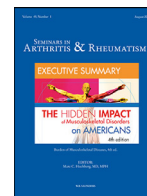




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Current perspectives on fertility, pregnancy and childbirth in patients with Rheumatoid Arthritis

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ABSTRACT

Rheumatoid Arthritis (RA) is common in the reproductive age. Women with RA have an impaired fertility related to the use of certain medication and active disease. RA usually improves during pregnancy, however almost half of the patients still have active disease in third trimester. Pregnancy outcomes are slightly less favorable, especially in women with high disease activity. Managing RA during pregnancy is challenging, because treatment options are limited. Accumulating evidence shows the safety of Tumor Necrosis Factor inhibitors in pregnant RA patients and patients with a wish to conceive.

This paper reviews the current perspective on fertility, pregnancy and childbirth in women with RA and discusses treatment options before and during pregnancy.

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Introduction

Rheumatoid Arthritis (RA) is one of the most common chronic diseases in women in their reproductive age. For women with RA it is harder to achieve parenthood. This is related to the disease itself and the use of medication [1–3].

Treating RA before and during pregnancy can be challenging since some drugs are considered teratogenic and active disease is associated with adverse fertility and pregnancy outcomes. Disease activity improves during pregnancy, but less than previously anticipated [4]. A significant number of patients has active disease and the use of anti-rheumatic drugs is still required. Information on the safety of medication during pregnancy, especially information on Tumor Necrosis Factor Inhibitors (TNF), is accumulating. Therefore more treatment options are available before and during pregnancy than previously considered.

Fertility

For women with RA it is harder to conceive a child. Multiple studies show that family size is reduced in women with RA and this may already be present before their diagnosis of RA [2]. Time to pregnancy (TTP) is a reliable way to measure fertility. A TTP greater than 12 months is considered as subfertility. In the general population the median percentage of subfertility is 9%, for RA patients this percentage is 25–42% [1,2].

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Several factors are thought to contribute to the impaired fertility in RA patients. Some anti-rheumatic drugs have been associated with impaired fertility outcomes. Non-steroidal anti-inflammatory drugs (NSAIDs) and high doses of prednisone (>7.5 mg daily) prolong the TTP [1]. For NSAIDs, the inhibition of the production of prostaglandins which play a role in ovulation and implantation, is most likely to be responsible. The negative effect of prednisone on fertility could be related to a direct effect on the endometrium and ovary and/or suppression of the hypothalamic-pituitary-ovarian axis [2,3]. Less is known on beneficial effects of anti-rheumatic drugs on fertility. A small retrospective study showed that in RA patients with a wish to conceive, treatment with biologic disease-modifying anti-rheumatic drugs (bDMARD) at the time of conception could shorten the TTP [5].

Active disease is associated with subfertility. In a large prospective cohort on RA and pregnancy, a TTP > 1 year was found in 67% of women with high disease (DAS28-CRP > 5.1). Whereas for women in remission (DAS28-CRP ≤ 2.6) a TTP > 1 year was found in only 30% of the study cases [1].

Earlier menopause has been observed in RA patients. Therefore, it has been hypothesized that RA patients have a smaller ovarian reserve. The most reliable marker for ovarian reserve is anti-Müllerian hormone (AMH). In patients with early RA no differences in serum AMH were found compared to healthy controls [6]. In patients with established RA decreased levels of serum AMH are found, however this was not associated with TTP [7]. These results imply a role of the disease or medication use in the decreased levels of serum AMH. Sexual problems are common in RA and therefore a lower intercourse frequency might partially account for the subfertility [2,3]. It should be noted that studies on this topic are not

performed in patients in their reproductive age [3]. In addition, smaller family size in RA patients might reflect personal choices related to chronic disease [2].

At fertility work-up in 41% of sub fertile RA patients no cause for the subfertility can be identified, compared to 8–28% in the general population. Indicating that disease related factors contribute to the prolonged TTP in RA patients [8].

As a result of impaired fertility rates, RA patients are more likely to receive fertility treatment. Assisted reproductive technology (ART) was found safe and effective in one study [8]. However, data from the nationwide Danish Health Registries showed a reduced chance of a live birth in women with RA receiving ART compared to a healthy reference group. The authors suggested that this was related to an impaired chance of embryo implantation. In their study, the use of prednisone before conception increased the odds ratio for live birth [9]. The reason for this is unknown.

Pregnancy

Disease activity improves during pregnancy, a recent systematic review and meta-analyses by Jethwa et al. found a combined improvement rate of RA during pregnancy of 60%. The authors found a combined flare rate post-partum of 46.7% [10]. Furthermore, the flare in disease activity has been described after a miscarriage [2,3].

The improvement rates in older studies are much higher; 75–95% [2]. In contrast to the recent prospective studies, the older studies used self-reported measures for disease activity, disease activity was often scored retrospectively and these studies were of smaller sample size. In addition, in these older studies various definitions of disease activity were used and patients were not seen before conception. Management of RA has improved in the last 25 years with the introduction of a treat-to-target approach and new and effective treatment options. This resulted in women entering pregnancy with lower disease activity and therefore the potential to improve in disease activity was decreased [2,3].

Rheumatoid factor (RF) and Anti-citrullinated protein antibody (ACPA) serum levels are not influenced by pregnancy. However, RF and/or ACPA status has an effect on the spontaneous improvement during pregnancy [11]. Patients without these antibodies are more likely to improve than patients with antibodies. Another study showed that disease activity itself is a clinical feature associated with the disease course of RA during pregnancy: RA patients in low disease activity in the first trimester are likely to have low disease activity or remission in the last trimester [12].

Pregnancy outcomes

Data on pregnancy outcomes in RA patients are well documented and reported in previous literature [2,3]. Compared to the general population, pregnancy outcomes in RA patients are slightly less favorable and related to active disease. In patients with well-regulated disease pregnancy outcomes are comparable to the general population [4,13].

Hypertensive disorders and preeclampsia are more common in women with RA compared to the general population. Data from the Norwegian birth registry showed that the risk of preeclampsia in RA patients is 5.0% compared to 3.4% in unaffected women [2]. Women with RA have an increased risk of small for gestational age (SGA) infants and intrauterine growth restriction (IUGR). The risk of SGA is 10%, compared to 3% in the general population. Increased disease activity is an independent risk-factor for lower birthweight among newborns in RA patients. The risk of IUGR is almost doubled for RA patients compared to the general population (odds ratio (OR) 1.93, 95% Confidence interval (CI) 1.81–2.05) [2,3,13].

Pregnant RA patients have an increased risk for preterm delivery (PTD) (defined as birth before 37 weeks of gestational age). This

increased risk is 9–15% compared to 6–8% in the healthy population. Risk factors for PTD are the use of prednisone during pregnancy and the severity of the disease. The risk of premature rupture of membranes (PROM) (OR 1.548, 95% CI 1.474–1.626) and antepartum hemorrhage were found slightly elevated in RA patients (OR 1.229, CI 1.152–1.312) [2,3,13].

RA patients have an increased risk of cesarean delivery. This increased risk is associated with disease activity. In the PARA cohort, the cesarean section rate was 22% for the active disease group (DAS28-CRP > 3.2) and 10% in the group with DAS28-CRP ≤ 3.2 [4].

The risk of miscarriages might be increased in women with RA. One study did not show an increased risk of miscarriages, however data from the Norwegian birth registry showed that RA patients have an increased risk of miscarriage (OR 1.32, CI 1.19–1.47) [2]. It should be noted that this study included both planned and unplanned pregnancies. Many of the unplanned pregnancies will therefore be conceived whilst taking methotrexate (MTX). MTX induces miscarriages and therefore the risk of miscarriages might be overestimated. Information on medication was not available in this study.

Offspring of RA patients

Offspring of RA patients do not have an increased risk on major congenital malformations. Long-term follow-up of offspring of RA patients revealed no differences in anthropometric measurements compared to children born to healthy mothers [2,3].

Medication during pregnancy and lactation period

Treatment algorithms with conventional and biologic disease modifying drugs, applying a treat-to-target approach have resulted in better outcomes for RA patients. However, applying a treat-to-target approach in pregnancy can be challenging; because of a lack of safety data not every treatment option is compatible with pregnancy. An overview of the safety of anti-rheumatic drugs during pregnancy and breastfeeding is given in Table 1.

Conventional disease modifying anti-rheumatic drugs (cDMARD), NSAIDs and glucocorticoids

In 2016, a European League Against Rheumatism (EULAR) task-force published points to consider for use of anti-rheumatic drugs in the preconception period, pregnancy and postpartum [14].

Sulfasalazine (SSZ) (in a daily dose up to 2000 mg) and Hydroxychloroquine (HCQ) (in a daily dose 200 mg–400 mg) are considered safe to use during pregnancy. Azathioprine and Cyclosporine too, are proven to be safe for the use during pregnancy. MTX and Leflunomide should be avoided before and during pregnancy [14].

The use of NSAIDs is associated with impaired fertility outcomes; the TTP is prolonged when taking NSAIDs. NSAIDs could be prescribed during the 1st and 2nd trimester, however impaired renal function of the child and oligohydramnios have been described. It is advised to stop NSAIDs during the 3rd trimester because they can impair labor and cause premature constriction of the ductus arteriosus [2].

Prednisone is largely metabolized by the placenta. The use and period of prednisone before and during pregnancy should be limited however. Prednisone use is associated with preterm delivery [15] and high dose prednisone use (> 7.5 g daily dose) is associated with prolonged TTP [1]. Prednisone use is associated with IUGR and PROM too [2,3].

Biologic disease modifying anti-rheumatic drugs (bDMARD)

TNF inhibitors are the best-studied biologic agents during pregnancy and safety data on TNF inhibitors during pregnancy is reassuring.

Table 1
Anti-rheumatic drugs and their compatibility during pregnancy and breastfeeding [14].

Medication	Pregnancy	Lactation
Hydroxychloroquine	No increased risk on congenital malformations, may be used throughout pregnancy	Safe during lactation period
Sulfasalazine	No increased risk on congenital malformations, may be used throughout pregnancy up to 2000 mg daily with folate supplementation	Safe during lactation period in healthy babies
Glucocorticoids	No increased risk on congenital malformations, may be used throughout pregnancy at lowest possible dose. Prednisone use is associated with preterm delivery [15] and high dose prednisone (>7.5 g daily dose) use is associated with a prolonged time to pregnancy [1].	Safe during lactation period
Methotrexate	Proven teratogenic. Not recommended for use during pregnancy. Must be stopped 1–3 months before planned pregnancy	Should be avoided during lactation period
Leflunomide	May be teratogenic, insufficient data available. Not recommended for use during pregnancy. Washout period with Cholestyramine is recommended before pregnancy	Insufficient data available, should be avoided during lactation period
NSAIDs	No increased risk on congenital malformations. Should be stopped in third trimester of pregnancy	Safe during lactation period
Certolizumab	No increased risk on congenital malformations, may be used throughout pregnancy	Safe during lactation period
Infliximab	No increased risk on congenital malformations. Advised to be stopped before 20th week of pregnancy	Safe during lactation period
Adalimumab	No increased risk on congenital malformations. Advised to be stopped before 20th week of pregnancy	Safe during lactation period
Etanercept	No increased risk on congenital malformations. Advised to be stopped before 32nd week of pregnancy	Safe during lactation period
Golimumab	No increased risk on congenital malformations, insufficient data available. Not recommended for use during pregnancy	Safety data is scarce, expert consensus is that it is safe during lactation period
Other biologicals (Rituximab, Anakinra, Ustekinumab, Tocilizumab)	No increased risk on congenital malformations (Rituximab, Anakinra, Ustekinumab), insufficient data available. Not recommended for use during pregnancy	Insufficient data available, should be avoided during lactation period

TNF inhibitors differ in structure; Adalimumab, Infliximab, and Golimumab are entire monoclonal IgG1 antibodies, Etanercept only contains a part of the Fc-region of IgG1 and Certolizumab is a PEGylated fragment antigen-binding (Fab) and contains no Fc region [14]. Active transport of TNF inhibitors over the placenta into the fetal circulation is mediated through binding to the fetal Fc receptor and occurs as early as week 18 of gestation. Adalimumab and Infliximab have high affinity for the fetal Fc receptor, Etanercept binds weakly to this receptor and Certolizumab does not bind to this receptor at all since it does not contain a Fc-region. Hence the level of TNF inhibitor that can be detected in the cord blood is associated with the type of TNF inhibitor [14]. In addition, placental transfer increases over time and therefore the timing of administration during pregnancy is associated with the level of TNF inhibitor that can be detected in the cord blood. The lowest levels of anti-TNF in the cord blood are observed for Certolizumab and Etanercept. Exposure to Infliximab and Adalimumab, especially later in pregnancy, results in higher levels of the drug detectable in the umbilical cord blood compared to Etanercept and Certolizumab. Both Infliximab and Adalimumab can be detected in the fetal circulation up to one year for Infliximab and up to 9 months for Adalimumab [16].

The best timing to stop anti-TNF treatment, so that no levels of TNF inhibitors in the umbilical cord can be detected, is yet to be discovered. The EULAR taskforce recommends stopping Infliximab and Adalimumab treatment at 20 weeks of gestation and Etanercept at 30–32 weeks of pregnancy. The EULAR taskforce advises that the use of Certolizumab throughout the whole pregnancy is safe [14]. Due to a lack of safety data, the use of Golimumab is not advised during pregnancy [14].

When taking all data together no increased risk of congenital malformations in infants exposed to TNF inhibitors was found, and most importantly no specific pattern of malformations could be observed [17].

Vinet et al. showed in a large sample size, using the US claim data, no excess risk of serious infections after in utero exposure to anti-TNF biologic treatment [18].

Safety data on other biologic agents such as Tocilizumab, Anakinra, Abatacept, Tofacitinib and Rituximab is not sufficient enough and the use of these agents is not advised during pregnancy [14].

Disease activity after stopping anti-TNF during pregnancy

There is only limited data available on the effect of stopping anti-TNF treatment on disease course in pregnant patients. Most literature suggests that stopping TNF inhibitors just before or during a pregnancy results in a flare during pregnancy or in the peri- and postpartum period. Contrary, Förger et al. showed that in patients with inactive disease, discontinuing TNF inhibitors before the 20th week of gestation did not result in active disease later in pregnancy [19]. However, it should be noted that in this study patient-reported outcome measures were used to assess disease activity and that the value of these measures during pregnancy are still point of discussion.

Vaccination after exposition to anti-TNF in utero

Infants who are exposed in the 2nd or 3rd trimester of pregnancy to anti-TNF treatment should not receive live attenuated vaccines in their first 6 months of life [14]. Infants who are exposed to anti-TNF treatment before the 22nd week of gestation can get vaccinated, including live vaccines, conform the standard vaccine protocols [14].

Vaccination appears to be effective in infants exposed to TNF inhibitors in utero.

Cheent et al. presented a case where vaccination at 3 months resulted in a severe and lethal *Bacillus Calmette Guerin* (BCG) infection after in utero exposition to infliximab [20]. Other studies found only mild reactions to the administration of live vaccines in the first months of life after exposure to anti-TNF in utero.

Breastfeeding and anti-TNF

Breastfeeding during the use of TNF inhibitors Infliximab, Adalimumab, Etanercept, and Certolizumab is appropriate; minimal transfer of the TNF inhibitor into breast milk occurs [14].

Conclusion

Fertility is impaired in woman with RA, this is related to both the disease itself as well as medication use. Pregnancy outcomes are slightly impaired in women with RA and this is associated with disease activity. Tight disease control during pregnancy and in the postpartum period for patients with active disease is advised to limit complications.

Disease activity of RA improves during pregnancy, however a substantial percentage of women with RA has active disease during pregnancy and therapeutic interventions are required. Fortunately, accumulating evidence shows the safety of many medications including TNF inhibitors before and during pregnancy.

Challenges remain: although a treat-to-target approach is advised during pregnancy, the feasibility of such an approach has never been studied. In addition, it is unknown whether fertility outcomes and pregnancy outcomes are comparable with healthy controls when patients are in clinical remission. More information is needed on the safety of vaccination with live attenuated vaccines on infants exposed to anti-TNF in utero and the consequences of stopping anti-TNF during pregnancy. Answers to these questions are expected from large prospective cohorts and European collaborations.

References

- [1] Brouwer J, Hazes JM, Laven JS, Dolhain RJ. Fertility in women with rheumatoid arthritis: influence of disease activity and medication. *Ann Rheum Dis* 2015;74(10):1836–41.
- [2] de Jong PH, Dolhain RJ. Fertility, pregnancy, and lactation in rheumatoid arthritis. *Rheum Dis Clin North Am* 2017;43(2):227–37.
- [3] Ince-Askan H, Dolhain RJ. Pregnancy and rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2015;29(4–5):580–96.
- [4] de Man YA, Dolhain RJ, van de Geijn FE, Willemsen SP, Hazes JM. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum* 2008;59(9):1241–8.
- [5] Shimada H, Kameda T, Kanenishi K, Miyatake N, Nakashima S, Wakiya R, et al. Effect of biologic disease-modifying anti-rheumatic drugs for patients with rheumatoid arthritis who hope to become mothers. *Clin Rheumatol* 2019;38(5):1453–8.
- [6] Brouwer J, Laven JS, Hazes JM, Schipper I, Dolhain RJ. Levels of serum anti-Mullerian hormone, a marker for ovarian reserve, in women with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2013;65(9):1534–8.
- [7] Brouwer J, Dolhain RJEM, 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.
- [8] 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.
- [9] Norgard BM, Larsen MD, Friedman S, Knudsen T, Fedder J. Decreased chance of a live born child in women with rheumatoid arthritis after assisted reproduction treatment: a nationwide cohort study. *Ann Rheum Dis* 2019;78(3):328–34.
- [10] Jethwa H, Lam S, Smith C, Giles I. Does rheumatoid arthritis really improve during pregnancy? A systematic review and meta-analysis. *J Rheumatol* 2019;46(3):245–50.
- [11] de Man YA, Bakker-Jonges LE, Goorbergh CM, Tillemans SP, Hooijkaas H, Hazes JM, et al. Women with rheumatoid arthritis negative for anti-cyclic citrullinated peptide and rheumatoid factor are more likely to improve during pregnancy, whereas in autoantibody-positive women autoantibody levels are not influenced by pregnancy. *Ann Rheum Dis* 2010;69(2):420–3.
- [12] Ince-Askan H, Hazes JMW, Dolhain R. Identifying clinical factors associated with low disease activity and remission of rheumatoid arthritis during pregnancy. *Arthritis Care Res (Hoboken)* 2017;69(9):1297–303.
- [13] Kishore S, Mittal V, Majithia V. Obstetric outcomes in women with rheumatoid arthritis: results from nationwide inpatient sample database 2003–2011. *Semin Arthritis Rheum* 2019;49(2):236–40.
- [14] Gotestam 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. *Ann Rheum Dis* 2016;75(5):795–810.
- [15] de Man YA, Hazes JM, van der Heide H, Willemsen SP, de Groot CJ, Steegers EA, et al. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. *Arthritis Rheum* 2009;60(11):3196–206.
- [16] Julsgaard M, Christensen LA, Gibson PR, Gearty RB, Fallingborg J, Hvas CL, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology* 2016;151(1):110–9.
- [17] Chaudrey KH, Kane SV. Safety of immunomodulators and anti-TNF therapy in pregnancy. *Curr Treat Options Gastroenterol* 2015;13(1):77–89.
- [18] Vinet E, De Moura C, Pineau CA, Abrahamowicz M, Curtis JR, Bernatsky S. Serious infections in rheumatoid arthritis offspring exposed to tumor necrosis factor inhibitors: a cohort study. *Arthritis Rheumatol* 2018;70(10):1565–71.
- [19] Forger F, Bandoli G, Luo Y, Robinson L, Johnson DL, Chambers CD. No Association of Discontinuing Tumor Necrosis Factor Inhibitors Before Gestational Week Twenty in Well-Controlled Rheumatoid Arthritis and Juvenile Idiopathic Arthritis With a Disease Worsening in Late Pregnancy. *Arthritis Rheumatol* 2019;71(6):901–7.
- [20] Cheent K, Nolan J, Shariq S, Kiho L, Pal A, Arnold J. Case report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. *J Crohns Colitis* 2010;4(5):603–5.