REVIEW
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Review of Pregnancy and Fertility issues in women with Rheumatic Diseases

R Kalpee
Department of Internal Medicine, University of Pretoria, Pretoria, South Africa

Introduction

Rheumatic diseases occur more commonly in women and often during child bearing age. SLE is 10-15 times more common in women than in men.[1] Most SLE patients present with their disease between 15 and 64 years age.[2] Most women with rheumatic diseases wish to have children even with functional disability present.

When evaluating a patient with a rheumatic disease and pregnancy there are three considerations that the attending practitioner should have:

1. What is the effect of the rheumatic disease on the pregnancy and pregnancy outcome?
2. What is the effect of the pregnancy/post partum phase on the rheumatic disease?
3. Is the drug therapy (disease modifying anti rheumatic drugs, DMARD) safe in pregnancy?[3]

In this review the focus will be on immunology of pregnancy and auto immune disease, fertility, pregnancy in the more common and relevant rheumatic diseases and safety of disease modifying anti rheumatic drugs.

Immunology

T cells are key players in the immune response with various T cell subsets directing the immune reaction according to physiological and pathological stressors. Pregnancy has long been understood as a Th2-predominant condition. This theory was consistent with earlier observations that SLE (a predominantly Th2 disease) may be exacerbated in pregnancy and Th1 mediated autoimmune disease (Rheumatoid arthritis) appear to clinically improve during pregnancy.[4] The Th2 committed cells mainly produce Interleukin 4(IL4), interleukin 10(IL10) and interleukin 13(IL13). IL10 down- regulates pro-inflammatory cytokines.[5] Most studies however have shown no distinct predominance of Th2 cytokine secretion pattern during pregnancy, but rather an up regulation of several cytokines at different stages of pregnancy. Cytokine expression at the foetal-maternal interface is regulated according to the stage of pregnancy to create optimal conditions for foetal development.[6] IFNy and TNF alpha are necessary during the early stages of pregnancy to support successful implantation and placenta development but may be detrimental at later stages of pregnancy. At term the human placenta expresses high mRNA levels of IL10.[7]

Apart from the Th1 and Th2 cells a third subset of CD 4+ T helper cells, Th17 cells also activates the immune system. The important cytokine in this subset is IL 17, which is proinflammatory. Th17 cells are typically found at sites of inflammation and in the circulation in Rheumatoid Arthritis, SLE and Anklyosing Spondylitis. This subset of cells is also found in pregnancy pathology like pre eclampsia and recurrent pregnancy loss.[8]

Balancing the proinflammatory cytokine milieu is the CD4 subset of T regulatory (Treg) cells that produces anti inflammatory cytokines (IL10 and TGF-beta). Maternal Treg cells suppress an aggressive allogenic response directed against the foetus. Their absence could impair the continuation of pregnancy by resulting in immune rejection of the foetus.[9] T reg cells suppress the potential action of auto reactive cells, preventing auto immunity.[10] In patients with SLE, Treg cells are reduced in number and are dysfunctional. This predisposes women with SLE to pregnancy complications.[11]

A prospective study comparing RA pregnant women with healthy pregnant women found an expansion of CD4+CD25 Treg cells during the pregnancy and a reduction post partum in both groups. The number of Treg cells inversely correlated with disease activity of RA in the third trimester and post partum. In this study higher levels of IL10 were measured in the third trimester compared with undetectable levels of IL10 post partum. This finding was found irrespective of the health status.[12] Hence multiple studies have shown that the post partum period is susceptible to flares of rheumatoid arthritis.[13,14]

Fertility

Women with rheumatic disease have fewer children than age matched controls from the general population.[15] Fertility problems in women with rheumatic disease occur not only in diseases with extensive systemic inflammation and autoantibody production but also in patients with

Correspondence
R Kalpee
Department of Internal Medicine, University of Pretoria,
PO Box 667, Pretoria, 0001

predominantly inflammatory joint disease.[16] These women also have a prolonged time to pregnancy compared to women in the general population and often require assisted reproduction.[17]

The aetiology of reproductive failure in women with rheumatic diseases is multifactorial. It can be related in several auto immune diseases to immunological pathophysiology.[18] Apart from innate immunity, several auto-antibodies have been associated with impaired fertility.[19] Interestingly the presence of anti-phospholipid antibodies (lupus anticoagulant, anti cardiolipin and anti-beta 2 glycoprotein I) not only reported to be associated with recurrent pregnancy loss but also possibly involved in infertility.[20] There is currently no evidence to routinely investigate for or treat antiphopholipid antibodies in patients with infertility.

The use of cytotoxic therapy especially cyclophosphamide is associated with premature ovarian insufficiency. Ovarian failure is dependent on the cumulative dose and age of the patient. Women less than 20 years of age have a 13% risk, ages 20-30 years a 50% risk and over the age of 30 years a 100% risk of premature ovarian failure. The risk is greater with 15 monthly pulses (50% risk with 8g/m and 90% with 12g/m total dose). It is rare in patients who have received the Euro-Lupus protocol (500mg IV every 2 weeks, 6 doses).[21,22] The use of gonadotropin-releasing hormone may be protective.

In patients receiving assisted reproductive therapy, the most threatening adverse event is thrombosis in women undergoing ovarian stimulation. This risk can be reduced by using stimulation protocols with GnRH antagonists and agonists.[23] The risk of lupus exacerbation has been associated with ovarian hyperstimulation and high oestrogen levels. There are no prospective studies evaluating this. The risk of a flare appears to be low in well controlled disease and higher in active disease.[24]

Anti-Mullerian hormone (AMH) may be a useful measure of ovarian reserve in patients with SLE. In a Chinese cohort low AMH levels were found in patients exposed to cyclophosphamide.[25] However in another study, despite AMH levels being low in patients with SLE and lower in patients who received cyclophosphamide, the risk of failure to conceive was associated with the cumulative dose of cyclophosphamide and older age and not with AMH levels.[26]

In patients with Rheumatoid arthritis, the use of NSAIDs is possibly associated with infertility. NSAIDs inhibit the COX system and prostaglandin production. This affects fertility by preventing ovulation and hindering implantation.[27]

SLE and pregnancy including neonatal lupus syndromes

Pregnancies in patients with SLE are considered to be high risk .The adverse pregnancy outcomes in SLE include spontaneous abortion, intrauterine fetal death, intrauterine growth restriction (IUGR), premature birth, premature rupture of membranes, neonatal lupus and perinatal mortality. Maternal complications in SLE include increased SLE activity (flares), pulmonary emboli and arterial hypertension, especially in patients with renal involvement.[28]

Predictors of poor pregnancy outcomes in SLE

The PROMISSE study is the largest (385 patients) multicentre, multi-ethnic, multiracial prospective study assessing the frequency of adverse pregnancy outcomes in patients with lupus. This study however excluded patients with a urinary protein-creatinine ratio greater than 1000mg/g, creatinine level greater than 1.2 mg/dl, prednisone use greater than 20mg/d and multifoetal pregnancy. The predictors of adverse pregnancy outcomes found in this study were: the presence of lupus anticoagulant, antihypertensive use, physician global assessment of greater than 1 and a low platelet count. Non Hispanic white race was found to be protective. Maternal flares, higher disease activity and smaller increases in C3 levels later in pregnancy also predicted adverse pregnancy outcomes. Severe flares were infrequent in patients with inactive or stable disease and in the absence of risk factors; outcomes were favourable.[29]

The PROMISSE study suggested that patients with a history of lupus nephritis had an increased risk for adverse pregnancy outcomes, however this association was not significant in multivariate analyses and patients with significant renal involvement were excluded from the study.[29] Interestingly, a retrospective study found higher frequencies of preterm delivery and preeclampsia in women with prior lupus nephritis.[30] This reaffirms findings of earlier studies. Chronic renal insufficiency is associated with higher rates of foetal loss and foetal growth restriction.[31] Of note is that quiescent disease at conception in patients with prior lupus nephritis is a predictor of favourable pregnancy outcomes.[32]

In fact the risk of flares (especially renal) and the risk of maternal and foetal complications depend on lupus activity before conception and on whether kidney damage has occurred.[33] The disease should be in remission for 6months before conception for a favourable outcome.[34]

Predicting the risk of a flare may be possible using serology and complement levels. A retrospective study evaluating 267 pregnancies in SLE, found that adverse pregnancy outcomes was associated with positive anti-dsDNA abs and low complement in the second trimester.[35] Interestingly the PROMISSE study found no association with anti-ds DNA and adverse pregnancy outcome.[29]

Discerning preeclampsia from lupus nephritis

Both conditions can co exist. Differentiating pre eclampsia from lupus nephritis has obvious management implications Often the diagnosis of lupus nephritis is seen in the presence of lupus disease activity elsewhere. However lupus nephritis can occur as the sole organ activity.

In the absence of a renal biopsy proving lupus nephritis, falling levels of C3 and/or C4 and the presence of urinary red blood cell casts is more consistent with a diagnosis of lupus nephritis.

Incidentally C3 and C4 rise during normal pregnancy and pre-eclampsia, because they are part of the acute phase reaction.[36]

Neonatal Lupus syndrome

Neonatal Lupus Syndrome is related to the presence of anti-SSA/Ro and anti- SSB/La antibodies in mothers with different rheumatic diseases (Sjogrens syndrome, SLE or rarely RA) but it also occurs in mothers without any connective tissue disease.[37]

Prospective studies of pregnancies in women with these antibodies and no previously affected children have an estimated risk of cardiac neonatal lupus at approximately 2%. The risk of recurrent cases of cardiac neonatal lupus in mothers with a previously affected child is 17%.[38]

Antibodies reactive with Ro and/or La ribonucleoproteins cross the placenta, enter the fetal circulation via trophoblast Fc Rn receptors, and injure the fetus, most often during the 16–24th gestational weeks.[39]

The most common manifestations include transient rashes, thrombocytopenia, haemolytic anaemia and permanent congenital heart block (CHB). A rash is present in 15-20% of patients.[40]

The clinical impact of autoantibody-associated congenital heart block (CHB) is significant. More than 80%of cases of CHB are detected before 30 weeks gestation, with a peak incidence at 20 to 24 weeks. There is a 15% mortality rate before 3 months of age, and an 80% cumulative probability of survival at 3 years. More than 65% of surviving newborns require pacemakers.[41]

Late onset cardiomyopathy has been described in children from mothers with ant-SSA antibodies despite early pacing.[42] Follow up of these patients is crucial. Interestingly cardiomyopathy could be the sequelae of endocardial fibroelastosis, another manifestation cardiac toxicity of these antibodies. This is seen on fetal echocardiography as hyper-echogenic heart areas.[43]

There are two concerns in the management of congenital heart block, the first is how can one detect the condition early and the other is what intervention can potentially reverse this?

Monitoring by fetal ultrasound in women with anti-SSA antibodies is recommended: weekly from 16-26 weeks and thereafter 2 weekly has been suggested by Lateef et al.[44] and Friedman et al.[37] Furthermore measuring the mechanical PR interval on fetal ultrasound is recommended in these patients.[37]

To date, no pharmacological therapy has resulted in permanent reversal of third degree congenital heart block in neonatal lupus. However, the maternal use of fluorinated steroids during pregnancy has shown some efficacy in treating second degree heart block and cardiac disease beyond the atrioventricular node, and β-agonists have been used to increase fetal heart rates in utero. Intravenous immunoglobulin (IVIG) has been studied for prevention of disease, and has been used in treatment of associated cardiomyopathy. Hydroxychloroquine (HCQ) is currently being studied as a potentially promising approach to prevention of cardiac neonatal lupus.[45]

Fluorinated steroids such as dexamethasone or betamethasone cross the placenta during pregnancy, while non-fluorinated steroids (such as prednisone) are inactivated by placental 11 β-dehydrogenase-type 2 expressed in syncytial trophoblast cells, which cover placental chorionic villi and form an interface between the foetal and maternal circulation.[46] The value of the treatment is controversial.

Earlier studies showed some benefit. Data from the PRIDE Study confirmed the irreversibility of 3rd degree block and progression of 2nd to 3rd degree despite dexamethasone. A potential benefit of dexamethasone in reversing 1st or 2nd degree was supported in rare cases, but should be weighed against potential steroid side effects such as growth restriction.[47] Another more recent study found no benefit; the use of fluorinated steroids at detection of isolated heart block did not prevent development of extra nodal disease, improve survival or prevent pacemaker insertion.[48]

In an Italian study of 28 cardiac neonatal lupus cases, treatment with dexamethasone produced a rapid improvement in the degree of fetal hydrops in 3 of 5 cases, and several case reports have also documented efficacy of fluorinated steroids for treating hydrops.[49]

Plasma exchange in women at risk for having a child with cardiac neonatal lupus may theoretically lower the levels of the pathogenic anti- Ro and La antibodies required for disease development. However, this treatment has never been used independent of steroids and only case report has been published.[45]

IVIG use has also shown minimal benefit at doses of 400mg/kg. IVIG at doses consistent with replacement does not prevent the recurrence of CHB or reduce maternal antibody titres.[50] It is not certain if higher doses may be more efficacious.

IVIG has shown promise in the treatment of fetal cardiac disease specifically when associated with cardiomyopathy. Brucato et al. treated two fetuses with complete heart block and severe myocarditis with IVIG 400 mg/kg/d for five days with prompt resolution of the echocardiographic signs of myocarditis and corresponding clinical improvement.[51]

Triple therapy combining plasmapheresis, IVIG and glucocorticoids may stop the natural evolution of the fetal cardiac involvement in positive anti-Ro/SS-A antibody patients. This was shown in a small case series but further studies are necessary to validate this.[52]

The use of hydroxychloroquine (HCQ) has shown promising results in preventing congenital heart block in patients with anti-SSA/Ro ab. In an international cohort of 257 pregnancies in mothers with a previous child with cardiac neonatal lupus; recurrence rate of cardiac neonatal lupus in fetuses exposed to HCQ was 7.5% (3/40) compared to 21.2% (46/217) in the unexposed group.[53] We await the results of the PATCH study (The Preventive Approach to Congenital Heart Block with hydroxychloroquine) to support this.

Antiphospholipid syndrome (APLS) and pregnancy

APLS is frequently diagnosed following investigation for recurrent miscarriages, pregnancy morbidity being one of the major manifestations of the syndrome. In pregnancies that do not end in miscarriage or fetal loss, there is a high incidence of early onset pre-eclampsia, IUGR, placental abruption and premature delivery.[54]

The presence of lupus anticoagulant is a predictor of adverse pregnancy outcomes in lupus and in APLS.[29,54] In general, women testing positive for APS antibodies but negative for lupus anticoagulant did well, regardless of treatment. However, women with lupus anticoagulant did poorly, regardless of treatment.[55] Furthermore, women who have had thrombotic complications have poorer outcomes than those with only obstetric complications.[56]

Management of APLS in pregnancy

Women with previous thrombosis require LMWH prophylaxis in pregnancy. LMWH has also been shown to improve outcomes in those with previous placenta mediated adverse outcomes such as severe early-onset pre-eclampsia with growth restriction.[57] However, the use of LMWH to prevent recurrent early pregnancy loss is controversial, with large randomized trials in the general population not demonstrating improved outcome.[58] Low dose aspirin (75-100 mg/day) is often prescribed to reduce the risk of miscarriage and pre-eclampsia.

According to the 14th International Congress on Antiphospholipid Antibodies Task Force Report; on Obstetric Antiphospholipid Syndrome; the treatment of obstetric events related to APLS is not supported by consistent findings from well-designed studies. More scientific studies are needed.[59]

Rheumatoid Arthritis (RA)

The effect of pregnancy on disease activity in women with RA

Retrospective studies between 1940 and 1980, comprising a total of 345 pregnancies, indicated that about 75% (range 54–86%) of patients experienced improvement of symptoms and signs of RA during pregnancy.[60] However more recent population based studies have shown that this remission may be overestimated and that only a quarter of patients remained in remission throughout the pregnancy.[61] Interestingly, patients negative for both rheumatoid factor (RF) and cyclic citrullinated autoantibodies (CCP) were more likely to improve during pregnancy.[62]

Effect of RA on pregnancy outcome

Patients with severe RA are at greater risk of preterm delivery and SGA neonates.[63] This was found to be worse in patients with high disease activity.

Maternal disease activity postpartum

According to retrospective and prospective studies, most patients had recurrent disease within 3–4 months of delivery.[6] This flare is irrespective of the presence or absence of antibodies.[62]

Scleroderma

Pulmonary hypertension occurs in 8-12% of patients with scleroderma and is the most frequent cause of death. In pregnant women, the mortality associated with pulmonary hypertension ranges from 17-33%. Women with proven pulmonary hypertension on transthoracic echo or cardiac catherisation should be strongly advised against pregnancy.[64]

Scleroderma renal crises are rare but may complicate the third trimester when rising blood pressure and proteinuria are often mistaken for pre-eclampsia. Diagnosis may be confirmed histologically on renal biopsy. Patients with progressive rapid skin involvement are at risk.[65] In these exceptional circumstances, a trial of an angiotensin-converting enzyme (ACE) inhibitor (usually contraindicated in pregnancy) is indicated.[66]

Management of rheumatic diseases in pregnancy

Safety of Disease modifying anti rheumatic drugs (DMARDs) in Pregnancy

The European League against Rheumatism (EULAR) recently established a taskforce to define points to consider on use of antirheumatic drugs before pregnancy, and during pregnancy and lactation.[67]

According to this taskforce compatibility with pregnancy and lactation was found for antimalarials, sulfasalazine, azathioprine, ciclosporin, tacrolimus, colchicine, intravenous immunoglobulin and glucocorticoids.

Methotrexate, mycophenolate mofetil and cyclophosphamide require discontinuation before conception due to proven teratogenicity. Insufficient documentation with regard to foetal safety implies the discontinuation of leflunomide, tofacitinib, abatacept, rituximab, belimumab, tocilizumab, ustekinumab and anakinra before a planned pregnancy.

Of the biologic DMARDs, Certolizumab and Etanercept (both TNF inhibitors) may be considered due to the minimal trasplacental passage of the drug.[67]

Specific Management issues

SLE

Corticosteroids

In the management of lupus flares in pregnancy the use of non-fluorinated corticosteroids is safe. Prednisone is largely metabolized by the placenta, with minimal foetal exposure. However, doses of prednisone greater than or equal to 20 mg increases the risk of both pre-eclampsia and gestational diabetes in lupus pregnancies. Thus, the dose of prednisone should be below 20mg.[36]

In moderate to severe SLE flares in pregnancy intravenous methylprednisolone, 1000 mg daily for three days may control the SLE flare, avoiding the need for a high daily maintenance dose.[36] This may be used in conjunction with IVIG for severe flares.[67]

Hydroxychloroquine

Hydroxychloroquine should be continued during pregnancy, because cessation of hydroxychloroquine leads to increased disease activity, lupus flares, and preterm birth.[68] A recent publication confirmed this. Furthermore the use of hydroxychloroquine may also be beneficial in preventing congenital heart block in neonatal lupus.[52] We extrapolate from this data that chloroquine has the same benefit because of the similar mechanism of action. However the retinal toxicity is higher with chloroquine and patients should be screened for this.[3]

Azathioprine
Azathioprine has a long track record of use in pregnancy, with an acceptable safety profile. A recent study confirmed this.[69] In patients with lupus nephritis planning a pregnancy, mycophenolate mofetil should be changed to azathioprine as maintenance therapy.[36]

Cyclosporine
Cyclosporine may be used in combination with azathioprine, for lupus nephritis activity in pregnancy.

Management of Rheumatoid Arthritis
As recommended by EULAR, the management of a flare of RA during pregnancy can be safely done with hydroxychloroquine, sulfasalazine and prednisone.[67] NSAIDs should be avoided during the second and third trimesters because of their effect on the ductus arteriosus.[36]

Methotrexate should be stopped 3 months before conception and a safer DMARD choice instituted when planning a pregnancy.[67] The use of biologic DMARDs should be reserved for refractory cases and under a rheumatologist's supervision.

Conclusion
In both rheumatoid arthritis and SLE, conception at a time of disease remission allows for better pregnancy and maternal outcomes. Therefore, pregnancy planning is crucial.

Managing a pregnant woman with rheumatic disease should be by a multidisciplinary team, involving a rheumatologist, obstetrician/gynaecologist.

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