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Overview of Rheumatologic Disorders in Pregnancy

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ABSTRACT

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Pregnancy can lead to remission and flare in rheumatological conditions. Rheumatological diseases in quiescent phase can be managed better in pregnancy without much complication. Rheumatoid arthritis and spondyloarthropathies got remission in pregnancy, and SLE and other rheumatological conditions get worsened. Most of the treatment regimes for rheumatic diseases are modified during pregnancy for better outcome in terms of foetus and mother health.

Keywords: Rheumatology, Pregnancy, Antenatal Rheumatologic Condition, Pregnancy Complications

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INTRODUCTION

Pregnancy can be challenging to manage in patients with rheumatic diseases for a range of reasons including the impact of physiological and immunological changes of pregnancy on underlying disease activity, the varied presentation of rheumatic disease during pregnancy, and the limited treatment options.[1] Rheumatic disorder or rheumatism is a non-specific term for medical problems affecting the joints and connective tissue. For years, women with potentially serious systemic rheumatologic disorders have been advised not to get pregnant. In fact, with careful medical and obstetric management, most of these women can have successful pregnancies.[2] Only the warning note "women should not consider getting pregnant until their rheumatic disease is under control". During pregnancy, the effects of inflammation when rheumatic disease becomes active as well as the then necessary anti-inflammatory and/or immunosuppressive drugs can complicate the condition. Those diseases with the potential to affect the kidney are more likely to affect pregnancy outcome than others.

Rheumatic conditions which improve during pregnancy

1. Rheumatoid Arthritis (RA)
2. Spondyloarthropathies

Rheumatic conditions which worsen during pregnancy

1. Systemic lupus erythematosus (SLE)
2. Rheumatic fever
3. Progressive Systemic Sclerosis
4. Mechanical backache
5. Carpal Tunnel Syndrome

Rheumatoid arthritis and pregnancy

Pregnancy induces a change of the immune system in order to permit tolerance towards the semi-allogeneic foetus. This natural immunomodulation leads to amelioration of the disease in most patients with rheumatoid arthritis during pregnancy.[3] RA is less common in women of child-bearing age than in older women (0.1–0.2% vs 2–5%), but its occurrence in pregnancy is increasing as women delay child-bearing.[4] Contrary to previous studies, recent prospective studies show that only 48–66% of women with RA experience improvement in pregnancy and only 20% becoming quiescent by the third trimester.[5,6] This change may be because of new treatment regimes, as women receive more aggressive treatments and enter pregnancy with more stable disease so they have fewer margins to improve.[5,6] A recent study shows that pregnant women with RA, with positive rheumatoid factor and anti-cyclic citrullinated antibody (anti-CCP) were less likely to improve during pregnancy. However, all women had the same chance of flare up on postpartum regardless of their serological profile, and antibody levels had no relationship with activity either pre- or

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post-partum.[7] Postpartum flares usually occur within the first 4 months in most patients with chronic inflammatory arthritis.[7,8] The new-onset of RA is three to five fold more likely during this postpartum period.[6,9]

Some studies on pregnancies in women with RA suggest that pregnancy outcomes are worse than in the general population,[10,11] and some have found that hypertensive disorders, including preeclampsia, are more frequent and often results in preterm deliveries.[10] Children born to women with RA are more likely to be small for gestational age, to be born preterm and to have lower birth weight, which seems to be particularly associated with disease activity and corticosteroid treatment.[11,12] The chance of fetal deaths is high in women with RA.[12]

Drugs for RA in pregnancy

NSAIDs are usually safe drugs in pregnancy if they are used in short limited courses, but may be associated with renal and cardiac failure, hypertension and fluid overload in the mother, and oligohydramnios and renal impairment in the fetus if used for long period of time. A systematic review, evaluating the risk of NSAID use in patients with inflammatory arthritis suggests a higher rate of cardiac malformations in infants exposed to NSAID during the first trimester.[13] Their use should be stopped towards the end of pregnancy (>30–32 weeks) owing to increased risk of early closure of ductus arteriosus of the baby.[14] Short acting NSAIDs (Ibuprofen, Naproxen) are relatively safe, and there are no reliable data on the use of selective COX-2 inhibitors, and they should therefore be avoided.

Non-fluorinated corticosteroids (hydrocortisone, prednisone and methylprednisolone) are largely metabolized by placental 11β-hydroxysteroid dehydrogenase, and thus minimal amounts reach the fetal circulation (<10% of total dose).[14] The dose of prednisolone should be limited to less than 20 mg/day; higher doses are acceptable if they are required to treat aggressive disease.[15] It is recommended to give stress doses of hydrocortisone at delivery in patients on long-term therapy. Also the non-fluorinated corticosteroids are minimally excreted into breast milk (5–25%) and, hence, compatible with breastfeeding. At high doses (prednisone > 40 mg/day) consider timing breastfeeding to 4 hours after the dose.[14]

The gestational disease modifying anti rheumatoid drugs (DMARD) therapy and the pre-conceptional use of DMARD and TNF-inhibitors most probably supported the disease ameliorating effect of pregnancy in most of the RA patients and suppressed levels of anti-citrullinated protein antibodies (ACPA).[3] A decreasing effect on rheumatoid factor (RF) and ACPA has been studied in DMARD like methotrexate, sulfasalazine, antimalarials or minocycline.[16,17] Hydroxy chloroquine (HCQ) is the preferred drug due to its low rate of side effects. Its safety profile for both the mother and the baby has been widely studied, with no reported fetal neurosensory toxicity or malformations.[18,19] But chloroquine has been associated with increased risk of retinopathy in the mother and fetal ototoxicity.[20] HCQ is recommended to continue throughout and after pregnancy in RA. Post-conception use of rheumatologic doses of methotrexate (MTX) was associated with an increased risk of major birth defects and spontaneous abortion.[21]

Except, azathioprine, sulfasalazine, ciclosporin and tacrolimus the majority of the immunosuppressive drugs are contraindicated during pregnancy and breastfeeding.[14]. The use of sulfasalazine and cyclosporine should be justified and the aim should be to keep them at the lowest effective dose. In women of child-bearing age, taking pregnancy-contraindicated immunosuppressants such as methotrexate, mycophenolate mofetil, leflunomide or CYC, safe and effective contraception is necessary. If planning for pregnancy, these drugs should be switched to safer alternatives (e.g., azathioprine, sulfasalazine and tacrolimus) and conception should be postponed for at least 3 months, in order to monitor new flares or side effects from the change in drug regime.[14] Cyclosporine therapy during pregnancy should be carefully considered, may be a safe alternative for patients with autoimmune disease refractory to conventional treatment.[22] The administration of immunosuppressive drugs during pregnancy does not generally hamper the correct development of the newborn's immune system or its response to scheduled vaccinations.[23]

A meta-analysis showed that sulfasalazine is not related to teratogenic effects, but women should be advised to take high-dose folic acid (5 mg/day) from 3 months prior to conception until at least the end of the first trimester, in order to prevent neural tube defects.[24] The same folic acid dosage is recommended in women who were taking methotrexate. Leflunomide is a pyrimidine synthesis inhibitor contraindicated in women who are or may become pregnant.[25] Because of the long half-life of the active metabolite of leflunomide, it may be detectable in plasma up to two years after withdrawal of the drug. Cholestyramine 8 mg tds is recommended to enhance elimination for 10–14 days or until plasma levels of leflunomide are undetectable.[14]

Spondyloarthropathies

Spondyloarthropathy is any joint disease of the vertebral column; and spondyloarthropathy with inflammation is called spondylarthritis. In contrast, spondylopathy is a disease of the vertebra itself, but lots of conditions involve both spondylopathy and spondyloarthropathy. Although there are much lesser data than for RA, pregnancy has been shown to significantly improve peripheral arthritis (as with RA) and uveitis in most patients, but in 25% of patients with predominantly spinal disease, it deteriorates in pregnancy. It is difficult to distinguish whether this is due to inflammatory or mechanical changes in pregnancy.[26] A study showed that Improvement in pain of ankylosing spondylitis occurs predominantly in the first trimester, with significant improvement in pain than stiffness, but pain worsened in later stages of pregnancy, likely secondary to biomechanical loading.[27]

NSAIDs such as ibuprofen, naproxen, and aspirin are the most commonly used drugs for spondylitis treatment. In moderate to severe cases, other drugs may be added to the treatment regimen. DMRDs, such as methotrexate, normally used for the treatment of severe cases are not indicated in pregnancy.

Systemic lupus erythematosus (SLE)

SLE can lead to multiple medical and obstetric complications during pregnancy. A study showed that lupus patients have a 20-fold increased risk of maternal mortality and a higher rate of hypertension, renal impairment, pregestational diabetes, pulmonary hypertension, major infections, thrombotic events and other hematologic complications, compared with normal population.[28] Also the risk of preeclampsia, cesarean section, preterm labor and intrauterine growth restriction (IUGR) was two to four fold higher in women with SLE, particularly in patients with renal impairment, chronic hypertension and women on high-dose oral steroids.[28] But patients with SLE in remission without major organ involvement are likely to have a normal pregnancy outcome.

Fetal growth retardation secondary to placental insufficiency is frequent in pregnancy in lupus,[29] even in those with mild disease, with an incidence of 6–35% of small for gestational age babies.[30] About 25% of all lupus pregnancies end in preterm (<37 weeks) delivery.[31] The disease activity, hypertension and hypothyroidism have been identified as risk factors for preterm delivery in SLE.[32,33]

Compared to one in ten pregnancy loss in control population in lupus patients it is up to one in five pregnancies, with a high percentage of stillbirths (up to 4 to 6 fold). Hypertension and proteinuria (>500 mg/day) are the major cause of pregnancy loss, and also thrombocytopenia and secondary APS have been recognized as other risk factors for pregnancy loss.[30]

Women with active lupus during the 6 months prior to conception or high clinical activity in pregnancy can have worse pregnancy outcomes compared with those with low or no activity, which is often associated with corticosteroid use.[32,34] Patients with active lupus nephritis (LN) are at particularly high risk for poorer pregnancy outcome, therefore they should be advised to postpone pregnancy as a minimum 6 months (ideally 12–18 months) after the last LN flare.[35] Women with creatinine >2.5–2.8 mg/dl (GFR <35 ml/min), and on dialysis or with renal transplant present the highest complication rates.[36] Pregnant women with SLE have a 3 to 4 fold increased chance of developing preeclampsia, compared with the general population.[34] Features indicative of lupus nephritis are active urinary sediment, low or falling complement levels, high or increasing anti-dsDNA, and evidence of lupus flare involving other organs before 20 weeks of gestation.

Treatment of SLE in pregnancy

The mainstay of treatment in pregnancy is the control of disease activity and observance of major organ involvement. Antimalarials are one of the mainstays in treatments of SLE in pregnancy because of their protective properties on activity, damage, long-term survival and thrombosis.[20] HCQ is the preferred drug due to its low rate of side effects, and its safety profile for both the mother and the baby has been widely researched, with no reported fetal neurosensory toxicity or malformations.[18] But chloroquine has been associated with increased risk of retinopathy in the mother and fetal ototoxicity.[20] HCQ should be continued throughout the pregnancy and in postpartum period in lupus patients.

When treating SLE with a corticosteroid, prednisone should be used because less than 10% of the dose of these drugs crosses the placenta. If we use fluorinated corticosteroids, such as dexamethasone and betamethasone, which may easily cross the placenta can lead to foetal complications (i.e. congenital heart block or to hasten lung maturity prior to a preterm birth). Babies exposed to high dose prednisone in utero may have adrenal insufficiency at birth.[37] The dose of prednisolone should be limited to less than 20 mg/day, higher doses are acceptable if they are required to treat aggressive disease.[15]

Belimumab is a human monoclonal antibody, and the first biologic drug licensed for the treatment of SLE. Experience in pregnancy is scarce, hence the current recommendation is to withdraw it at least 4 months prior to conception.[38] Rituximab is another monoclonal antibody used in several severe case of SLE. There is heterogeneity of report for the use in pregnancy, and women should be counseled against pregnancy for 6–12 months after rituximab exposure due to the risk of neonatal B-cell depletion.[39] The current available data on infliximab-exposed pregnancies show that in women who remain on this treatment during the third trimester, cord blood levels of infliximab are 2 to 3 fold higher than in the mother's circulation.[40] Based on few cases available in the literature, certolizumab, which does not cross the placenta is considered to be safe due to the low levels detected in both cord blood and breast milk. Prophylactic calcium and vitamin D supplements should be prescribed to women on corticosteroids, heparin and/or at high risk for osteoporosis.

Mild flares during pregnancy can be treated with NSAIDs, HCQ and low-dose oral steroids. For moderate or severe disease, the use of methylprednisolone pulses or high-dose oral steroids followed by rapid reduction of oral steroids to low maintenance doses, combined with safe immunosuppressants, biologic agents and/or IVIG may be necessary. More severe cases may require a risk/benefit assessment and prioritization of the mother's welfare over fetal concerns, and therefore the use of stronger agents such as mycophenolate mofetil or CYC.

Intravenous immunoglobulin is a treatment option for SLE during pregnancy. It is studied to be relatively safe during pregnancy as the foetus is already exposed to maternal immunoglobulins during the latter half of pregnancy. Immunoglobulin can be effective therapy for moderate to severe SLE flares, and it has been shown to diminish SLE activity and promote better pregnancy outcome in a small cohort of 12 patients with SLE.[41]

Scleroderma

Once scleroderma was considered a strict contraindication for pregnancy, with careful timing of pregnancy and close monitoring, successful pregnancies outcome can be achieved for this.[42] It was found that the live birth rate was 84% for women with limited scleroderma, 77% for women with diffuse scleroderma, and 84% in a historical control group.[43] An increased risk for premature births and low birth weight (<2500gm at term) has been reported.[44,45]

Raynaud's phenomenon may improve with pregnancy, which is secondary to a physiological increase in cardiac output, while gastroesophageal reflux disease (GERD) worsens, especially during the later part of pregnancy. Renal complication of scleroderma in pregnancy is the worst complication to anticipate. Renal crisis can be managed by using angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, and considered as life-saving treatments for scleroderma renal crisis, but carry significant risk for foetal anomalies.[46] Most of the complications occur late in pregnancy and include renal atresia, pulmonary hypoplasia, and foetal death.[47] Renal crisis during previous pregnancy is not a strict contraindication for future pregnancy, but it is recommended that a woman wait several years until her disease is stable before trying to conceive.

Vasculitis in pregnancy

Pregnancy in women with vasculitis in remission are in low risk of complications, and therefore, pregnancy should ideally be planned after a period of quiescent disease. Disease flare ups can happen at any stage of pregnancy and postpartum.

C-reactive protein level is the reliable marker of disease activity during pregnancy, and not the erythrocyte sedimentation rate (ESR).[48] It is essential to exclude infection for the correct management of Vasculitis, because both Vasculitis and infection mimic each other.[49] Among all forms of systemic vasculitis, Takayasu's arteritis need special attention as it is a disease characteristically diagnosed in women of child-bearing age. Hypertension and preeclampsia are the most serious complications in pregnant women with Takayasu's disease, and they can affect the mother and the child.[50] Maternal blood pressure should be controlled very accurately on the two superior limbs. Patients with stenosis of aorta and/or its principal branches need comprehensive cardiovascular assessment together with antenatal review to plan for the best mode of delivery and anesthesia.[49]

Vasculitis flare may also mimic preeclampsia, but active urinary sediment and other systemic clinical manifestations usually point towards vasculitis, whereas isolated proteinuria with presence of other features such as hypertension, headache, epigastric pain and edema may indicate the preeclampsia.

Treatment of vasculitis in pregnancy

Steroids and azathioprine are the mainstay of treatment for vascultis in pregnancy. A low-dose of prednisone (<7.5–10 mg) and azathioprine are maintenance

treatment during pregnancy. However, in life threatening situation like severe fare ups, Cyclophosphamide (CYC) should be considered as the drug of choice. But azathioprine is contraindicated during the first and early second trimesters, intravenous immunoglobulins (IVIG) can be a useful option to control the disease until CYC can be used.[49]

END NOTE

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