Coping with rheumatoid arthritis or ankylosing spondylitis during pregnancy

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Abstract

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are disorders affecting young female who eventually express their wish of getting pregnant. The physician must be prepared to answer all questions, pointing out the advantages of a planned pregnancy. The main goal achieved with the close cooperation of the obstetrician and the resident or rheumatologist, is to maintain the rheumatic illness inactive with the safest possible drugs for the mother and the unborn child. Nothing can stop a woman with RA or AS from being a mother. In general, one can say pregnancy is a period of immune tolerance, and an improvement on rheumatic conditions can even be expected.

Key words: rheumatoid arthritis, ankylosing spondylitis, drugs, pregnancy.

Introduction

Rheumatoid arthritis and ankylosing spondylitis often affect young female in fertile age. The wish of having a child is common to almost all women and those who suffer from such conditions are not an exception. Sometimes fearfully go to their doctor making simple questions for which we need to have well based answers: Can I get pregnant? How will my disease progress during pregnancy and labor? Will my disease affect my unborn child? What am I allowed to take as pain killer during pregnancy? Will I be able to breast feed?

In the last few years, new therapies have been developed and dosages adjusted for known medicines, used in both diseases, and rather effective controlling their activity. It is only normal that both the patient and the doctor feel uncomfortable leaving a therapy which has virtually silenced the disease, risking an exacerbation. Another problem is that the pregnancy may occur in a non-planned manner, while the patient takes its usual medication emerging the issue on whether to stop the pregnancy. As a matter of fact, in the USA, 50% of pregnancies are not planned and more than 50% of women only recognize that they are pregnant after the 4th week of pregnancy.[1,2]

Pregnancy immunology

Among the immune changes occurring during the pregnancy the change on the cytokines role must be mentioned, a predominance of Th2 cells (instead of Th1), an increase on the complement liver synthesis, a decrease on activity of *Natural Killer* cells, an increase on soluble TNF α receptors and an increase on antagonists for interleukin-1 receptors.[3] All these changes lead to facing pregnancy as an immune tolerance period, as the fetus is like a half-graft.[4] There is reference in literature that the level of this "tolerance" will be proportional to the disparity between the fetus and the mother HLA.[3]

Rheumatoid arthritis and pregnancy

Rheumatoid arthritis is a disorder affecting three fold more women than men, occurring often in fertile age. As this disease is more and more controlled, possible due to more effective drugs now available, enables women to be more sexually active and the wish of motherhood acquires another dimension.

The concentration decrease on free TNG and interleukin-1, occurring in pregnant women may be responsible for the improvement, sometimes for the remission even of rheumatoid arthritis.[3] There are changes at cell immunity level reducing the production of cells T-Helper, cytokines, TNF-α and IL-12. Humoral immunity is also affected during pregnancy

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reducing IgG production.[5] Around 70 to 80% of women with rheumatoid arthritis improve their symptoms related with the disease during pregnancy, a fact noticed from the first trimester onwards and kept until after the immediate post-partum.[3,6] About 90% of patients have a rheumatoid arthritis exacerbation in the post partum period, usually in the first three months, what coincides with the increase on the rheumatoid factor. There are authors advocating that breast feeding might deteriorate arthritis due to prolactin action. For this reason, many advocate that the therapy should be reintroduced just after labor balanced with the lactation benefits. Most studies do not show an increase on the fetal or maternal morbidity or abortion in rheumatoid arthritis, although a trend towards low weight children and preeclampsia can be noticed.[3] Fetal losses in patients with rheumatoid arthritis is around 17% which is similar to the 16% in the general population.[5]

In a random prospective study with 10 rheumatoid arthritis patients who got pregnant, three had a disease remission and four got better. The disorder activity got worst in six patients in a period from 6 to 12 weeks after labor.[6]

Ankylosing spondylitis and pregnancy

Ankylosing spondylitis (AS) symptoms do not change in 80% of the cases, during pregnancy. However, there is a condition worsening in 60 to 90% of patients up to six months after labor.[6] In the only known prospective study, involving nine pregnant patients with ankylosing spondylitis, the BASDAI - Bath Ankylosing Spondylitis Activity Index has shown an improvement in four of them. Morning stiffness decreased in seven from the nine patients in the third trimester.[6] 20% of pregnant patients who improve AS have other simultaneous diseases, as psoriasis, inflammatory bowel disease or small joint arthritis.

Allowed and forbidden drugs

Pain killers and anti-inflammatories

Non-steroidal anti-inflammatory (NSAIDs) drugs are allowed to control pain. Its use should be limited to five days and followed by a frequent fetal monitoring, due to the risk of oligoamnios. Its withdrawal is compulsory six to eight weeks before labor. Without this labor complications may happen, making it longer due to interference in the uterine contractions and increasing the hemorrhage being deleterious for the fetus, causing the early closure of the *ductus arteriosus*, pulmonary hypertension, oligoamnios and kidney dysgenesia.[3,1,7] According to the American Academy of Pediatrics, ibuprofen and indomethacin and naproxen are not incompatible with breastfeeding.[7] Cycle-oxygenase inhibitors 2 (Cox-2) can also be used with the same rules applied to conventional anti-inflammatory.[8]

Paracetamol is a potent pain killer also allowed to be used during pregnancy for pain management.

Prednisone and methylprednisolone cross the placenta in very low concentrations, being accepted a relative risk of 3.4 to cleft palate, being recommended the use of doses lower than 10 mg/day.[3,1] The reason for the low concentration of these corticoids in the fetus, is due to their metabolization in the placenta by the 11-hydroxigenase, resulting in the fetus being exposed only to 10% of the mother´s dose.[7] Breastfeeding is allowed.

Disease modifying antirheumatic drugs (DMARDs)

Hydroxychloroquine

According to current data, it does not have an added risk with a safe profile during pregnancy therefore, when the rheumatic disease is active, it should not be withdrawn before or during the pregnancy.[1,8,9] The existing studies did not prove either there was an eye lesion in the dose of 200 to 400 mg/day,[2,5] although higher dosages usually used in acute malaria have resulted in eyetoxicity.[9] Food and Drug Administration (FDA) has classified hydroxychloroquine as a C grade drug to be used in pregnant women as there is no proven evidence that is absolutely safe, however it should be used if the benefits are higher that any possible risk. The American Academy of Pediatrics finds hydroxychloroquine compatible with breastfeeding.

Sulphasalazine

It is considered a safe drug in all stages of pregnancy.[5] The major part of the experience accumulated on the sulphasalazine effects during pregnancy comes from patients suffering of inflammatory bowel disease (IBD), proving the absence of lesion on the mother or the fetus. One of the studies reaching such conclusion involved 400 women with ulcerative colitis.[2] Two other studies found a 2-3 fold risk of emerging

defects on the neural tubes, cardiovascular or oral fissures when there is exposure in early pregnancy reinforcing the recommendation to administer folic acid to the mother.[1] To the FDA, it is a B grade drug, without verified teratogenic effects although the risk cannot be totally ruled out.[9] The concentration reaches around 50% in the milk, from what is present in the mother and the American Academy of Pediatrics advice is to monitor breastfeeding, mainly if the mother is a slow acetylator reaching higher levels of sulphapiridine.[7]

Methotrexate

Methotrexate (MTX) is used in almost all patients with rheumatoid arthritis, and its benefit is well demonstrated, whether isolated or associated to other therapies, acting synergistically. The toxicity induced by the drug, in the trophoblastic and embrionary tissues is clearly demonstrated, being used even as an abortive in cases of ectopic pregnancy or voluntary termination.[10] FDA classifies this as X grade, i.e., human and animal studies indicate that the adverse effects well outweigh the benefits.[9]

Therefore, there is a general consensus that in a planned pregnancy, methotrexate should be suspended around 3 months after conception, due to its long half life. The biggest problem is the wanted and non planned pregnancy that occurs rather often. In all literature it can be verified that the critical period for teratogenesis is between the 8th and 10th weeks of gestation.[11,10] The abnormalities induced in the fetus are craniofacial, limbs and central nervous system, (anencephaly, hydrocephaly and meningomyelocele). On the other hand, several studies seem to prove that the teratogenic effects caused by

MTX are dose-dependent and must be higher than 10mg/week to be verified.[1] It is worth mentioning a study based on the response to a survey sent to several sites, from 1993 to 2001, including a total 28 gestations exposed to MTX (22 rheumatoid arthritis, 2 Takayasu´s arteritis, 22 psoriatic arthritis, 1 ankylosing spondylitis, 1 dermatomyositis). The outcome was of 19 newborn babies, 5 elective abortions and 4 spontaneous abortions. Only one baby has shown a *minor* abnormality (bilateral metatarsus varus and eyelid angioma).[11] This same article has associated other 15 pregnancies mentioned in literature as also having had contact with MTX, verifying the existing of one only case (2,9%) of abnormalities due to the drug (brachycephaly, neural defects, small femur). In anot*her report inclu*ding 10 pregnancies where mothers were in low dosage MTX therapy, 5 normal babies at the end of term, and 5 abortions 3 of which were miscarriages and 2 elective.[4] Therefore it is suggested that the use of MTX in low dosage be withdrawn immediately after the period absence, it does not require a therapeutic abortion.[11] It is wise for a woman who conceived while in a MTX low dosage to have a fetal ultrasound done at the 12th and 18th week. If these are normal, they should be informed of the existing literature data, in a way they can take a decision on whether to terminate the pregnancy.[12]

Leflunamide

There is a clear contraindication during pregnancy and lactation, due to its teratogenic potential to the embryo. Its very long half-life, underlies the recommendation to withdrawal 2 years before conceiving and even so, the drug *wash-out* should be made with resin altering the enterohepatic circulation (cholestyramine 8g 2x/day during 11 days and testing levels).[8,13] In 164 exposures to leflunamide, 43 pregnancies were terminated, 36 miscarriages and 85 had living newborn babies, 7 of them with birth defects.[9] FDA classifies it as X grade to be used in pregnancy, i.e., the risks clearly outweigh any benefits.[9]

Gold Salts

Nowadays it is a therapy seldom used to manage rheumatoid arthritis, however it still is an option. There aren´t many studies about its use during pregnancy, and only one reported case with cleft palate.[3] Although the risks might seem to outweigh the benefits and being accepted to carry on injectable therapy during pregnancy, when the woman has her rheumatoid arthritis well under control with this drug, although a higher monitoring during pregnancy is needed, breastfeeding must be avoided.[7] FDA classifies as a C grade, meaning that are demonstrated birth defects in animal studies, but its use in pregnant women must be pondered, if the benefits are deemed as significant.[9]

Cyclosporine

There is a significant experience gathered related with cyclosporine during pregnancy, emerging from transplanted women. In a wide study involving 410 pregnancies, women who kept therapy during pregnancy did not show a higher risk of birth defects,

prematurity or low weight, regarding the control.[1] FDA classifies as a C grade to be used in pregnant women (the risks for the fetus are not excluded but the expected benefit can outweigh them).[9,4] Breastfeeding should be discouraged.[7]

Biologic agents

Anti-TNF's

Infliximab, Etanercept and Adalimumab are approved to be used in rheumatoid arthritis and ankylosing spondylitis, and all contraindicated in pregnancy.[3] To all of them, FDA classified as a B grade, i.e., the existing data is not enough therefore the risk is undetermined. However, it is worth pointing out that there is no study or case report associating any of them to the Anti-TNF's causing embryotoxicity, teratogenicity or increase on fetal loss.[8]

Infliximab is a monoclonal antibody neutralizing TNFα activation, inducing monocytes apoptosis, what means a huge anti-inflammatory strength. Most experience of Infliximab use in pregnant women comes from women with Crohn´s disease. In two retrospective studies, one with 58 and the other with 10 pregnancies, no deleterious effect was proven either to the mother or to the normal fetus development.[1] In Katz et al. study involving 96 pregnancies with direct exposure to Infliximab, 64 newborn babies alive (67%) and 14 abortions (15%) were recorded. As far as modern knowledge goes, Infliximab must be suspended shortly after conceiving or as soon as this is known.[13]

It is referred in literature a study with Etanercept, involving 14 women, who only suspended treatment when they knew they were pregnant, without occurring any abnormality.[14]

It is described a case using Adalimumab, having as outcome a full term normal baby.[1]

Rituximab

Rituximab is a monoclonal antibody directed against CD20 antigen expressed in mature B lymphocytes. Its effect depend on the effective depletion of B lymphocytes, achieved through several mechanisms; cell immunity (activation of *natural killer* cells, complement cascade and promoting lymphocytes B CD20+ apoptosis). Already approved for the treatment of non Hodgkin lymphoma, it was recently accepted in the USA and Europe, for the treatment of rheumatoid arthritis, which is kept active after the treatment with a TNF inhibitor.[15] Current data clearly support the important role reserved to B lymphocytes in the physiopathology of rheumatoid arthritis (RA). Rituximab has already proven that remission can be induced in patients with active RA. The REFLEX study has involved 520 patients with active RA, in spite of using anti-TNF, has demonstrated the therapy benefit.[15]

It is unknown the level of safety to use Rituximab in pregnancy. I only found 3 cases reported in literature (two of non-Hodgkin lymphoma and another of autoimmune hemolytic anemia), 2 in which the drug was taken in the 1st trimester of pregnancy and 1 in the 2nd trimester.[16,17] The outcome was of all normal full term children, with significant changes in the B cells count or the immune system. However, it is known that Rituximab chimeric IgG antibody, crosses the placenta and interacts with the fetus B cells. Therefore, it is a contraindicated therapy in pregnancy, but there is no data supporting a therapeutic abortion when it was taken in the pre- or postconception period.

Immunosuppressants

Cyclophosphamide

It is a drug with an absolute contraindication for use in pregnancy, it should only be considered where there is a life threat to the mother, without an alternative therapy.[1] It leads to cranio-facial defects in the first trimester and myelotoxicity in the later stage of pregnancy. As it is present in a significant concentration in the mother´s milk, breast feeding is excluded.[7]

Azatioprine

It is a medicine which can be administered during pregnancy, in dosages lower than 2mg/Kg/day, as the fetus liver does not convert it in an active metabolite.[8] Experience comes from keeping therapy in transplanted women. Most published studies in this group of patients has shown 190 healthy babies, without any structural defect.[1] FDA classified it as a D Grade, i.e., evidence of fetal risk which can be acceptable due to the expected benefit. It should not be given during breastfeeding.

Discussion and conclusion

Pregnancy can be planned or unexpected. Rheuma-

toid arthritis patients can expect a disease activity improvement in 80% of cases occurring immediately in the first trimester. However, 90% of these experiment a disease reactivation in the immediate post-partum. On the other hand, 80% of women with ankylosing spondylitis do not have any change on the disease activity during pregnancy, but most get significantly worst within 6 months after birth.

It is important to notice that there is no medication used in these two diseases to which the FDA had classified as A, regarding its use in pregnancy, i.e., there are no appropriate well controlled studies excluding any risks to the mother and fetus, in any stage of pregnancy. Therefore, any therapy must be pondered regarding the balance between the expected benefit and the potential risk.

When the disease is active, the therapy is needed and must be chosen in the sense to obtain the best possible control and a risk minimization.

For the disease modifying agents, hydroxychloroquine and sulphasalazine are safe options. Azatioprin and cyclosporine may be used with caution and only when the expected benefits outweigh the risks. As pain killer, paracetamol in low dose is safe for the mother and the fetus as well as non-steroid anti-inflammatory drugs, if withdrawn 8 weeks before labor. It is also allowed the use of prednisone or methylprednisolone, when the inflammation is preponderant, in lower dosages than 10 mg/dia. Methotrexate and leflunamide are contraindicated and must be prophylactically withdrawn in planned pregnancy. Biological agents should be withdrawn as soon as pregnancy is known. ■

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