



Continuing medical education

## Rheumatoid arthritis: How to use drugs during pregnancy and lactation?☆

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### ABSTRACT

Rheumatoid arthritis is a disease that is highly prevalent in women of childbearing age. A review is done about the characteristics of the placental barrier, the passage of drugs through it and the use of drugs during pregnancy: those which are potentially safe drugs, those drugs that can only be used if there is a life threatening condition for the mother, drugs that are contraindicated and those with insufficient data on safety and therefore should be avoided, the latter group comprises biological drugs. Also a review is done about the use of drugs during lactation, a period that a flare of rheumatoid arthritis can occur.

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### Artritis reumatoide: ¿cómo usar los fármacos en el embarazo y la lactancia?

#### RESUMEN

La artritis reumatoide es una enfermedad que tiene una alta prevalencia en mujeres en edad fértil. Se realiza una revisión de las características de la barrera placentaria, el paso de medicamentos a través de ella y del uso de fármacos durante el embarazo: los que son potencialmente seguros, los fármacos que sólo pueden ser usados si la vida materna se ve comprometida, los fármacos que están contraindicados y aquellos con información insuficiente sobre seguridad y que por tanto deben ser evitados, en este último grupo se ubican los fármacos biológicos. También se realiza una revisión acerca del uso de fármacos durante la lactancia, periodo en el cual es frecuente un rebrote de la artritis reumatoide.

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### Introduction

Rheumatoid arthritis (RA) is a disease that affects approximately 1% of the general population, of whom the majority of patients are women and most of reproductive<sup>1</sup> age, so the coincidence of RA and pregnancy is not an uncommon finding. The management of RA during this period is complicated, however disease activity improves substantially during pregnancy<sup>1-3</sup> and complete remission

occurs in about 16% of patients<sup>2</sup>; those with disease activity from mild to moderate at the start of pregnancy will improve in over 48% of cases.<sup>3</sup> However, 39% may suffer an arthritis outbreak during the acute postpartum,<sup>3</sup> and disease activity may be present in 10-20% of patients<sup>4</sup> at some time during the pregnancy. The outcome of pregnancy in women with well-controlled RA is comparable to the general population.<sup>1</sup>

RA has a disease pathogenesis linked more to cellular (Th1) than humoral immunity (Th2). The reduction of inflammatory activity in RA during pregnancy appears to be associated with increased Th2 activity, with increased cytokine levels, such as IL-4 and IL-10, which may be immunosuppressive in RA. Other mechanisms may be the decreased function of polymorphonuclear cells in synovial fluid by alphafetoprotein,<sup>5</sup> an increased number of TNF- $\alpha$  receptors and increased plasma levels of the IL-1 receptor antagonist.<sup>6</sup>

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**Table 1**

Classification of drugs useful in rheumatoid arthritis according to the risk / benefit during pregnancy

Risk categories	Drugs	FDA Classification
Potentially safe during pregnancy	NSAID,* steroids, azathioprine and 6-mercaptopurina, sulphasalazine, antimalarials, IV immunoglobulins, cyclosporine and tacrolimus	B, C, D
May be used if patients life is compromised	Cyclophosphamide, chlorambucil and gold salts	C, D
Insufficient information on safety, avoidance recommended	Biologic drugs	B, C
Contraindicated	Methotrexate, leflunomide and mycophenolate	D, X

FDA indicates Food and drug administration; NSAID, non steroidal anti-inflammatory drugs.

On the other hand, breastfeeding seems to favor outbreaks of RA<sup>3</sup>: Most women with RA have an outbreak of the disease during the postpartum, usually within 3 months.<sup>1</sup> The cause of this behavior is not known, but may be related to the proinflammatory effect of prolactin.<sup>7</sup>

## Pregnancy

### Placenta and placental barrier

The role of the placenta is fetal nutrition (although during the first weeks its origin is trophoblastic), gas exchange, excretion of fetal waste products and other hormonal and immunological functions.<sup>8,9</sup>

In the mature placenta, fetal blood comes through two umbilical arteries, moves through the capillaries of the villi and returns to the fetus via the umbilical vein. On the other hand, the maternal blood flow comes from the uterine arteries, enters the maternal sinus surrounding the villi and returns to her by the uterine veins.<sup>9</sup>

The placental barrier is composed of chorionic villi (fetal blood) and trophoblastic lacunae (maternal blood) and vascular systems between a layer of trophoblast cells and connective tissue, the latter far thinner as pregnancy progresses and the placenta ages.<sup>9</sup>

Placental transfer is regulated by anatomical, physiological and biochemical factors such as the barrier thickness, hydrostatic pressure, blood flow to both sides of the barrier and placental metabolism.<sup>8,10</sup>

Placental<sup>10</sup> transfer mechanisms:

1. Simple and facilitated diffusion.
2. Active transport.
3. Pinocytosis and phagocytosis.

Most drugs, such as steroids, cross the placental barrier by simple diffusion and some do by facilitated diffusion.<sup>8,10</sup>

### Classification and review of drugs used in pregnancy

The Food and Drug Administration (FDA) of the United States classifies drugs according to the risk involved in their use during pregnancy, based on animal and human studies, into 5 groups: A, B, C, D and X. In this review we will classify rheumatoid arthritis drugs for use during pregnancy in terms of risk-benefit, (Table 1).<sup>11</sup>

#### Potentially safe drugs during pregnancy (category B, C, D, FDA)

The drugs that are mentioned below can be used during pregnancy with some level of security. However, there are reports of cases that are associated with certain birth defects, and they will be discussed separately.

• Nonsteroidal anti-inflammatory drugs (NSAIDs) are safe drugs in principle, but the administration of NSAIDs during pregnancy has been associated with gastroschisis (ibuprofen),<sup>12</sup> heart malformations and cleft palate, the latter linked to the use of naproxen.<sup>13</sup> They should not be given after 32 weeks of pregnancy due to the possibility of early closure of the ductus arteriosus and pulmonary hypertension, and other malformations such as renal dysgenesis, necrotizing enterocolitis and cerebral cystic lesions with intraventricular hemorrhage<sup>14</sup> and are currently classified as FDA group D.

Recently, a possible negative effect of meloxicam on the closure of the neural tube has been published; this study has been conducted in chick embryos with supratherapeutic doses of the drug and the authors concluded that further studies with lower doses were needed.<sup>15</sup>

• Corticosteroids: the most commonly used are short-acting steroids such as prednisone, prednisolone and methylprednisolone, and fluorinated, slow acting steroids such as dexamethasone and betamethasone. The latter reach high concentrations in the fetus, and are used to accelerate fetal maturation and, if administered to pregnant women with RA, to control their disease, with betamethasone preferable; however, in patients with RA, the most commonly used are prednisone, prednisolone and methylprednisolone that, although crossing the placental barrier, do not reach large concentrations in the fetus.<sup>16</sup>

In utero exposure to fluorinated corticosteroids should be considered when evaluating postnatal steroid therapy.<sup>4</sup>

The use of corticosteroids has been associated in children with cleft palate (if used in the first quarter and especially at doses higher than 15 mg/kg body weight per day), premature rupture of membranes, intrauterine growth retardation and preterm birth and, in the mother: hypertension, gestational diabetes, infection, and osteoporosis.<sup>4,17</sup>

• Sulfasalazine: it belongs to a group of folic acid antagonists and may cause cleft palate, cardiac abnormalities (septal defects) and abnormalities of hematopoiesis.<sup>18,19</sup> The use of this drug should be accompanied by folic acid supplements.<sup>18</sup>

In males it may cause reversible infertility<sup>20</sup> and there is very little information on toxicity.

• Antimalarials: the use of hydroxychloroquine has not shown differences when compared with normal pregnant women in terms of prognosis and complications of pregnancy.<sup>21</sup> Malformations of the free edge of the ears in patients who have used chloroquine have been described.<sup>4</sup> Hydroxychloroquine is preferable to chloroquine.

• Azathioprine and 6-mercaptopurine: these drugs are not considered first-line treatment of RA; the combination of "Azathioprine" [Mesh] AND "Arthritis, Rheumatoid" [Mesh] AND "Pregnancy" [Mesh] in PubMed did not generate any items for RA patients, but in other pathological situations such as organ transplantation, Crohn's disease and patients with systemic lupus erythematosus, the use of these drugs has been linked to low birth weight, prematurity, jaundice, respiratory distress and chromosomal abnormalities.<sup>19,22</sup> The FDA classifies it as D.

• Cyclosporine: the prevalence of congenital malformations was similar to that expected in the normal pregnant population, but it has been associated with low birth weight, congenital malformations with no definite pattern, and hypertension and gestational diabetes.<sup>16,23</sup>

• Tacrolimus: the evidence of their effects has been obtained from pregnancies in patients with RA, but over all from transplant patients, and the largest series corresponds to Kainz et al (2000), who found no negative effects of this drug on pregnancy.<sup>24</sup>

• Immunoglobulins IV: cross the placental barrier from the 2<sup>nd</sup> and especially the 3<sup>rd</sup> trimester (32 weeks). A possible association with the transmission of hepatitis C and production of hemolytic anemia in the neonate<sup>16,19</sup> exists.

*Drugs that may be used if the mother life is compromised (Category C, D, FDA)*

- Cyclophosphamide: cyclophosphamide embryopathy varies according to time of pregnancy in which the drug is used and the risk of teratogenicity is greatest in the first trimester.<sup>15</sup> Embryopathy involves alterations of the cranium, craniofacial structures, ears, limbs and visceral organs, as well as growth retardation.<sup>19,25</sup>
- Chlorambucil: Exposure to this drug may cause agenesis/hypoplasia and renal defects in bone formation.<sup>16</sup>
- Gold salts: This is a currently unused drug for the treatment of RA. Fetal toxicity is unlikely. A recent study considers these drugs as a possible option for women with RA who are planning a pregnancy.<sup>26</sup>

*Contraindicated drugs (Category D, X, FDA)*

- Methotrexate: This drug is widely distributed in maternal tissues and persists in the liver for about 4 months after exposure.<sup>16</sup> The most vulnerable period for the use of methotrexate is between 5 and 8 weeks of gestation, but fetal malformations occurred after 11 weeks.<sup>4</sup> This drug is an inductor of abortion, can cause fetal growth retardation, abnormal skull ossification, hypoplastic brow ridges, low-set ears, micrognathia and limb abnormalities.<sup>4,19</sup> The probability of fetal malformations is dose-dependent.<sup>14</sup>
- Leflunomide: an active metabolite (teriflunomide) remains detectable up to 2 years.<sup>16</sup> The data on congenital malformations in humans is scarce and a recent study evaluated the effects of leflunomide in 64 pregnant women and found no significant changes suggesting an increased risk of adverse effects in pregnant women who are undergoing the process of "washout" of the active metabolite of leflunomide with cholestyramine.<sup>27</sup> This procedure is carried out after stopping the drug and consist, both in women and in men and boys, of the administration of cholestyramine 8 g 3 times daily for 11 days; alternatively one can use 50 g of powdered activated carbon 4 times a day for 11 days. Additionally, plasma levels of active metabolite of leflunomide (A771726), must be measured and a representative of the drug marketing firm must be contacted, who will provide instructions for processing and shipping of samples to the reference lab. In any case, to allow a pregnancy it is necessary to demonstrate that the metabolite concentrations are below 0.02 mg/l by performing two tests separated by 14 days.
- Mycophenolate: probably produces a characteristic phenotype, with cleft lip and palate, microtia and changes in the external ear canal,<sup>28</sup> along with other congenital malformations.<sup>19</sup>

*Drugs with inadequate safety information should be avoided (Category B, C, FDA)*

In this group we place the biologic drugs. Evidence of use of biological drugs during pregnancy is scarce and scattered and studies seldom have a control group. The FDA classified, in general, the anti-TNF as category B.

The reports of using anti-TNF therapy, especially infliximab during pregnancy suggest that when necessary and after agreement with the patient, these drugs could be used, appearing that the benefit outweighs the risk and, on the other hand, their use would not constitute sufficient condition for termination of pregnancy.<sup>29,30</sup>

- Etanercept, has been associated with a specific set of birth defects known by the mnemonic device of VACTERL: V-vertebral anomalies, anal atresia A-, C-cardiac defects (ventricular septum), TE-tracheoesophageal fistula, R-renal anomalies; L-limb abnormalities (radial dysplasia).<sup>16</sup> The evidence is not consistent with respect to

the production of these congenital malformations,<sup>31</sup> with a recent report of a pregnant woman with RA who received etanercept throughout pregnancy without complications.<sup>32</sup>

- Infliximab: the largest study involves 131 pregnant women with direct exposure. The results are similar to those expected in unexposed pregnant women.<sup>33</sup>
- Adalimumab: Some series report abortions, preterm delivery, hip dysplasia or absence of structural defects and problems during pregnancy.<sup>34</sup>
- Golimumab: No data available.
- Certolizumab: performing a PubMed search with keywords for search "MESH: certolizumab and pregnancy", a single article in a patient with Crohn's disease who used the drug during the first and third trimesters with normal offspring was found.<sup>35</sup>
- Anakinra: no human data.
- Rituximab: mothers who have used this drug reduce the concentration of B-lymphocytes in children with rapid recovery and no apparent consequences. Reports of haematological complications, preterm delivery, or severe infection are not conclusive as to his relationship with this drug.<sup>36</sup>
- Abatacept: No human studies of drug exposure.

*Management of rheumatoid arthritis before and during pregnancy*

In an ideal situation in patients with RA who plan their pregnancy there are two options (Figure): early or active disease and stable disease or in remission. In the first case we should postpone pregnancy to achieve remission or reach stable disease with drugs available, without distinction, with the exception of leflunomide. Once remission is reached, suspending the drugs incompatible with pregnancy, waiting the recommended time in case before conception (Table 2) and adjusting the drug treatment to be compatible with pregnancy.<sup>4</sup>

In case of exacerbations of the disease, treatment will depend on the type of exacerbation (Table 3): acute arthritis in one or more joints, infiltration with corticosteroids and / or NSAID pain: paracetamol at doses up to 4 g / day is safe during pregnancy, Systemic exacerbation corticosteroids (doses <15 mg / day in 1st trimester), antimalarials (preferably hydroxychloroquine), azathioprine (dose <2 mg / day), cyclosporine (monitor / control the maternal blood), sulfasalazine (folic acid supplement).<sup>4</sup>

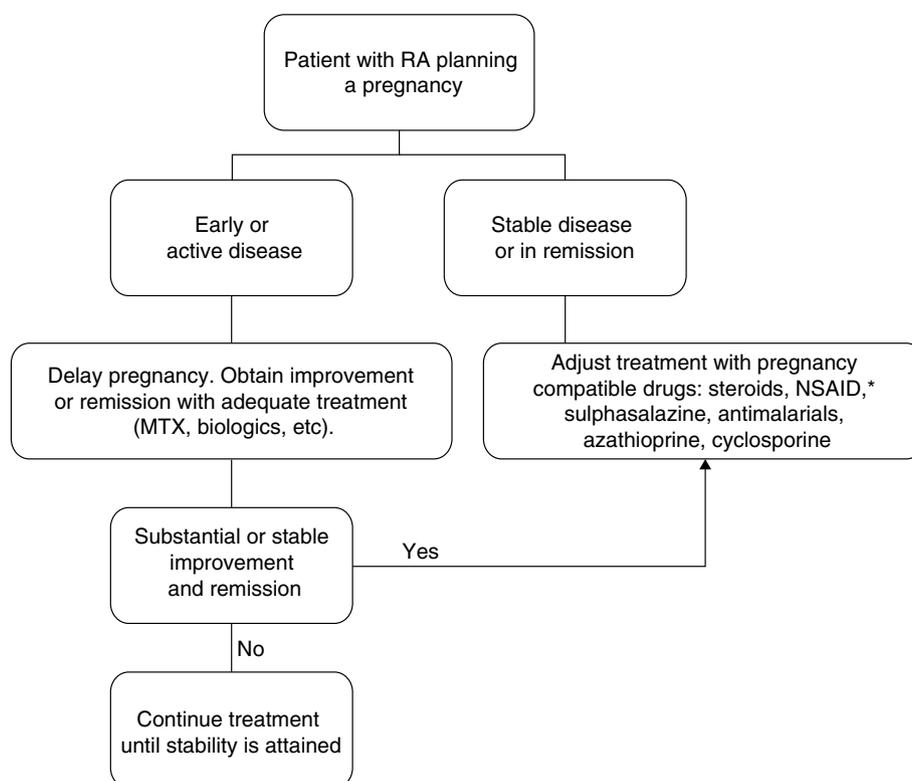
In patients with inadvertent exposure to some of the potentially harmful drugs during pregnancy, we must identify the drug in question, the dose used, gestational age at time of consumption of the drug and request an ultrasound between 11-12 weeks and 18-20 weeks to search for a pattern of expected malformations according to the drug used, as well as consider amniocentesis or chorionic villus biopsy if necessary. If these studies are normal, gross pathology is unlikely to occur in the fetus.<sup>4</sup>

**Breastfeeding**

During pregnancy, estrogen secreted by the placenta cause the breast ductal system to grow and branch out. At the same time it increases the glandular stroma and fat is deposited in it. But stimulation with prolactin is essential for lactation to occur normally.<sup>9</sup>

The passage of drugs into breast milk depends on several factors such as: binding of these to plasma proteins (negative effect), lipid solubility (positive effect), the basic character of the drug (positive effect), the moment of milk production (fasting, postprandial) and pharmacokinetics, as drugs that are poorly absorbed or have a strong first-pass metabolism are less problematic during the lactation.<sup>10</sup>

It is usually considered that the "relative dose of the drug" the child will receive should not exceed 10% of the following relationship:



**Figure 1.** Algorithm for the management of pregnancy in patients with rheumatoid arthritis. MTX indicates methotrexate; NSAID, non steroidal anti-inflammatory drugs; RA, Rheumatoid Arthritis. \*Suspend before 32 weeks.

Source: taken with permission from: Østensen and Förger.<sup>4</sup>

**Table 2**

Waiting time according to drug before conception

Drug	Recommendation
Methotrexate	Suspend 3 months before conception
Leflunomide	Suspend when planning a pregnancy and administer cholestiramine or activated carbon, after which and when active metabolite is <0.02 mg/dl: wait 1.5 months for women and 3 months for men
Abatacept	Suspend 10 weeks before conception
Rituximab	Suspend 12 months before conception
Infliximab	Suspend after first missed menstrual period or positive pregnancy test
Etanercept	Suspend after first missed menstrual period or positive pregnancy test
Adalimumab	Suspend after first missed menstrual period or positive pregnancy test

Source: taken with permission: Østensen and Förger.<sup>4</sup>

**Table 3**

Treatment of relapses

Type of relapse	Compatible drugs	Precaution
Acute arthritis in 1 or more joints	Intraarticular steroid, NSAID (diclofenac, ibuprofen, ketoprofen, naproxen)	Suspend NSAID before 32 weeks of pregnancy
Dolor	Paracetamol	1–4 g are safe during whole pregnancy
Systemic relapse	Oral steroids	Use ≤15 mg a day during the first trimester
	Antimalarials	Preferably hydroxyclozoquine
	Azathioprine	Use ≤2 mg per kg a day
	Cyclosporine	Monitor/control maternal blood pressure
	Sulphasalazine	Supplement with folic acid

NSAID indicates non-steroidal anti-inflammatory drugs.

Source: taken with permission from: Østensen and Förger.<sup>4</sup>

dose the child will receive in milk (mg) / maternal dose (mg) x 100%, to be considered safe. For example, NSAIDs have a “relative dose” of 1% and are therefore considered safe. The dose of the child in breast milk depends on the concentration of drug in milk and milk volume consumed (estimated at 0.15 l / kg daily).

Almost all drugs coming into breast milk, with the exception of insulin and low molecular weight heparins, and passage is usually by passive diffusion and use of any topical medication such as creams, nasal sprays or inhalers provide less risk to infants than drugs administered systemically.<sup>10,37</sup> The clearance of drugs in the newborn can be significantly reduced compared to adults, especially in prematures.<sup>37</sup>

NSAIDs, azathioprine, 6-mercaptopurine, sulfasalazine, antimalarials (avoid in premature infants of less than 1 month) and IV immunoglobulins are compatible with breastfeeding. Breastfeeding is not contraindicated with the use of steroids, but if the dose is greater than 40 mg daily breastfeeding should be considered 4 h after ingesting the drug. Cyclosporine, tacrolimus, cyclophosphamide, methotrexate, leflunomide, mycophenolate, chlorambucil, gold salts and biological agents are not compatible with breastfeeding.<sup>16,19</sup>

## Conclusions

Pregnancy often improves the outcome of RA, but a large portion of patients will require some treatment and some will present a relapse, so the decision of becoming pregnant in a patient with RA should be delayed until an adequate control of the disease is obtained and once the drugs have been modified for their safe use regarding the fetus. For their part, nursing is a period that favors relapses of RA and very often changes the treatment.

## Conflict of interest

The authors have no conflict of interest.

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