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REVIEW

Antirheumatic drugs and reproduction in women and men with chronic arthritis

Chiara Bazzani,¹ Laura Andreoli,^{1,2} Michele Agosti,² Cecilia Nalli,¹
Angela Tincani^{1,2}

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ABSTRACT

The impact of rheumatic disease on fertility and reproduction can be remarkable. Many disease-related factors can influence patients' sexual functioning, perturb fertility and limit family planning. Antirheumatic pharmacological treatment can also have a crucial role in this field. Proper counselling, preferably provided by a multidisciplinary team of rheumatologists, obstetricians, gynaecologists and neonatologists, is recommended for patients taking antirheumatic drugs, not only at the beginning, but also during the course of treatment. Paternal exposure to antirheumatic drugs was not found to be specifically associated with congenital malformation and adverse pregnancy outcome, therefore discontinuation of these drugs while planning for conception should be weighed against the risk of disease flare. Drugs in Food and Drug Administration (FDA) category 'X' should be withdrawn in a timely manner in women who desire a pregnancy. Meanwhile, disease control can be achieved with anti-tumour necrosis factor (TNF)- α agents, which are not teratogenic drugs. If maternal disease control is permissive, they can be stopped as soon as the pregnancy test turns positive and be resumed during pregnancy in case of a flare.

INTRODUCTION

Rheumatic diseases can influence quality of life of affected patients by interfering with a number of aspects, including sexuality and reproduction. The purpose of this brief review is to analyse the possible effects of antirheumatic drugs on fertility and reproduction in rheumatic patients affected by chronic arthritis, with particular focus on biological treatments. This is a concise overview of the topics presented at the International Congress 'OsteoRheumatology 2014', organised in Genova, Italy, in October 2014.

FERTILITY

Women with rheumatic diseases have a lower number of births, a reduced period of reproduction and a longer inter-pregnancy interval

Key messages

What is already known about this subject?

- Rheumatic diseases can interfere with reproduction. The approach to reproductive problems and pregnancy management in rheumatic patients represents a great challenge.

What does this study add?

- The purpose of this brief paper is to review the possible effects of antirheumatic drugs on fertility and reproduction in rheumatic patients affected by chronic arthritis, with particular focus on biological treatments.

How might this impact on clinical practice?

- Interdisciplinary approach and proper counseling with more effective physician-patient communication about family planning and desire for pregnancy should be encouraged to optimize pregnancy outcomes.

with difficulties in achieving subsequent pregnancy, in comparison with healthy controls.¹ The reasons for impaired sexual functioning and reproduction in rheumatic patients are complex and multifactorial. Some problems can be related directly to the disease process itself. Rheumatic symptoms such as chronic pain, fatigue, stiffness and impaired joint function can reduce libido and limit sexual satisfaction. Hormonal disorders, pelvic organ involvement and autoimmunity disorders can decrease patients' fecundity, and preclude successful pregnancy. Psychological problems (isolation, depression, anxiety), usually related to chronic and disabling disease, can limit interpersonal dynamics, and negatively influence sexual relationships and family planning.² Among factors that are directly disease-related, high disease activity is one of the most important aspects and may contribute essentially both to the longer time to conceive and worse pregnancy outcome in women affected by rheumatoid arthritis.³ Interactions between other kinds of chronic inflammatory arthritis (ankylosing spondylitis,



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¹Rheumatology and Clinical Immunology Unit, Spedali Civili di Brescia, Brescia, Italy
²Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

Correspondence to

Dr Chiara Bazzani;
bazzani@bresciaeumatologia.it

psoriatic arthritis, juvenile idiopathic arthritis) and fertility or pregnancy have been less investigated than those in rheumatoid arthritis. In spite of this fact, decreased fecundity (but not infertility) seems to characterise these patients as well.^{4 5}

DISEASE ACTIVITY DURING PREGNANCY

Previous retrospective studies, mainly based on patients' self-reports and conducted in a period of limited treatment options, demonstrated that disease activity improved during pregnancy in the majority of women affected by rheumatoid arthritis.⁶ More recently, prospective studies have shown that these patients not only achieve disease remission during pregnancy less frequently, but also have less improvement in disease activity during pregnancy than previously thought.^{7 8} In 2008, de Man *et al*⁷ showed that the proportion of women with at least moderate disease activity (DAS 28>3.2) during pregnancy was about 40%. During the third trimester, only 27% were in complete remission (DAS 28<2.6) and consequently had a significant reduction in drug prescriptions. During post-partum period, 39% of women had increased disease activity but only 4% had a severe flare. No profound effect of pregnancy on ankylosing spondylitis disease activity was described, even if some prospective studies proved disease worsening during the first and early second trimester of gestation and after delivery.^{9 10} Few papers are published about the course of psoriatic arthritis during gestation. Available reports seem to support an amelioration of disease activity during pregnancy.¹¹

PREGNANCY OUTCOME

Several studies have demonstrated a slight increase in obstetric complications in women affected by chronic arthritis. While a high frequency of miscarriages is not observed, some reports revealed an increased prevalence of small for gestational age infants, preterm delivery and caesarean sections in these patients.^{12 13} In some studies conducted in rheumatoid arthritis patients, an increased rate of pre-eclampsia was observed.^{14 15} Adverse pregnancy outcomes, in particular low birth weight, seem to be directly related to a higher level of disease activity, even if birth weight could also be indirectly influenced by the use of prednisone, through the promotion of a lower gestational age.¹⁶

ANTIRHEUMATIC TREATMENTS AND PREGNANCY IN CHRONIC ARTHRITIS PATIENTS

Disease modifying antirheumatic drugs and maternal exposure

Although some women affected by chronic arthritis sometimes have a transient reduction in disease activity and arthritis symptoms during pregnancy, treatment with antirheumatic drugs is frequently required during

gestation.^{7 17} So, while planning a pregnancy, it is important to choose a treatment that is effective in controlling disease activity, but that does not affect fertility nor fetal health. Most antirheumatic drugs have no effect on the gonads, however, as shown in [table 1](#), they can sometimes cause fertility disorders or induce an increased risk of malformations/complications in newborns. The first step in the management of patients desiring pregnancy is the timely withdrawal of teratogenic medications. For a long time, methotrexate and leflunomide, the most widely used disease modifying antirheumatic drugs (DMARDs) in arthritis patients, have been investigated for their potential teratogen effect. To date, the use of these drugs during the preconception period and pregnancy has been contraindicated in women as well as in men and therefore safe contraception is strongly recommended to patients taking these medications.¹⁸ However, recent studies have shed light on the teratogenic potential of these drugs. Even though preclinical animal studies suggest that leflunomide could be a human teratogen, the results of two studies conducted by the Organization of Teratology Information Specialists (OTIS) have not demonstrated an increase in the rate of major birth defects in children of women treated with leflunomide during the first trimester of gestation or in the preconception period.^{19 20} In these two studies, most of the patients (75% and 95%, respectively) underwent cholestyramine washout procedure after leflunomide withdrawal.^{19 20} Methotrexate is a potent teratogen when used at high doses for cancer treatment, but its fetotoxic effect when administered at a low weekly dose according to rheumatologic practice is still not well defined.²¹ A study published in 2014 described an increased risk of major birth defects and spontaneous abortion in women exposed to methotrexate, at dosages typically used in rheumatic patients, only in the postconception period, while no abnormalities were noted in women exposed before conception.²² For its potential embryotoxicity and teratogenicity in animal and human pregnancy, methotrexate discontinuation is suggested 3–6 months before conception.²³

DMARDs and paternal exposure

Preconception exposure to DMARDs in male patients has been suspected to be a risk factor for babies' health. However, recent studies have been reassuring about the lack of negative influence of DMARDs on offspring after paternal exposure. One study excluded an increased risk of adverse pregnancy outcome after paternal low-dose methotrexate therapy and the authors concluded that a 3-month MTX-free interval until conception is probably not necessary in male patients.²⁸ A longitudinal observational study proved that preconception paternal exposure to DMARDs in the 12 weeks prior to conception was not associated with increased adverse pregnancy outcome.²⁹ Some drugs can impair men's fertility; this is the case with sulphasalazine (SSZ). Animal reproductive studies with SSZ and a population-based case-control

Table 1 Antirheumatic drugs and risk during pregnancy (modified and updated from Hazes *et al*²³)

Drug class	FDA category	Effects on pregnancy or exposed babies	Clinical recommendations in female patients
NSAIDs	B (in early stage of pregnancy) C (after week 30)	Late in pregnancy can cause premature closure of the ductus arteriosus, increase the risk of neonatal bleeding, impairment of fetal renal function and development of oligohydramnios	Compatible with pregnancy in first half of the pregnancy ²³
STEROIDS	C	In doses >10 mg/day during pregnancy they can have adverse side effects both on mothers (diabetes, hypertension, osteopaenia, infections) and fetuses (prematurity, low birth weight, IUGR, infections, adrenal suppression, oral cleft)	Compatible with pregnancy in doses up to 10–15 mg/day (prednisolone equivalent) ^{23 24}
METHOTREXATE	X	Potential embryotoxicity and teratogenicity in animal and human pregnancy	Discontinuation 3–6 months before conception ²³
LEFLUNOMIDE	X	Potential embryotoxicity and teratogenicity in animal and human pregnancy	Discontinue 2 years before pregnancy or use cholestyramine washout procedure ²³
SULFASALAZYNE	B	No increase in malformation in human pregnancy	Compatible with pregnancy; Folate supplements needed ²³
ANTIMALARIALS	C	Malformations of the inner ear after treatment with higher than the recommended dose of chloroquine ²⁵	Hydroxychloroquine compatible with pregnancy ²³
CYCLOSPORIN A	C	Increase in premature delivery and low birth weight, but no increase of congenital malformations	Compatible with pregnancy in patients with autoimmune disease refractory to other immunosuppressive treatment ²⁶
AZATHIOPRINE	D	No increase in malformation in human pregnancy; potential teratogenicity in animal models	Compatible with pregnancy ²³
TNF α INHIBITORS	B	No increase in miscarriage or birth defects	Discontinuation after pregnancy detection. If used during pregnancy, they should be discontinued before gestational week 30 ²⁴
ABATACEPT	C	No conclusive human data	Discontinuation 3 months before conception ²⁴
TOCILIZUMAB	C	No conclusive human data	Discontinuation 3 months before conception ²⁴
RITUXIMAB	C	No increase in miscarriage or malformation. Exposure during the second and third trimesters possibly causes B cell depletion in the fetus	Discontinuation 12 months before conception ²⁷
ANAKINRA	B	Animal data: no harm in offspring. No conclusive human data	Discontinuation after pregnancy detection ²⁴

The US FDA pregnancy risk categories are as follows: A, no risk in controlled clinical studies in humans; B, animal studies show no risk and human data is reassuring even if well-controlled studies of pregnant women have not been conducted; C, human data are lacking and animal studies show risk (or have not been undertaken); D, positive evidence of human fetal risk: use only if potential benefit outweighs the risk; X, studies in animals or reports of adverse reactions show positive evidence of risk: contraindication during pregnancy. FDA, Food and Drug Administration; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumour necrosis factor.

study demonstrated no significant increase in female infertility or in congenital abnormalities in newborns.³⁰ However, treatment with SSZ can lead to infertility in men and male rats, inducing oligospermia, reduced sperm motility, and increased seminal abnormalities.³¹ The effect cannot be reduced by folate supplementation, but spermatogenesis improves about 2 months after withdrawal of the drug.³¹ Proper counselling should be offered to male patients trying to outweigh the risk of

disease flare on drug withdrawal against the impact of the drug on reproduction.

Tumour necrosis factor (TNF)- α inhibitors

While the relationship between DMARDs and their impact on reproduction has always been intriguing, in recent times, more attention has been devoted to the effects of biological antirheumatic drugs on fertility and pregnancy. Thanks to the widespread use of these

potent drugs in the past 10 years, a great improvement in patients' quality of life has induced a better perception of social needs such as family planning. An increasing number of affected women ask their rheumatologists about the possibility of having a baby and continue their biological antirheumatic treatment during gestation as well. Tumour necrosis factor (TNF)- α inhibitors, the first introduced and most studied antirheumatic biological drugs, do not impair fertility in men,^{32 33} and seem to be potential therapeutic agents for treating some types of female infertility, such as endometriosis.³⁴ Although randomised studies in pregnant women have not been conducted owing to ethical issues, anti-TNF- α drugs are not considered fetotoxic (Food and Drug Administration, FDA pregnancy category B),³⁵ in agreement with the results of preclinical studies. The published experience mainly consists of preclinical/animal reproduction studies, case reports from inadvertent drug exposure during pregnancy, registries and large observational studies of pregnant patients with arthritis or inflammatory bowel disease.^{26 36} In the absence of randomised controlled trials, the manufacturers of TNF- α inhibitors advise discontinuing these agents before a planned pregnancy. In fact, most biologic agents are complete IgG antibodies or IgG-derived-molecules that can be actively transferred through the placenta by Fc-receptors. This active transplacental transport significantly changes according to the different structural features of biological compounds and is more effective for complete monoclonal antibodies.²³ The transport generally starts at the beginning of the second trimester and increases until term,³⁷ when maternal and fetal drug serum levels can be equal, or concentrations in cord blood even higher.³⁸ So, if fetal exposure to IgG-drugs is very low in the first trimester during organogenesis, it can be more relevant when drugs are administered in the second part of gestation. In the past few years, numerous new pregnancies, with a first trimester exposure to these drugs, have been reported with a good pregnancy outcome.²⁴ According to the majority of the experts, anti-TNF- α agents can be considered safe in the early stage of pregnancy. If maternal disease is in remission, the treatment could be discontinued after the pregnancy test turns positive in order to limit the transplacental passage of the drug. On the other hand, some patients who discontinued the treatment in the early stages of pregnancy need to resume it during gestation because of severe disease flares. In these cases, to avoid an impaired immune response and a higher infective risk in the babies, TNF- α inhibitors should be discontinued at latest at gestational week 30, especially if they are complete monoclonal antibodies.²⁴ In a study assessing the course of inflammatory bowel disease in pregnant women, the authors demonstrated that cord blood concentrations of infliximab were lower among women who received the drug 10 weeks or less before delivery than those treated closer to it.³⁹ In our experience, between 1999 and 2013, we identified 74 exposed pregnancies in

women affected by different rheumatic diseases with peripheral chronic arthritis and treated with TNF- α inhibitors.⁴⁰ Biological treatment was stopped after a mean of 41 days since documented pregnancy. Live births were reported in 66% (49/74) of pregnancies. In our cohort, spontaneous abortion and fetal death rate was 15% and 7%, respectively. The same proportion was observed in retrospective studies about TNF- α use in pregnancy⁴¹ and in the general population as well.⁴² Elective termination was performed in 7 women (9%), with a higher rate in the group of patients exposed to biological agent plus methotrexate or leflunomide and with lower maternal age. We observed neither a high rate of malformations (2%) nor any relevant obstetric or neonatal adverse events. Six pregnancies were exposed to TNF- α inhibitors in the second/third trimester, because of high maternal disease activity. All these cases ended in live births. No fetal/neonatal complications were noted also in this subgroup of pregnancies and in particular no infectious events were reported in the newborns. In agreement with previously published data, our study concluded that women who inadvertently become pregnant while taking TNF- α inhibitors should be reassured that continuation of pregnancy does not represent a risk of negative obstetric or neonatal outcomes.

Other biological drugs

Published data about biological agents other than TNF- α inhibitors during pregnancy is limited. Some information comes from the rituximab global drug safety database. It includes data about more than 200 pregnancies occurring before 2009 in women affected by malignant diseases or different types of autoimmune diseases and treated with rituximab, the IgG1 monoclonal antibody with B-cell-depleting function.²⁷ The analysis of 153 pregnancies with known outcomes demonstrates no excess of neonatal deaths or congenital birth defects. Few neonatal infections or haematological abnormalities were seen among exposed babies.²⁷ Although no severe complications were observed, women are recommended to delay pregnancy for at least 12 months after rituximab exposure. Experience of pregnancy exposure to abatacept,⁴³ tocilizumab⁴⁴ and anakinra^{45 46} has largely been limited to conference abstracts or simple case reports. Owing to insufficient experience, no conclusion can be drawn on the compatibility of these drugs with pregnancy.

LONG-TERM FOLLOW-UP OF EXPOSED BABIES

At present, no statement about long-term safety of biological drugs administered during gestation can be made, given that the long-term follow-up of the exposed babies has not been fully assessed. Few data are currently available on the health, development, immune competence and infection susceptibility of the exposed infants. An uncontrolled study published in 2014 on 25 babies exposed to anti-TNFs prenatally for maternal inflammatory bowel disease demonstrated normal growth and

psychomotor development, and a relatively high frequency of infections, among infants.⁴⁷ We obtained similar results in a case-control study that investigates the health and developmental conditions of 21 children who were exposed in utero to anti-TNF- α agents in comparison with 21 non-exposed children born to mothers with the same rheumatic disease. Data about the babies' clinical conditions are derived by an *ad-hoc* created questionnaire submitted to the mothers. Our preliminary data demonstrate that children exposed in utero to anti-TNF- α drugs display good birth outcome, and normal growth and response to vaccinations. Infectious disorders are reported in the first year of life but with a benign course, and no significant differences between exposed and non-exposed children were noted (L Andreoli, C Bazzani, M Agosti, *et al*; personal communication. Long-term follow-up of children born to mothers with Chronic Arthritides and exposed in utero to anti-TNF- α agents: a case-control study. 8th International Conference on Reproduction, Pregnancy and Rheumatic Diseases; 25-27 September 2014, Trondheim, Norway). In order to draw conclusions, these findings have to be verified in a larger cohort.

CONCLUSION

The approach to reproductive problems and pregnancy management in rheumatic patients represents a great challenge. The turning point is represented by preconception counselling. Optimising pregnancy outcomes is based on informing male and female patients about potential risks related to the disease, planning for pregnancy during a period of clinical remission or, at least, low disease activity, and ensuring that ongoing treatments are both effective and compatible with pregnancy. TNF- α inhibitors can be considered safe while seeking for conception and in the first part of gestation, representing a possible therapeutic choice in patients affected by aggressive forms of chronic arthritis and desiring to have a baby. An interdisciplinary approach with the cooperation of rheumatologists, obstetricians, gynaecologists and neonatologists is crucial before and during pregnancy, and more effective physician-patient communication about family planning and desire for pregnancy should be reached. A prospective collection of additional exposures and new multicentric follow-up studies investigating perinatal infections, vaccination responses and global development of children is obviously needed to confirm the safety of antenatal exposure to anti-rheumatic biological drugs.

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