primary health care - a qualitative study of nurses' experiences. J Clin Nurs. 2017;26(11-12):1545-54.
46. Helland Y, Garratt A, Kjeken I, Kvien TK, Dagfinrud H. Current practice and barriers to the management of sexual issues in rheumatology: results of a survey of health professionals. Scand J Rheumatol. 2013;42(1):20-6.
47. Leonardi-Warren K, Neff I, Mancuso M, Wenger B, Galbraith M, Fink R. Sexual Health: Exploring Patient Needs and Healthcare Provider Comfort and Knowledge. Clin J Oncol Nurs. 2016;20(6):E162-E7.
48. Beebe S, Payne N, Posid T, Diab D, Horning P, Scimeca A, et al. The Lack of Sexual Health Education in Medical Training Leaves Students and Residents Feeling Unprepared. J Sex Med. 2021;18(12):1998-2004.
49. Research USDoHaHSFaDACfDEa. Testicular Toxicity: Evaluation during Drug Development Guidance for Industry, Draft Guidance. 2015.
50. Sasaki JC, Chapin RE, Hall DG, Breslin W, Moffit J, Saldutti L, et al. Incidence and nature of testicular toxicity findings in pharmaceutical development. Birth Defects Res B Dev Reprod Toxicol. 2011;92(6):511-25.
51. Organization WH. WHO laboratory manual for the examination and processing of human semen. Sixth edition ed. Geneva2021.
52. van de Meeberg MM, Hebing RCF, Nurmohamed MT, Fidder HH, Heymans MW, Bouma G, et al. A meta-analysis of methotrexate polyglutamates in relation to efficacy and toxicity of methotrexate in inflammatory arthritis, colitis and dermatitis. Br J Clin Pharmacol. 2023;89(1):61-79.

ADDENDUM

NEDERLANDSE SAMENVATTING

Het doel van dit proefschrift is om inzicht te geven in de invloed van immuun-gemedieerde inflammatoire ziekten (IMIDs) en de behandelingen ervan op de seksuele en reproductieve gezondheid van mannen.

Deel I. Algemene inleiding

Dit deel omvat de algemene inleiding (**hoofdstuk 1**) en introduceert de lezer in de verschillende kernconcepten relevant voor dit proefschrift, zoals de mannelijke geslachtsorganen en de hormonale assen die hierop van invloed zijn, de seksuele en reproductieve gezondheid bij mannen en de epidemiologie van IMIDs bij mannen. Verder presenteert het kort de geschiedenis en de huidige stand van zaken van "Reproductieve Reumatologie". Tot slot beschrijft het hoe het gebrek aan kennis over het "mannelijke perspectief" en andere problemen die patiënten en zorgverleners op dit gebied ervaren een negatieve invloed kunnen hebben op de patiëntenzorg. Dit rechtvaardigt het uitvoeren van verder onderzoek , zoals beschreven in dit proefschrift.

Deel II. De impact van immuun-gemedieerde inflammatoire ziekten op de seksuele en reproductieve gezondheid van mannen.

In dit deel wordt de beschikbare wetenschappelijke literatuur over de impact van verschillende reumatische (**hoofdstuk 2**) en cutane (**hoofdstuk 3**) IMIDs op de seksuele en reproductieve gezondheid van mannelijke patiënten beschreven.

De resultaten van de uitgevoerde systematische reviews geven aan dat de seksuele en reproductieve gezondheid aangetast kan zijn bij mannen met een IMID (reumatisch en cutaan). De ernst en omvang van de beperkingen op de seksuele en reproductieve gezondheid variëren sterk per ziekte. In vergelijking met gezonde controles (11-41%) werd bijvoorbeeld een hogere prevalentie van erectiestoornissen gerapporteerd bij patiënten met reumatoïde artritis (RA) (33-62%), systemische lupus erythematosus (SLE) (12-68%), psoriasis (34-81%) en systemische sclerose (SSc) (60-100%).Er was slechts weinig onderzoek verricht naar vruchtbaarheid van mannen met een IMID, maar sommige onderzoeken meldden een hogere frequentie van vruchtbaarheidsproblemen (bijv. lage spermakwaliteit of hogere DNA-fragmentatie-index van sperma) bij patiënten met SLE.

Helaas brachten de systematische reviews een belangrijk probleem aan het licht, namelijk dat de algehele kwaliteit van de onderzoeken die in de systematische reviews waren opgenomen laag tot matig was. Daarom worden aanbevelingen gedaan

over hoe toekomstig onderzoek over dit onderwerp uit te voeren(d.w.z. geschikte onderzoeksopzet, gebruik van gestandaardiseerde methoden om uitkomsten van belang te rapporteren, rekening houden met relevante confounders). Concluderend kan worden gesteld dat IMIDs en seksuele en reproductieve gezondheid van mannen van invloed op elkaar zijn en dat verder onderzoek van goede kwaliteit hiernaar dringend nodig is.

Deel III. Wat is de invloed van inflammatoire artritis op de reproductieve gezondheid van mannen?

Het doel van dit deel was om de invloed van inflammatoire artritis (IA) op twee belangrijke uitkomsten van de mannelijke reproductieve gezondheid te beschrijven: vruchtbaarheid (**hoofdstuk 4**) en zwangerschapsuitkomsten (**hoofdstuk 5**).

In een multicenter cross-sectionele studie, iFAME-Fertility, werd voor het eerst aangetoond dat IA gediagnosticeerd voor en tijdens de piek van de reproductieve leeftijd (respectievelijk <30 en 31-40 jaar) geassocieerd was met verminderde vruchtbaarheid bij mannen. 628 mannen met de diagnose IA namen deel aan het onderzoek. Het vruchtbaarheidscijfer van mannen (d.w.z. het gemiddeld aantal biologische kinderen per man) bleek bij mannen gediagnosticeerd vóór en tijdens de piek van de reproductieve leeftijd statistisch significant lager te zijn (respectievelijk 1,32 en 1,60; p=<0,005) dan bij mannen gediagnosticeerd met IA na de piek van de reproductieve leeftijd (1,88) en mannen in de Nederland bevolking (1,79). Bovendien was het percentage onvrijwillige kinderloosheid hoger bij deze mannen en rapporteerden ze vaker problemen met hun reproductieve gezondheid (bijv. onvruchtbaarheid, lage spermakwaliteit). Of deze reproductieve gezondheidsproblemen direct verband houden met de ziekte zelf, de immunosuppressieve behandeling die deze patiënten vaak gebruiken of met andere redenen, is niet bekend.

Om de invloed van IA op de vruchtbaarheid van mannen verder te onderzoeken, werden in deze studie ook de zwangerschapsuitkomsten van partners van mannen met IA geëvalueerd. In totaal meldden 408 mannelijke deelnemers met de diagnose IA 897 eenlingzwangerschappen die resulteerden in 794 levendgeboren kinderen. Vergeleken met zwangerschappen die voor de diagnose IA waren verwekt, hadden zwangerschappen die na de diagnose IA waren verwekt een hoger percentage miskramen (12,27% vs 7,53%, p=<0,05). Dit verhoogde risico was nog steeds aanwezig na correctie voor relevante confounders, zoals leeftijd [OR 2,03 (95% CI 1,12, 3,69) p=0,015]. Geconcludeerd werd dat zwangerschappen van partners van mannen met

de diagnose IA een significant hoger risico op een miskraam hadden. Hoewel deze bevindingen moeten worden bevestigd door grote prospectieve onderzoeken, dienen reumatologen zich bewust te zijn van deze verhoogde kans op een miskraam bij vaders met IA.

Deel IV. Testiculaire toxiciteit van immunosuppressieve middelen.

Dit deel richt zich op het testiculaire toxiciteitsprofiel van immunosuppressieve geneesmiddelen. Het beschrijft de resultaten van een systematische review over het effect van blootstelling aan immunosuppressieve geneesmiddelen op verschillende uitkomsten van de mannelijke seksuele en reproductieve gezondheid (**hoofdstuk 6**). Daarnaast worden de resultaten gepresenteerd van een studie waarin prospectief het testiculaire toxiciteitsprofiel van een van de meest voorgeschreven immunosuppressiva, methotrexaat, is onderzocht (**hoofdstuk 7**).

In de zoekstrategie van de systematische review werden trefwoorden met betrekking tot de mannelijke seksuele functie, vruchtbaarheid, zwangerschapsuitkomsten en de gezondheid van het nageslacht gelinkt aan een lijst van immunosuppressieve geneesmiddelen. Er werden 161 artikelen geschikte artikelen gevonden. Van deze artikelen hadden er 50 betrekking op reproductieve gezondheidsuitkomsten en 130 op seksuele gezondheidsuitkomsten. Met uitzondering van grote Scandinavische cohorten, bevatten de meeste geïdentificeerde artikelen een slechts klein aantal deelnemers. Een duidelijk negatief effect op de spermakwaliteit werd waargenomen bij sulfasalazine en cyclofosfamide, een mogelijk negatief effect werd vastgesteld bij colchicine, methotrexaat en sirolimus. Er werd geen negatief effect waargenomen voor acitretine, azathioprine, ciclosporine, isotretinoïne, tumor necrose factor-α (TNF-α) remmers en verdolizumab. In drie artikelen resulteerde blootstelling aan TNF-α-remmers bij patiënten met de diagnose ankyloserende spondylitis in een verbeterde spermakwaliteit. De informatie met betrekking tot de uitkomsten van zwangerschap en nakomelingen was beperkt, maar er werd geen groot negatief effect gemeld geassocieerd met blootstelling van de vader aan immunosuppressiva.

Concluderend kan worden gesteld dat er slechts beperkt bewijs is over de veiligheid, maar ook over de schadelijkheid van immunosuppressiva bij mannen met een kinderwens. Het kleine aantal deelnemers in de meeste onderzoeken en het gebrek aan standaardisatie over hoe de seksuele en reproductieve gezondheidsuitkomsten bij mannen die blootgesteld zijn aan immunosuppressiva geëvalueerd en gerapporteerd moeten worden, dragen hier in belangrijke mate aan bij. Toekomstig onderzoek naar dit

onderwerp is nodig en zou bij voorkeur gedaan moeten worden met grotere en goed onderbouwde studies die gestandaardiseerde methoden gebruiken.

In de iFAME-MTX studie werden belangrijke markers van testiculaire toxiciteit onderzocht, bij mannen voor en drie maanden na het starten van MTX. In dit onderzoek liet MTX geen effect zien op conventionele markers van de sperma-analyse, de hormonen betrokken bij de mannelijke vruchtbaarheid of op DNA-schade aan sperma. Om een verklaring te kunnen geven waarom MTX de spermakwaliteit niet aantast, werd de concentratie van MTX in de spermacellen bepaald.

Dit liet zien dat de concentratie van MTX en met name de bioactieve vorm van MTX, MTX-polyglutamaat (MTX-PG) heel laag is. Omdat folylpolyglutamaatsynthetase verantwoordelijk is voor intracellulaire polyglutamylering en daarmee voor de bioactivatie van MTX, werd dit enzym in de spermacellen gemeten. Deze concentratie bleek heel laag te zijn.

Dit onderzoek toont voor het eerst aan dat het enzym dat verantwoordelijk is voor intracellulaire polyglutamylering en daarmee voor de bioactivatie van MTX, namelijk folylpolyglutamaat synthetase (FPGS), extreem laag actief is in spermatozoa. Dit resulteert uiteindelijk in zeer lage intracellulaire MTX-PG-concentraties (d.w.z. de bioactieve vorm van MTX) in spermatozoa. Hierop kon worden geconcludeerd dat behandeling met MTX niet geassocieerd is met testiculaire toxiciteit, wat overeenkomt met de zeer lage concentratie intracellulaire MTX-PG. Daarom werd aanbevolen dat MTX kan worden gestart of voortgezet bij mannen met een actieve wens om vader te worden.

Deel V. Let's talk about sex!...

In dit deel wordt de impact van IA op de seksuele gezondheid van mannen (**hoofdstuk 8**) beschreven. Tevens werd onderzocht wat de verschillende standpunten van mannelijke patiënten gediagnosticeerd met IA en reumatologen zijn met betrekking tot het bespreken van seksuele en reproductieve gezondheid in de spreekkamer (**hoofdstuk 9**).

Om de impact van IA op de seksuele gezondheid van mannen te begrijpen, moet niet alleen de fysieke component, maar ook de emotionele, mentale en sociale componenten van seksuele gezondheid meegenomen worden. Deze componenten zijn vanwege hun subjectieve aard moeilijk te analyseren en te interpreteren. Vragenlijsten genereren voornamelijk kwantitatieve gegevens en kunnen makkelijk relevante subjectieve informatie missen. Hoewel focusgroepen solide kwalitatieve gegevens opleveren en

gebruikt worden om gevoelige onderwerpen te onderzoeken, kan interactie tussen groepsleden de kwaliteit van de verkregen informatie van de leden verminderen. Q-methodologie combineert de sterke punten van kwalitatieve en kwantitatieve benaderingen. Het is een krachtige methodologie voor het systematisch verkennen en verklaren van patronen in subjectiviteiten (standpunten, meningen, overtuigingen) rond gevoelige onderwerpen en het identificeren van consensus en contrasten daartussen.

Met behulp van Q-methodologie werden drie standpunten over de algemene impact van IA op de seksuele gezondheid van volwassen mannen geïdentificeerd:

- 'Artritis heeft een negatieve invloed op mijn seksuele gezondheid': Deze groep mannen ervaren een dramatische impact van IA op alle componenten van seksuele gezondheid (fysiek, emotioneel, mentaal en sociaal).
- 'I am keeping up appearances': Bij deze mannen heeft IA ook een negatieve impact op de seksuele gezondheid, maar zij onderscheiden zich door hun copingmechanisme ("ik ben een man") dat mogelijk een ernstiger negatieve impact maskeert.
- 'Ik ben tevreden met mijn seksuele gezondheid': Deze mannen ervaren geen significante impact van IA op hun seksuele gezondheid.

Twee van deze standpunten onthulden een negatieve invloed die verder gaat dan de fysieke daad van seks. Daarom kan geconcludeerd worden dat IA een ernstige invloed kan hebben op de emotionele, mentale en sociale componenten van seksuele gezondheid.

Het blijft een uitdaging om de seksuele en reproductieve gezondheid van mannen tijdens het spreekuur te bespreken. In hoofdstuk 9 worden de verschillende standpunten van mannelijke patiënten gediagnosticeerd met IA en van reumatologen besproken met betrekking tot het bespreken van seksuele en reproductieve gezondheid in de spreekkamer. Ook deze studie maakt gebruik van de Q-methodologie. Er werden drie standpunten van reumatologen en drie standpunten van patiënten geïdentificeerd:

Reumatologen:

- 'Laten we het hebben over uw kinderwens': Een actieve kinderwens is het meest invloedrijke aspect voor deze groep reumatologen. Bovendien bespreken ze met hun jonge patiënten regelmatig de bijwerkingen van immunosuppressiva op de vruchtbaarheid.
- 'Laten we het hebben over bijwerkingen': Bij deze reumatologen zijn de bijwerkingen van immunosuppressiva op de vruchtbaarheid (en in mindere mate, seksualiteit) de belangrijkste aspecten om dit onderwerp te bespreken.

- ‘Laten we het hebben over uw gewrichten’: Deze reumatologen bespreken dit onderwerp zelden met hun patiënten, hun prioriteit is om de ziekte onder controle te krijgen. Alleen bij mannen met een actuele kinderwens, wordt dit besproken. Als ze dit onderwerp al bespreken, moet de patiënt het initiatief nemen.

Patiënten:

- ‘Laten we het hebben over mijn kinderwens’: Bij deze mannen staat hun actuele kinderwens centraal, ze willen namelijk informatie krijgen over de bijwerkingen van immunosuppressiva op vruchtbaarheid.
- ‘Laten we het hebben over seks’: Voor deze mannen is seksuele en reproductieve gezondheid een belangrijk aspect van hun kwaliteit van leven. Dit moet besproken worden en hiermee moet rekening gehouden worden tijdens hun behandeling. Ze willen meer informatie krijgen over seksualiteit en niet noodzakelijk over vruchtbaarheid.
- ‘’Laten we het hebben over mijn gewrichten’:Deze mannen vinden een gesprek over seksuele en reproductieve gezondheid veel minder belangrijk als de ziekte actief is. Hun prioriteit is om de ziekte onder controle te krijgen, “daarna komt de rest”. Ze vertrouwen op hun reumatologen om hen hierover te informeren wanneer dat nodig is.

Samengevat, reumatologen worden vaker beïnvloed door twee aspecten; de kinderwens van de patiënt of de (jonge) leeftijd van de patiënt en het bespreken van mogelijke bijwerkingen van medicatie op de vruchtbaarheid. Patiënten worden echter beïnvloed door veel meer verschillende aspecten, zoals het bespreken van mogelijke bijwerkingen van medicatie op hun seksuele functie, ongeacht of ze een actuele kinderwens hebben.

Deel VI. Discussie

Dit deel is gewijd aan de algemene discussie van dit proefschrift. De belangrijkste bevindingen van dit proefschrift worden verder besproken en vergeleken met soortgelijk onderzoek over dit onderwerp. Verder worden de implicaties voor reumatologen, andere zorgverleners, patiënten en onderzoekers besproken. Tot slot bevat dit deel ook praktische aanbevelingen voor de aanpak van dit onderwerp op in de spreekkamer en voor de implementatie van deze bevindingen in de klinische praktijk.

PhD PORTFOLIO

Name	Luis Fernando Perez
Department	Rheumatology
Research School	Netherlands Institute for Health Sciences
PhD period	August 2017 – November 2022
Promotors	Prof. dr. R.J.E.M. Dolhain Prof. dr. J.M.W. Hazes

PhD training	Year	Workload (ECTS)
General academic and research skills		
Basiscursus Regelgeving Klinisch Onderzoek (BROK)	2018	1.5
Workshop EndNote	2018	0.3
Workshop Systematic Literature Retrieval in multiple databases	2018	0.3
Integrity in Scientific Research	2018	0.3
Introduction to Medical Writing	2020	2
In-depth statistical courses, NIHES		
Principles of Research in Medicine and Epidemiology	2018	0.7
Clinical Trials	2018	0.7
Methods of Public Health Research	2018	0.7
Fundamentals of Medical Decision Making	2018	0.7
Practice of Epidemiologic Analysis	2018	0.7
Health Economics	2018	0.7
Study Design	2018	4.3
Biostatistical Methods I: Basic principles	2018	5.7
Biostatistical Methods II: Classical Regression Models	2018	4.3
Intermediate course in R	2019	1.4
Clinical Translation of Epidemiology	2019	2.0
Clinical Epidemiology	2019	3.7
Principles in Causal Inference	2019	1.4
Clinical Translation of Epidemiology	2019	2.0
Clinical Epidemiology	2019	3.7
Repeated Measurements	2020	1.7
Q-methodology	2019	2.5
Topics in Meta-analysis	2019	0.7
Introduction to Global Public Health	2019	0.7
Principles of Epidemiologic Data-analysis	2019	0.7
Planning and evaluation of screening	2019	1.4
Principles of Research in Medicine and Epidemiology	2018	0.70

PhD training	Year	Workload (ECTS)
National conferences		
Nederlandse Vereniging voor Reumatologie (NVR)	2019	1.0
Nederlandse Vereniging voor Reumatologie (NVR) Najaarsdagen, Papendal [1 oral presentation)	2022	2.0
International conferences		
European League Against Rheumatism (EULAR) Annual Meeting, Amsterdam, the Netherlands	2018	1.0
European League Against Rheumatism (EULAR) Annual Meeting, Madrid, Spain [1 poster presentation]	2019	1.0
European League Against Rheumatism (EULAR) Annual Meeting, online, [3 oral presentations]	2021	3.0
European League Against Rheumatism (EULAR) Annual Meeting, Copenhague, Denmark [2 oral presentations]	2022	3.0
European League Against Rheumatism (EULAR) Annual Meeting, Milan, Italy [3 oral presentations]	2023	3.0
RheumaPreg, 2021, Italy [2 oral presentations]	2021	2.0
RheumaPreg, 2023, London, United Kingdom [2 oral presentations]	2023	2.0
Mexican congress of Rheumatology, Merida, Mexico [2 oral presentations, 1 poster]	2022	2.0
Austrian Congress of Rheumatology, Vienna, Austria [1 oral presentation]	2023	1.0
Seminars and workshops		
Department Journal Club Rheumatology	2018-2023	1.0
Department research meetings	2017-2023	1.0
Teaching		
Supervision systematic review medical students	2021	1.0

PUBLICATIONS

Publications included in this thesis in chronological order

Perez-Garcia LF, Te Winkel B, Carrizales JP, Bramer W, Vorstenbosch S, van Puijenbroek E, Hazes JMW, Dolhain RJEM. **Sexual function and reproduction can be impaired in men with rheumatic diseases: A systematic review**. Semin Arthritis Rheum. 2020 Jun;50(3):557-573. doi: 10.1016/j.semarthrit.2020.02.002. Epub 2020 Feb 14. PMID: 32165034.

Perez-Garcia LF, Dolhain R, Te Winkel B, Carrizales JP, Bramer WM, Vorstenbosch S, van Puijenbroek E, Hazes M, van Doorn MBA. **Male Sexual Health and Reproduction in Cutaneous Immune-Mediated Diseases: A Systematic Review.** Sex Med Rev. 2021 Jul;9(3):423-433. doi: 10.1016/j.sxmr.2020.07.004. Epub 2020 Sep 1. PMID: 32883623.

Perez-Garcia LF, Dolhain RJEM, Vorstenbosch S, Bramer W, van Puijenbroek E, Hazes JMW, Te Winkel B. **The effect of paternal exposure to immunosuppressive drugs on sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes: a systematic review**. Hum Reprod Update. 2020 Nov 1;26(6):961-1001. doi: 10.1093/humupd/dmaa022. PMID: 32743663; PMCID: PMC7600290.

Perez-Garcia LF, Röder E, Pastoor H, Bolt JM, van Exel J, Dolhain RJEM. **It is not just about sex: viewpoints of men with inflammatory arthritis on the overall impact of the disease on their sexual health.** RMD Open. 2021 Sep;7(3):e001821. doi: 10.1136/rmdopen-2021-001821. PMID: 34580174; PMCID: PMC8477326.

Perez-Garcia LF, Röder E, Goekoop RJ, Hazes JMW, Kok MR, Smeele HTW, Tchetverikov I, van der Helm-van Mil AHM, van der Kaap JH, Kok P, Krijthe BP, Dolhain RJEM. **Impaired fertility in men diagnosed with inflammatory arthritis: results of a large multicentre study (iFAME-Fertility)**. Ann Rheum Dis. 2021 Dec;80(12):1545-1552. doi: 10.1136/annrheumdis-2021-220709. Epub 2021 Aug 9. PMID: 34373257; PMCID: PMC8600610.

Perez-Garcia LF, Röder E, Smeele HTW, Goekoop R, Hazes JMW, Kok MR, Tchetverikov I, van der Helm-van Mil A, van der Kaap J, Kok P, Krijthe BP, Dolhain RJEM. **Paternal inflammatory arthritis is associated with a higher risk of miscarriage: results of a large multicentre study (iFAME-Fertility). Rheumatology (Oxford).** 2022 Aug 3;61(8):3390-3395. doi: 10.1093/rheumatology/keab910. PMID: 34875039; PMCID: PMC9348772.

Perez-Garcia LF, Röder E, Krijthe BP, Kranenburg-van Koppen LJ, van Adrichem R, Zirkzee E, Griffioen PH, Peeters K, Lin M, Struys EA, Jansen G, van Doorn MB, de Jonge R, Dohle GR, Dolhain RJ. **Is methotrexate safe for men with an immune-mediated inflammatory**

disease and an active desire to become a father? Results of a prospective cohort study (iFAME-MTX). Ann Rheum Dis. 2023 Aug;82(8):1068-1075. doi: 10.1136/ard-2023-224032. Epub 2023 Jun 1. PMID: 37263756; PMCID: PMC10359513.

Publications outside this thesis in chronological order

Smeele HT, Perez-Garcia LF, Grimminck K, Schoenmakers S, Mulders AG, Dolhain RJ. **Systemic lupus erythematosus and COVID-19 during pregnancy.** Lupus. 2021 Jun;30(7):1188-1191. doi: 10.1177/09612033211002270. Epub 2021 Mar 14. PMID: 33715506; PMCID: PMC8120627.

Campos-Guzmán J, Valdez-López M, Govea-Peláez S, Aguirre-Aguilar E, Perez-Garcia LF, van Mulligen E, Castillejos-Molina R, Barrera-Vargas A, Merayo-Chalico J. **Determinants of sexual function in male patients with systemic lupus erythematosus.** Lupus. 2022 Sep;31(10):1211-1217. doi: 10.1177/09612033221107802. Epub 2022 Jun 15. PMID: 35702930.

Amezcua-Guerra LM, Pérez-García LF, Jiménez-Rojas V, Márquez-Velasco R, Silveira LH. **Anti-Ro52/TRIM21 antibodies are associated with aberrant inflammatory circuits in patients with systemic autoimmune rheumatic diseases**. Gac Med Mex. 2023;159(1):55-64. English. doi: 10.24875/GMM.M22000739. PMID: 36930561.

Schreiber K et al. **Global comment on the use of hydroxychloroquine during the periconception period and pregnancy in women with autoimmune diseases.** Lancet Rheumatol. 2023 Sep;5(9):e501-e506. doi: 10.1016/S2665-9913(23)00215-1. Epub 2023 Aug 21. PMID: 38251494.

ABOUT THE AUTHOR

Luis Fernando Perez was born in Laredo, Texas, in 1985, and spent his formative years along the dynamic border between Mexico and Texas. He completed his high school education in this vibrant cultural milieu before embarking on his journey in Medicine. Venturing to Monterrey, an industrial hub in northeast Mexico, Luis Fernando pursued his passion for medicine as he commenced his medical studies. Graduating with a degree in Medicine in 2009, he embarked on a path marked by dedication and scholarly pursuit.

Remaining in Monterrey, Luis Fernando undertook a rigorous four-year Internal Medicine residency, during which his interest for research blossomed. Serving in various capacities including chief resident, during his residency, Luis Fernando became increasingly fascinated by medical research, exploring the intricacies of healthcare investigations.

Driven by a strong desire to learn and grow, Luis Fernando eagerly pursued opportunities to expand his understanding of medicine, undertaking clinical and research visits in both the United States and Mexico during the latter years of his residency.

Following the successful completion of his Internal Medicine training, Luis Fernando commenced his specialized training in Rheumatology in the bustling metropolis of Mexico City. Here, amidst a vibrant academic atmosphere, his dedication to research was duly recognized with the prestigious young investigator award. This accolade opened doors for further exploration, prompting a transformative clinical and research visit at Radboud UMC in Nijmegen, the Netherlands.

During this enriching stint, Luis Fernando was exposed to the pioneering Reproductive Rheumatology clinic led by Prof. Dr. Radboud Dolhain at Erasmus MC in Rotterdam. Inspired by this experience and fueled by his passion for advancing medical knowledge, Luis Fernando made the decision to return to the Netherlands to pursue a Ph.D. In 2017, under the expert guidance of Prof. Dr. Radboud Dolhain and Prof. Dr. Mieke Hazes, he embarked on a doctoral journey focusing on the impact of rheumatic diseases on male sexual and reproductive health.

Upon the culmination of his Ph.D. journey and the acquisition of his medical License in the Netherlands, Luis Fernando transitioned into the field of academic rheumatology. With a commitment to advancing the frontiers of Reproductive Rheumatology, he embarked on a new chapter in December 2022, dedicating himself fully to clinical practice and ongoing research endeavors.

Committed to his mission, Luis Fernando remains dedicated to advancing the field of Reproductive Rheumatology.