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## Review Article

## Pregnancy in rheumatic diseases

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## ABSTRACT

Rheumatic disease inspite of improvement during pregnancy, is a challenging problem. The disease has a tendency to flare up in immediate postpartum stage and sometimes also during pregnancy. Hence, planning of pregnancy should be deferred to the stage when the rheumatic diseases are quiescent for six to twelve months. Drugs with teratogenic effects like methotrexate and leflunomide must be stopped three to six months prior to conception.

Lower dosage of corticosteroid is advocated with a limit upto 10 mg /day. In third trimester NSAIDs must be avoided. The safer drugs during pregnancy are sulfasalazine, hydroxychloroquine and azathioprine. Cholestyramine wash or use of charcoal for leflunomide is must if this drug has been taken within two years of planned conception.

With lack of evidence regarding teratogenic potentials of biologics, they are to be withheld prior to conception, with the exception of TNF inhibitors, may be allowed to continue.

During lactation, NSAIDs preferably short acting Ibuprofen should be given just after feeding. In lactation, the drugs considered safe are the same as used during pregnancy - low dose corticosteroids, sulfasalazine, hydroxychloroquine, and azathioprine. Similarly, anti TNF agents are also considered safe during lactation. Evidence-based recommendations regarding use of DMARDs and biologics is a powerful tool / guide for rheumatologists in pregnant and lactating women with rheumatic diseases. Counselling of male patients with rheumatic diseases regarding conception is also mandatory.

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## 1. Introduction

When a woman of child-bearing age is diagnosed with RA, the rheumatologist is entrusted with multiple responsibilities. A discussion of the need for contraception and safest time for conception is critical. The choice of disease-modifying anti-rheumatic drug (DMARD) or biologic response modifier ('biologic') can be influenced by the desire of the patient to start a family and must be taken into consideration, in addition to discussing the risk of the medication during preconception, pregnancy and lactation. In the case of an unplanned pregnancy while on therapy,

immediate discontinuation of the medications (if considered toxic or high risk) and referral to a high-risk obstetrician for monitoring and review of options is recommended.

With increasing ability to achieve low disease activity or remission, the desire to conceive puts up a complexity before conception, during pregnancy and postpartum stage as far as selection of DMARDs are concerned. While some medications can be safely used in pregnancy and lactation, safety profile of many others do not favor their use. Studies have well established that spontaneous improvement or stabilization of rheumatic diseases takes place during pregnancy,<sup>1,2</sup> but flares in the post-partum stage.

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Effect of pregnancy on RA was described by Dr Philip S. Hench in 1938. He observed remarkable improvement in the signs and symptoms of inflammatory arthritis (primarily RA) during pregnancy.<sup>3</sup> This observation formed the basis of the Nobel Prize-winning discovery of cortisone (substance X). Understanding of the immunological and hormonal changes of pregnancy and their influence on RA disease activity was realized in subsequent decades.<sup>4</sup>

“Pregnancy risk categories” of drugs has been established by the US Food and Drug Administration (FDA) which provides a broad guideline.

Number and function of immune cells (particularly regulatory T cells), changes in cytokine profiles and hormone levels work in conjunction to prevent maternal rejection of the developing, genetically distinct fetus during pregnancy.<sup>4</sup> This state of immune tolerance could be a key factor in understanding the improved disease activity state in rheumatic diseases.

In spite of the above logic, many pregnant women do require some therapeutic intervention during pregnancy because complete remission cannot be achieved without medication.<sup>2</sup> Rapid initiation of therapy is required in women developing a post-partum flare.<sup>2,5,6</sup> Safe use of analgesics and immunosuppressants before and during pregnancy, optimizing postpartum disease control will avoid potential risks to the neonate if breastfeeding is allowed.

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that can affect women in their reproductive years. With the expanded armamentarium of disease-modifying therapies available in the ‘biologic era’ and targeted approach to therapy, there is increasing ability to achieve adequate control of disease activity. However, the desire to start a family adds additional complexity to management decisions preconception, during pregnancy and following delivery given the lack of safety data and potential teratogenicity of available therapies. Male patients anticipating family planning often desire appropriate guidance in view of the potential effects on fertility and conception. Well-established data supporting the safe use of medications in pregnancy and lactation are available for a few medications, while for many others the safety profile is much less certain and guidance is based on the manufacturer’s recommendations. Based on the evidence available from animal and human data, the US Food and Drug Administration (FDA) has established pregnancy risk categories of drugs. This provides a broad guideline, which supports but does not take the place of open dialogue and shared decision making which is critical in discussing the risks and benefits of the treatment approach that may be unique to each individual patient. In this review, we seek to provide the rheumatologist with an overview on the safety profile of drugs used for RA preconception, during pregnancy. Preconception recommendations for men using RA medications are also discussed.

## 2. Effect of pregnancy on RA

Dr. Philip S. Hench described in 1938 a remarkable improvement in the signs and symptoms of inflammatory arthritis (primarily RA) during pregnancy,<sup>3</sup> an observation that led to the quest to find ‘substance X’ that resulted in the Nobel Prize-winning discovery of cortisone. Subsequently, the realization became clear that cortisone was not responsible for improvement. With understanding of the immunological and hormonal changes during pregnancy and its effect on rheumatic diseases,<sup>4</sup> induction of a similar immune environment in the non-pregnant state for amelioration of RA associated symptoms became the key area of research.

Most women are now known to experience a spontaneous improvement / stabilization of their rheumatic disease activity during pregnancy.<sup>1,2</sup> Invariably the disease finally flares in the post-partum stage. Changes in cytokine profiles, number and function of immune cells particularly regulatory T cells and hormone levels are responsible for prevention of maternal rejection of the developing fetus.<sup>4</sup> “State of immune tolerance” is the likely master mechanism behind the improved disease activity.

Preemptive dialogue with the patients on the safe use of analgesics and immunosuppressants before and during pregnancy and optimal disease control in the post-partum stage will avoid potential risks.

Unplanned pregnancy during DMARDs therapy should warrant immediate stoppage of high risk therapy and various options are taken into considerations.

### 2.1. Safer DMARDs in pregnancy

#### A. Hydroxychloroquine: FDA category C

Hydroxychloroquine has transplacental passage. Lower birth weight, earlier gestational age, and higher preterm delivery rates have been associated with use of hydroxychloroquine but there have been no differences in congenital abnormalities.<sup>7</sup>

Hydroxychloroquine is considered a safe option for women with mild disease and can be continued safely during a pregnancy.

#### B. Sulfasalazine: FDA category B

Sulfasalazine has transplacental passage.<sup>8</sup> Sulfasalazine has not been associated with low birth weight, congenital abnormalities, or prematurity<sup>9</sup> and risk of spontaneous abortion has been observed to be less than 3%.<sup>10</sup> It can be used safely during pregnancy. Folate supplementation should be encouraged during its use before and throughout pregnancy. It is a strong inhibitor of the reduced folate carrier.<sup>11</sup>

#### C. Azathioprine: FDA category D

With advent and introduction of newer drugs, use of azathioprine has got limited in spite of FDA approval. Prematurity, congenital abnormalities, lower gestational

age, and low birth weight in azathioprine treated mothers is likely. Occipital encephalocele, sternocleidomastoid anomalies and congenital cataract are accompanying congenital malformations<sup>9</sup> but in some studies these abnormalities are comparable with the general population.<sup>11</sup>

## 2.2. Unsafe DMARDs in pregnancy

### **Methotrexate:** Category X for pregnancy

Methotrexate is practiced as abortifacient,<sup>12</sup> and its continued use is likely responsible for spontaneous abortions in unplanned pregnancies. 'Aminopterin syndrome' characterized by abnormalities of fetal central nervous system, skeleton and heart, is invariably an outcome with use of methotrexate. Surprisingly, there are instances of no complications even after continued use of methotrexate during pregnancy, but the associated risks should never be underestimated.

Strict contraception using two different methods is essentially directed in women of childbearing age, otherwise use of methotrexate is an absolute contraindication. Its use must be stopped at least 3 months prior to the planned conception. In unplanned pregnancy, methotrexate must be discontinued instantly.

### **Leflunomide :** Category X medication for pregnancy

Leflunomide is invariably used in cases of methotrexate intolerance.<sup>13</sup> Use of leflunomide is contraindicated in childbearing age in either parent. Its long half-life leads to its presence even after complete stoppage of the drug. There are multiple associated risks during pregnancy like multiple anomalies, anencephaly, spina bifida occulta, patent ductus arteriosus, chondrodysplasia punctata, and congenital heart block.

It may take up to two years for complete elimination from the body after discontinuation.<sup>14</sup> Cholestyramine wash out procedures must be thoughtfully recommended prior to conception for elimination of leflunomide especially within two years time frame after stoppage of the drug. Cholestyramine 8 grams is given three times daily for 11 days. Plasma levels are checked twice at interval of 2 weeks. It should be below 0.02 mg/l. Additional cholestyramine may be required if the level is higher than 0.02 mg/l.<sup>15</sup> After elimination minimum three menstrual cycles is must before attempted conception.<sup>14</sup>

## 2.3. Biologic DMARDs (bDMARDs)

A. TNF $\alpha$  inhibitors - category B (Infliximab, Etanercept, Adalimumab, Certolizumab, Golimumab)

B. Rituximab

C. Anakinra

D. Abatacept

E. Tocilizumab

### 2.3.1. TNF $\alpha$ inhibitors

Rheumatic diseases refractory to methotrexate alone or in presence of poor prognostic factors are managed invariably with TNF $\alpha$  inhibitors.<sup>13</sup>

It is difficult to draw conclusions about use of TNF $\alpha$  within the first trimester or throughout pregnancy and its association with congenital anomalies.<sup>16</sup>

TNF $\alpha$  inhibitors vary in their composition. The risks either are dependent on the particular agent or the class of the drug. Infliximab and adalimumab demonstrated higher concentrations in both infant and cord blood at birth in comparison with the mother. On the other hand, certolizumab had lower concentration in infant and cord blood and is due to the absence of an Fc portion denying its bondage by the neonatal Fc receptor.<sup>17</sup> A patient who received two dosage of certolizumab during pregnancy had a full-term pregnancy with normal infant.<sup>18</sup>

### 2.3.2. Rituximab-category C

Rituximab is frequently reserved for patients who have failed to have their disease controlled by combination DMARDs or TNF $\alpha$  inhibitors.<sup>13</sup>

Rituximab is B cell depleting monoclonal antibody against CD20. It is claimed to control the disease in cases where DMARDs and or TNF $\alpha$  inhibitors have not provided good response.

Premature births, clubfoot, ventral septal defect, patent foramen ovale, patent ductus arteriosus, esophageal atresia and hematologic abnormalities are various foetal abnormalities in different series but patients receiving rituximab during their pregnancy had normal pregnancies also.<sup>19</sup>

In the light of associated foetal abnormalities, minimum 12 months after rituximab discontinuation must pass over for attempted conception.

### 2.3.3. Anakinra- category B

Anakinra, a recombinant interleukin-1 receptor antagonist, is recommended to be used in pregnancy only if ideally required. It also be used with caution due to lack of sufficient evidence.

### 2.3.4. Abatacept- category C

Abatacept binds to CD80/CD86 on antigen presenting cells. It thus inhibits T-cell activation. There is inadequate data to fully comment on the safety of abatacept during pregnancy. Though with use of this drug, there are reports of pregnancy during first trimester with full term normal infant, there are insufficient data to support its use during pregnancy.

### 2.3.5. Tocilizumab-category C

Tocilizumab is directed against interleukin-6 receptors. There has been increased risk of spontaneous abortion after its use in higher dosage. Use of this drug requires sufficient

evidence.

## 2.4. Targeted Synthetic DMARDs (tsDMARDs)

### 2.4.1. Tofacitinib-category C

Tofacitinib is known to be safe in the maximum recommended human dose but much higher dosage could have untoward effect on the foetus.

## 3. Conclusion

Women of childbearing age with rheumatic diseases require individual assessment during pregnancy for minimizing risk to the foetus. Achieving low disease activity prior to conception and maintaining it throughout pregnancy definitely provides better outcome for the mother and the child. In case of unplanned pregnancy, strategic consideration will include termination of pregnancy depending on which drugs particularly methotrexate and leflunomide were administered. Though, rheumatic diseases usually improve during pregnancy, NSAID, synthetic DMARDs, bDMARDs and tsDMARDs are various options for use in flares of the disease during pregnancy and these medicines have been categorized as safe and unsafe for pregnancy. Merits and demerits of each drug during pregnancy have been discussed emphasizing the safe use of low dose corticosteroid, sulphasalazine, hydroxychloroquine and azathioprine.

## 4. Conflict of Interest

The authors declare no potential conflict of interests.

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