

## Management of pregnancy in patients with rheumatoid arthritis

N Akasbi\*, FE Abourazzak, T Harzy

### Abstract

#### Introduction

Rheumatoid arthritis is a chronic systemic inflammatory disease that is highly prevalent in women of childbearing age. Rheumatoid arthritis has been known to improve during pregnancy and to fare in the postpartum period. Pregnancy can be challenging to manage in patients with rheumatoid arthritis. The general rule 'a woman with rheumatoid arthritis should postpone pregnancy until remission or stable disease' should be followed. Some drugs are compatible during pregnancy, others are not. The present review will discuss influences of the pregnancy on rheumatoid arthritis, the effect of the rheumatoid arthritis on the pregnancy itself, and the management of these patients during pregnancy.

#### Conclusion

Pregnancy should be delayed until an adequate control of the rheumatoid arthritis. Mostly, pregnancy improves the outcome of rheumatoid arthritis.

#### Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of an unknown aetiology that affects approximately 1% of general population. It occurs preferentially in women, often during childbearing age<sup>1</sup>. The management of RA during this period is difficult, and drug therapy before and during pregnancy needs to be discussed.

This article describes the maternal course, the foetal outcome and therapy during pregnancy in RA.

\* Corresponding author  
Email: akasbusinessrine@gmail.com

Rheumatology Department, Hassan II University Hospital, Fez 30070, Morocco

### Discussion

#### Fertility in women with rheumatoid arthritis

RA can impair the fertility and fecundity. Pain, stiffness and swelling in joints, fatigue and depression can make sexual intercourse difficult, reduce its frequency and may decrease libido. Some women do not want to become pregnant because they are afraid of genetic transmission of RA. Hence, the birth rate is lower among women with RA. This may be due to parenting suffering, especially in women with a severe postpartum flare of RA<sup>2</sup>.

#### Effect of pregnancy on disease activity in women with rheumatoid arthritis

Among rheumatic diseases, the interaction between pregnancy and RA is the most studied. According to retrospective studies, approximately 75–90% of patients with RA improve during pregnancy<sup>3,4</sup>.

A prospective study<sup>5</sup> including 84 RA patients demonstrates that patients reach remission during pregnancy and deteriorate during postpartum with a statistical significance. In this study, 48% of patients who had moderate disease activity (DAS28 > 3.2) in the first trimester had an improvement in disease activity during pregnancy. In another large prospective study<sup>5</sup> including 140 RA patients, 65% of patients experienced amelioration in pain and swelling compared with before pregnancy. Usually, patients who become pregnant with a stable or low disease activity gain less beneficial effects of pregnancy, but remain mainly stable. Patients with high disease activity at conception benefit the most from pregnancy.

Interestingly, patients who were negative for both rheumatoid factor (RF) and cyclic citrullinated autoantibodies (ACPA) were more likely to improve during pregnancy. In a Dutch study<sup>6</sup>, symptoms of RA subsided in 75% of RA women negative for both ACPA and RF compared with only 39% of women tested positive for these autoantibodies.

The improvement in RA symptoms and activity can be explained by the reduction of inflammatory activity of RA during pregnancy. During pregnancy, oestrogen and progesterone levels are increased. Consequently, the initial predominant immune cellular response (Th1 type) is decreased, whereas humoral response (Th2 type) is increased<sup>7</sup>. Recent studies have shown a shift of a Th1 to a Th2 immune response during pregnancy. Regulatory T cells could also contribute, as they increase during pregnancy. They have a major role in suppressing maternal autoimmune responses. These cells produce anti-inflammatory cytokines, such as interleukin-4 (IL-4), IL-10 and transforming growth factor- $\beta$ <sup>8</sup>. Another contributing cause to the remission of RA during pregnancy may be reduction in functioning of polymorph nuclear neutrophils in the synovial fluid by  $\alpha$ -fetoprotein, which reduces the degree of inflammation in synovial fluid<sup>9</sup>. Also, number of tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) receptors and plasma level of IL-1 receptor antagonists found to increase during pregnancy<sup>10</sup>. All these possibilities are not exclusive, and it is likely that the explanation for disease amelioration in RA is multifactorial.

Licensee OA Publishing London 2014. Creative Commons Attribution License (CC-BY)

**FOR CITATION PURPOSES:** Akasbi N, Abourazzak FE, Harzy T. Management of pregnancy in patients with rheumatoid arthritis. OA Musculoskeletal Medicine 2014 Feb 01;2(1):3.

### Pregnancy outcome in rheumatoid arthritis

Usually, women with rheumatic diseases in general have been found to have higher risk for adverse outcomes like preeclampsia, preterm delivery and small-for-gestational-age infants. It has previously been documented that caesarean sections are more prevalent among RA patients compared with healthy controls<sup>11,12</sup>.

However, a few authors have found that pregnancy outcomes in women with well-controlled RA are comparable to that in general population. De Man et al.<sup>13</sup> demonstrated that disease activity in RA was associated with lower birth weight, and the gestational age at delivery was significantly lower in women who were receiving prednisone and their delivery was more often premature.

The mechanism behind high levels of disease activity leading to lower birth weight is not well understood. However, some pathophysiologic hypotheses could explain this. First, vasculopathy due to endothelial dysfunction may result in maldevelopment of the placenta. Second, proper foetal development needs lower levels of foetal cortisol than maternal cortisol. In the placenta, the enzyme 11 $\beta$  hydroxysteroid dehydrogenase type 2 (11 $\beta$ HSD2) inactivates maternal cortisol. High cortisol levels in the mother due to the substitution and low 11 $\beta$ HSD2 levels in the placenta both are associated with decreased birth weight of infant<sup>14</sup>.

### Postpartum maternal disease activity

During the postpartum period, it is common for RA to flare. Two largest prospective studies have found RA relapse in 39%<sup>5</sup> and 62%<sup>15</sup> of patients, respectively.

In addition, new-onset RA has been reported to be 3–5 times more frequent within the first 6 months after delivery requiring an increase in drug therapy<sup>16</sup>. Causes of the relapse

during postpartum are unknown. It has been suggested that it may be due to increased prolactin levels associated with breastfeeding, as this hormone is pro-inflammatory. But, this physiopathological mechanism remains controversial.

### Management of rheumatoid arthritis with drugs during pregnancy

#### *Drugs for rheumatoid arthritis and pregnancy*

- **Nonsteroidal anti-inflammatory drugs:** Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally known as safe drugs. They have a known effect on the foetus at the end of the pregnancy by causing a premature closure of the ductus arteriosus, which can provoke pulmonary hypertension and respiratory problems. Another side effect is kidney dysfunction, which leads to oligohydramnios and neonatal anuria. Hence, they must not be indicated for women after 32 weeks of pregnancy<sup>17</sup>.
- **Corticosteroids:** The administration of corticosteroids during pregnancy has been associated with premature rupture of membranes, preterm delivery, intrauterine growth restriction, and maternal side effects such as hypertension and diabetes mellitus. The use of corticosteroids has been associated in children with cleft palate, especially with high doses<sup>18</sup>. However, in some cases, patients need corticosteroids to control RA symptoms.
- **Antimalarials:** Antimalarials are safe drugs during pregnancy. There is no foetal toxicity with hydroxychloroquine. This treatment should be maintained throughout pregnancy in patients with RA<sup>19,20</sup>.
- **Sulphasalazine:** Sulphasalazine is a combination of an aspirin-like anti-inflammatory component and a sulphur antibiotic-like component, used to treat RA as a disease-modifying drug. A registry-based Norwegian study has demonstrated

no increase in congenital malformations in children who were exposed to sulphasalazine during pregnancy<sup>21</sup>. This treatment could be maintained throughout pregnancy in patients with RA.

- **Methotrexate:** Methotrexate (MTX) is a folic acid antagonist that inhibits dihydrofolate reductase, which blocks synthesis of thymidine and inhibits DNA synthesis. It is a disease-modifying drug used to treat RA. MTX is teratogenic in both animals and humans. The vulnerable period for the use of MTX is between 5 and 8 weeks of gestation, but foetal malformations can occur after 11 weeks with a dose of 10 mg/week or greater<sup>22</sup>. Higher doses increase the risk for MTX embryopathy, which includes growth deficiency, microcephaly, hypoplasia of skull bones, wide fontanelles, coronal or lambdoidal craniosynostosis, upswept frontal scalp hair, broad nasal bridge, shallow supraorbital ridges, prominent eyes, low-set ears, maxillary hypoplasia, epicanthal folds, short limbs, talipes, hypodactyly and syndactyly<sup>23</sup>. MTX must be discontinued 3 months before pregnancy.
- **Leflunomide:** Leflunomide is an isoxazole immunomodulatory agent with antiproliferative activity. In some studies, leflunomide was found to be embryotoxic and teratogenic<sup>24</sup>. Other data found no significant differences in the overall rate of major structural defects in the exposed pregnant women<sup>25</sup>. Actually, as a rule, women treated with leflunomide are advised to avoid pregnancy and those who become pregnant are advised to stop the drug and to reduce foetal exposure through cholestyramine drug elimination procedure before pregnancy.
- **Anti-tumour necrosis factor- $\alpha$  therapy:** Anti-TNF- $\alpha$  agents are used in the treatment of patients with RA, especially in those who are refractory to synthetic disease-modifying anti-rheumatic drugs.

Licensee OA Publishing London 2014. Creative Commons Attribution License (CC-BY)

In general, placental transport of anti-TNF- $\alpha$  agents is minimal in the first trimester, which gives some reassurance regarding the risk for congenital malformations. In fact, there is no convincing evidence to support an increased risk for a specific congenital malformation with these drugs. In a few sporadic cases, the cause-effect relationship is not conclusive.

Anti-TNF- $\alpha$  agents are discontinued soon after a missed period or after a positive pregnancy test. In case of active disease refractory to other treatment, TNF- $\alpha$  inhibitors may be used during pregnancy. Monoclonal antibodies must be stopped between gestational weeks 20 and 30. Certolizumab pegol can be given throughout pregnancy<sup>22</sup>. In addition, live vaccines should be avoided in children with *in utero* exposure to biologics for at least the first 6 months of life<sup>26</sup>.

- Rituximab: Rituximab is a chimeric monoclonal antibody that targets the B-cell CD20 cell surface protein, which becomes indispensable for the treatment of RA in some cases. Rituximab results in B-cell depletion in the foetus of animals and humans when given in the second and third trimester, leading to lymphopaenia. Rituximab must be discontinued 6–12 months before pregnancy<sup>22</sup>.
- Tocilizumab: Tocilizumab is a humanised, monoclonal, anti-IL-6 receptor antibody. No documented data for human pregnancy are available. A few case reports studied have not indicated any adverse outcomes. Tocilizumab must be discontinued 3 months before pregnancy<sup>22</sup>.
- Abatacept: Abatacept is a selective T-cell costimulation modulator. There are no human studies of drug exposure. Abatacept must be discontinued 3 months before pregnancy<sup>22</sup>.
- Anakinra: Anakinra is a recombinant form of IL-1 receptor antagonist. It is recommended to

avoid anakinra because of lack of data with respect to its safety for the child. Animal data have not shown problems in offspring when exposed during pregnancy. Only three human pregnancies have been reported with the use of anakinra throughout pregnancy, and in one case through lactation as well. No side effects that affect children were observed<sup>26</sup>.

### Summary

- *RA drugs to stop before a planned pregnancy:* MTX, leflunomide, abatacept, tocilizumab and rituximab.
- *Drugs that can be continued until conception:* TNF- $\alpha$  inhibitors; complete monoclonal antibodies infliximab, adalimumab and golimumab are transported through the placenta; whereas lesser quantity of certolizumab pegol is observed to cross placenta and may be an ideal choice when active disease in pregnancy needs a TNF- $\alpha$  inhibitor.
- *RA drugs that are compatible during pregnancy:* antimalarial agents and sulphasalazine.
- *RA drugs that can be safely administered during pregnancy:* corticosteroids, analgesics such as paracetamol and NSAIDs until gestational week 32.

### Management of rheumatoid arthritis before and during pregnancy

A woman with RA should postpone pregnancy until remission or stable disease is achieved and has persisted for at least 6 months.

In patients with stable and controlled disease activity, treatment must be adjusted from incompatible drugs during pregnancy, such as MTX, leflunomide and biologic treatment to compatible drugs like antimalarial agents and sulphasalazine.

In patients with early RA or with active and uncontrolled disease activity, pregnancy should be preferentially postponed until improvement of disease activity or obtaining remission<sup>22</sup>.

### Management of rheumatoid arthritis with drugs during breastfeeding

NSAIDs, sulphasalazine, antimalarials are compatible during breastfeeding except in premature children aged less than 1 month. Corticosteroids are safe during breastfeeding, but if the dose is >40 mg/day, breastfeeding should be postponed 4 h after taking the drug. MTX and leflunomide are contraindicated<sup>27,28</sup>. All anti-TNF- $\alpha$  agents are compatible during the lactation. Abatacept and tocilizumab must be avoided.

### Conclusion

Pregnancy should be delayed until an adequate control of the RA. Mostly, pregnancy improves the outcome of RA. In case of active disease or relapse, drugs that need to be indicated during pregnancy should be reviewed carefully and those drugs must be compatible during with pregnancy. Further studies on the moving of antirheumatic drugs into breast milk and the resulting consequences are insistently needed.

### Abbreviations list

11 $\beta$ HSD2, 11 $\beta$  hydroxysteroid dehydrogenase type 2; IL, interleukin; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; TNF- $\alpha$ , tumour necrosis factor- $\alpha$ .

### References

1. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum.* 2002 Feb;46(2): 328–46.
2. Clowse ME, Chakravarty E, Costenbader KH, Chambers C, Michaud K. Effects of infertility, pregnancy loss, and patient concerns on family size of women with rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Care Res (Hoboken).* 2012 May;64(5):668–74
3. Goupille P. Grossesse et polyarthrite rhumatoïde. *Rev Rhum.* 1997;64:174 sp–82.
4. Hazes JM. Fetomaternal HLA differences and the onset and course of rheumatoid

- arthritis. *Rev Rhum Engl Ed.* 1998 Nov; 65(11):611–3.
5. 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 Sep;59(9): 1241–8.
6. De Man YA, Bakker LE, van den Goorbergh DD, Tillemans SPR, Hooijkaas H, Hazes JMW, et al. Women with rheumatoid arthritis negative for anti-CCP 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.* 2009.
7. Florea A, Job-Deslandre C. Rheumatoid arthritis and pregnancy. *Presse Med.* 2008 Nov;37(11):1644–51.
8. Meriño-Ibarra E, Delgado Beltrán C. Rheumatoid arthritis: how to use drugs during pregnancy and lactation? *Reumatol Clin.* 2011 Jul–Aug;7(4):262–6.
9. Gayed M, Gordon C. Pregnancy and rheumatic diseases. *Rheumatology (Oxford).* 2007 Nov;46(11):1634–40.
10. Østensen M, Förger F, Nelson JL, Schuhmacher A, Hebisch G, Villiger PM. Pregnancy in patients with rheumatic disease: anti-inflammatory cytokines increase in pregnancy and decrease post partum. *Ann Rheum Dis.* 2005 Jun;64(6): 839–44.
11. Chakravarty EF, Nelson L, Krishnan E. Obstetric hospitalizations in the United States for women with systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum.* 2006 Mar;54(3): 899–907.
12. Reed SD, Vollan TA, Svec MA. Pregnancy outcomes in women with rheumatoid arthritis in Washington State. *Matern Child Health J.* 2006 Jul;10(4): 361–6.
13. de Man YA, Hazes JM, van der Heide H, Willemsen SP, de Groot CJ, Steegers EA, Dolhain RJ. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. *Arthritis Rheum.* 2009 Nov;60(11): 3196–206.
14. Seckl JR. Glucocorticoid programming of the fetus; adult phenotypes and molecular mechanisms. *Mol Cell Endocrinol.* 2001 Dec;185(1–2):61–71.
15. Barrett JH, Brennan P, Fiddler M, Silman AJ. Does rheumatoid arthritis remit during pregnancy and relapse postpartum? Results from a nationwide study in the United Kingdom performed prospectively from late pregnancy. *Arthritis Rheum.* 1999 Jun;42(6):1219–27.
16. Lijima T, Tada H, Hidaka Y, Yagoro A, Mitsuda N, Kanzaki T, et al. Prediction of postpartum onset of rheumatoid arthritis. *Ann Rheum Dis.* 1998 Aug;57(8): 460–3.
17. Ostensen M. Nonsteroidal anti-inflammatory drugs during pregnancy. *Scand J Rheumatol Suppl.* 1998;107:128–32.
18. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology.* 2000 Dec;62(6): 385–92.
19. Clowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum.* 2006 Nov;54(11): 3640–7.
20. Costedoat-Chalumeau N, Amoura Z, Duhaut P, Huong DL, Sebough D, Wechsler B, et al. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group. *Arthritis Rheum.* 2003 Nov;48(11): 3207–11.
21. Viktil KK, Engeland A, Furu K. Outcomes after anti-rheumatic drug use before and during pregnancy: a cohort study among 150,000 pregnant women and expectant fathers. *Scand J Rheumatol.* 2012 May;41(3):196–201.
22. Østensen M, Förger F. Management of RA medications in pregnant patients. *Nat Rev Rheumatol.* 2009 Jul;5(7):382–90.
23. Hyoun SC, Običan SG, Scialli AR. Teratogen update: methotrexate. *Birth Defects Res A Clin Mol Teratol.* 2012 Apr;94(4): 187–207.
24. Brent RL. Teratogen update: reproductive risks of leflunomide (Arava); a pyrimidine synthesis inhibitor: counseling women taking leflunomide before or during pregnancy and men taking leflunomide who are contemplating fathering a child. *Teratology.* 2001 Feb;63(2):106–12.
25. Chambers CD, Johnson DL, Robinson LK, Braddock SR, Xu R, Lopez-Jimenez J, et al. Birth outcomes in women who have taken leflunomide during pregnancy. *Arthritis Rheum.* 2010 May;62(5):1494–503.
26. Hyrich KL, Verstappen SM. Biologic therapies and pregnancy: the story so far. *Rheumatology (Oxford).* 2013 Dec.
27. Bernas BL. Use of immunosuppressive drugs in pregnancy and lactation. In: *UpToDate*, Rose BD, editor. Waltham, MA: UpToDate; 2010.
28. Østensen M, Khamashta M, Lockshin M, Parke A, Brucato A, Carp H, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther.* 2006;8(3):209.