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Connective tissue disease in pregnancy

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ABSTRACT – Connective tissue diseases (CTD) include a variety of chronic multisystem disorders with a high percentage of autoimmune conditions. Many of these conditions affect women of childbearing age and, therefore, pregnancy poses an important challenge for doctors looking after such women. Knowledge of medication safety, the effect of pregnancy on such diseases and vice versa, together with preconception counselling and multidisciplinary team care, are the basic pillars needed to provide the best obstetric and medical care to these women. In this review, we discuss the management of the most common autoimmune CTD before, during and after pregnancy, along with the most relevant issues regarding appropriate medication.

KEY WORDS: Pregnancy, connective tissue disease, management, pre-pregnancy counselling, medications

Introduction

The changes in hormonal profiles found in pregnancy induce important immunomodulatory changes, with direct consequences on immune-mediated connective tissue diseases (CTD). Fertility in women with CTD is generally not affected, although patients with chronic kidney disease (CKD stage 3–5, with an estimated glomerular filtration rate (eEGR) of <50 ml/min), amenorrhoea because of previous high cumulative doses of cyclophosphamide and/or active disease might have reduced fertility.[1] Therefore, knowledge of the management of CTD in pregnancy is important for doctors looking after women of childbearing age with CTD.

Women who are keen to undergo assisted reproductive techniques should be counselled about the increased risk of disease flare (particularly women with systemic lupus erythematosus (SLE) and thromboembolic events. Identification of high-risk patients (Box 1), pre-cycle counselling, and adequate thromboprophylaxis, plan of management and surveillance are mandatory.[2]

Box 1. Relative contraindications to pregnancy.

- Severe connective tissue disease flare or stroke over the past 6 months
- Pulmonary hypertension
- Moderate to severe heart failure (left ventricular ejection fraction <40%)
- Severe restrictive lung disease (forced vital capacity <1 l)
- Chronic kidney disease stage 4–5 (estimated glomerular filtration rate <30 ml/min)
- Uncontrolled hypertension
- Previous severe early-onset (<28 weeks) pre-eclampsia despite therapy with aspirin plus heparin

Systemic lupus erythematosus

Effect of pregnancy on SLE

SLE flares during pregnancy have been related to irreversible organ damage.[3] However, whether pregnancy increases the risk of lupus flare is still unresolved,[4] although the puerperium might be a period of particular high risk. The risk of flare appears to be dependent on the disease activity 6–12 months before conception, because women with quiescent lupus over this period have less risk of flare during pregnancy, and vice versa.[5] Active lupus nephritis (LN) at conception, and even in remission, confers a higher risk of flare during pregnancy[6]. Pregnancy does not seem to endanger long-term renal function, although, generally, the higher the baseline creatinine, the greater the risk of deterioration.[6] Lupus flares during pregnancy and postpartum are usually non-severe (ie articular, dermatological and mild haematological), although severe flares with major organ involvement can occur. Given the multiple protective effects of hydroxychloroquine (HCQ),[7] all women should be encouraged to continue to take HCQ throughout pregnancy and postpartum.

Distinguishing pregnancy-related signs and symptoms from certain lupus features can sometimes be difficult (Table 1). In pregnancy, erythrocyte sedimentation rate (ESR) and serum C3 and C4 levels usually increase; therefore, they are not considered valid markers of disease activity, but relative variation rather than absolute levels might be helpful. In patients with permanent proteinuria, this can increase throughout pregnancy because of increased renal blood flow, without indicating active nephritis.[8] Up to a doubling of proteinuria from the baseline level in early pregnancy is to be expected.

Effect of SLE on pregnancy

Patients with SLE are at high risk of multiple medical (a two- to fourfold increased risk of pre-eclampsia and thrombosis compared with the general population) and obstetric complications (preterm delivery 25%; fetal growth restriction 6–35%; and a two- to sixfold risk of fetal loss compared with controls) during pregnancy, particularly in those with chronic hypertension, renal impairment and women taking high-dose oral steroids.[4] Conversely, patients with cutaneous lupus erythematosus only, or those with SLE in remission without major organ involvement, appear to have pregnancy outcomes comparable to those of the healthy population.

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Disease activity 6 months before conception, hypertension, CKD, non-reversible organ damage, hypocomplementaemia and secondary antiphospholipid syndrome (APS) have also been recognised as risk factors for poor pregnancy outcomes.[5]

Rheumatoid arthritis and other chronic inflammatory arthritides

In total, 48–66% of women with rheumatoid arthritis (RA) experience improvement in pregnancy, with approximately 20% becoming quiescent by the third trimester.[9] However, women with positive rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) appear to be less likely to improve during pregnancy.[10] Most women with psoriatic arthritis (PsA) generally improve or even remit during pregnancy, whereas the symptoms of most women with ankylosing spondylitis (AS) remain unaltered or worsen during pregnancy.[11]

Post-partum flares occur within the first 4 months in most patients with chronic inflammatory arthritides.[10] Hypertensive disorders might be more frequent in women with RA and are often related to preterm deliveries and growth-restricted babies.[12]

Systemic sclerosis

Pregnancy does not seem to affect disease activity in most (63–72%) women with systemic sclerosis (SSc). One-third will either experience an improvement or worsening of symptoms during pregnancy. SSc can be associated with an increased risk of developing hypertensive disorders in pregnancy, including pre-eclampsia.[13]

Clinically, symptoms of Raynaud's phenomenon generally improve because of the physiological vasodilation of pregnancy, whereas gastrooesophageal reflux disease symptoms worsen. Skin involvement usually remains stable or improves, but can worsen postpartum. Recent onset of scleroderma symptoms (<4 years), diffuse cutaneous involvement, or anti-Scl-70 (anti-topoisomerase-I) or anti-RNA-polymerase-III antibodies are associated with increased risk of active and aggressive disease compared with those women with longstanding SSc or with anti-centromere antibodies.[13]

Renal crises do not occur more frequently in pregnancy. In the unlikely even of a renal crisis, management must be with angiotensin-converting enzyme inhibitors (ACEI) despite the risks to the baby, because it is lifesaving treatment for the mother[13].

SSc is associated with increased risk of preterm delivery (14–29%), intrauterine growth restriction, longer hospitalisation and, in women with long-standing diffuse scleroderma, miscarriage. Women with limited scleroderma generally have better pregnancy outcomes compared with those with diffuse disease. Corticosteroids for fetal lung maturation should not be given because they can precipitate a renal crisis.[13]

Antiphospholipid antibodies and antiphospholipid syndrome

Antiphospholipid antibodies (aPL) are found not only in patients with SLE (30–40%), but also in patients with other CTDs, and in the general population (1–5%), and represent one of the major risk factors for poor obstetric outcome.[14] Women with lupus anticoagulant (LA) and those with thrombotic antiphospholipid syndrome (APS) have the worst obstetric outcomes.[15] A detailed discussion of APS in pregnancy is outside the remit of this review and readers are directed to a recent review on this topic.[14]

Neonatal lupus syndrome

Anti-Ro and/or anti-La antibodies can be found in patients with SLE, Sjögren's syndrome, RA, SSc and healthy asymptomatic carriers. These antibodies cross the placenta by active transport between the 16th and 30th weeks of gestation, and can cause several clinical syndromes in the fetus and neonate, known as Neonatal lupus syndrome (NNLS).[16]

Cutaneous neonatal lupus is the most common manifestation, and the risk of an affected child among anti-Ro and/or -La-positive mothers is approximately 5%. It generally presents within the first 2 weeks of life as erythematous geographical lesions in light-exposed areas that resemble those seen in subacute cutaneous lupus. The rash usually disappears within 3–6 months without residual scarring.[16]

Congenital heart block (CHB) is the most severe form of NNLS and affects approximately 2% of babies born to anti-Ro and/or -La-positive mothers. This risk increases to 18% if the mother has already had a child affected by CHB, and up to 50% if she has had two affected children.[16] CHB normally develops at 16–24 weeks of gestation. The risk of perinatal death among affected children is 10–20%, and most surviving children need a permanent pacemaker.[17] Current recommendations include serial fetal echocardiograms between 16 and 30 weeks for pregnant women with these antibodies.[16] In humans, neither steroid nor intravenous immunoglobulin (IVIG) treatment have been shown to reverse CHB once established. However, in mothers with SLE with anti-Ro and or -La antibodies, exposure to HCQ during pregnancy might decrease the risk of fetal CHB.[18]

Vasculitis

Overall, it appears that, if women embark on pregnancy with vasculitis in remission, their risk of complications is low. Unlike

Table 1. Differences between pre-eclampsia and lupus nephritis.

Pre-eclampsia	Lupus nephritis
• Headache	• Onset <20 weeks of gestation
• Visual problems (eg flashing lights)	• Active urinary sediment
• Epigastric or RUQ tenderness	• Low or falling complement levels
• Nausea or vomiting	• High or increasing anti-double-stranded DNA
• Clonus (>2 beats)	• Evidence of lupus flare involving other organs
• Increased liver function tests	
• Increasing serum uric acid level	
• Haemolysis	

RUQ = right upper quadrant.

the ESR, serum C-reactive protein (CRP) remains a reliable marker for disease activity during pregnancy.

Takayasu's arteritis (TA) generally does not worsen during pregnancy, but the most important factor for poor outcomes seems to be the development of hypertension and pre-eclampsia. Patients with aortic valve disease or stenosis of the aorta and/or its principal branches should receive comprehensive cardiovascular assessment before and throughout pregnancy.[19,20]

Remissions are achieved in a large proportion of women with Behçet's disease (BD). However, flare rates of between 25% and 65% have been reported, where the main manifestations were mucocutaneous, articular and ocular manifestations. However, the risk for the main obstetric complications appears not to be increased in women with BD.[20,21]

Medications during pregnancy and breastfeeding

Table 2 highlights the safety of the drugs most used for CTD during pregnancy and breastfeeding. Although traditionally avoided during pregnancy, non-steroid anti-inflammatory drugs (NSAIDs) are generally safe drugs to use during pregnancy if they are used in short, limited courses. Although they are not teratogenic, they can 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 periods. They should be withheld towards the end of pregnancy (>30–32 weeks) because of an increased risk of early closure of the baby's ductus arteriosus, and increased risk of maternal bleeding and of asthma in the child.[22] Colchicine use during pregnancy appears to be safe. In addition, the safety profile of HCQ has been widely researched, with no reported fetal neurosensory toxicity or malformations.[22]

A minimum proportion of non-fluorinated corticosteroids cross the placenta or appear in breast milk (5–20% of total dose). Given their adverse effects, minimum maintenance doses (prednisone <7.5 mg/day), combined with steroid-sparing agents are recommended. Stress doses of hydrocortisone at delivery are recommended in patients taking long-term therapy.[22]

Among immunosuppressive drugs, azathioprine (AZA), sulfasalazine (SSZ), cyclosporine (CS) and tacrolimus (FK-506) are considered safe during pregnancy and breastfeeding.[22,23] If pregnancy is being considered, mycophenolate mofetil (MMF), methotrexate (MTX), leflunomide (LFM) or cyclophosphamide (CYC) should be switched to safe alternatives (usually AZA) at least 3 months before conception, to monitor new flares or adverse effects from the change in drug regimen.[22] Women taking SSZ or those who have unplanned pregnancies while taking MTX should take high-dose folic acid (5 mg/day) from 3 months before conception until at least the end of the first trimester, to prevent neural tube defects.

Several groups have demonstrated no increased risk of malformations in fetuses exposed to anti-tumour necrosis factor drugs.[24] Such drugs are poorly excreted in breast milk and, hence, breastfeeding is considered to be safe. However, fatal disseminated Bacillus Calmette–Guérin (BCG) has been reported in babies of mothers who received biologics during pregnancy and it is imperative that women are advised to avoid live vaccines for their neonates.

With regards to rituximab, two recent retrospective series identified 240 exposed pregnancies with controversial results. Until more robust data are available, women should be counselled against pregnancy for 6–12 months after rituximab exposure because of the risk of neonatal B-cell depletion.[25] Neonates who were exposed to this biological during the second or third trimester should receive close white blood cell and infection surveillance.[22]

Warfarin and other vitamin K antagonists are teratogenic during organogenesis (6–10 weeks of gestation) and they should be avoided during this period.[22] Current recommendations include switching to low-molecular-weight heparin (LMWH) as soon as pregnancy is confirmed.[26]

Mild flares during pregnancy can be treated with HCQ and/or low-dose oral steroids (or occasionally NSAIDs during the first two trimesters). 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 might be necessary. More severe cases might require a risk–benefit assessment and prioritisation of the mother's welfare over fetal concerns and, therefore, the use of stronger agents, such as MMF, CYC or rituximab (RTX).

Pregnancy management plan

Pre-pregnancy counselling, risk assessment and stratification, a multidisciplinary approach, tailored antenatal and postnatal management plans, an experienced high-level neonatal unit, and early recognition of flares and complications (either medical and/or obstetric), are essential cornerstones for optimising the chance of successful outcomes for both mother and fetus.

The preconception visit should include a detailed summary of previous obstetric and medical history, current disease activity, last flare date, chronic organ damage, recent serological profile (RF, anti-CCP, aPL, anti-Ro/La, anti-double-stranded (ds)DNA, complement), baseline blood pressure, urine analysis and renal function. Likewise, the risk of pre-eclampsia, gestational diabetes and venous thromboembolism (VTE) should be estimated and appropriate management discussed. Harmful or unsafe medication should be stopped or changed to safer alternatives before pregnancy. Concomitant prophylactic calcium and vitamin D supplements should be prescribed to women receiving corticosteroids, who are at high risk for osteoporosis or vitamin D deficiency.[4] Uterine artery Doppler is recommended at approximately 22–24 weeks of gestation, because of its high negative predictive value for pre-eclampsia and/or IUGR.

Patients with SLE (especially lupus nephritis), RA, SSc, undifferentiated CTD (UCTD), and/or aPL have a higher risk of developing pre-eclampsia compared with the general population. Low-dose aspirin (LDA) (75 mg/day) started before 16 weeks of gestation significantly reduces the risk of perinatal

Table 2. Safety of drugs that are most used for connective tissue diseases during pregnancy and breastfeeding.

Drug	FDA class	Safety pregnancy	Breastfeeding
Non-steroid anti-inflammatory drugs	B (but D if >30 weeks of gestation)	Safe (if <30 weeks and intermittent use)	Safe
COX-II inhibitors	C (but D if >30 weeks of gestation)	?	?
Aspirin/dipyridamole	B	Safe	Safe
Hydroxychloroquine	C	Safe	Safe
Prednisolone/methylprednisolone	C	Safe	Safe
Azathioprine	D	Safe	Safe
Sulfasalazine	B	Safe (folate supplementation (5 mg/day) pre-conception and throughout pregnancy)	Safe
Ciclosporin	C	Safe	Probably safe
Tacrolimus	C	Safe	Safe
Mycophenolate mofetil	D	Avoid (consider during second to third trimester if severe disease)	Avoid
Methotrexate	X	Avoid	Avoid
Leflunomide	X	Avoid	Avoid
Cyclophosphamide	D	Avoid (consider during second to third trimester if severe disease)	Avoid
Anti-tumour necrosis factor agents	B	Safe (during first and second trimesters)	Probably safe
Certolizumab	B	Probably safe	Probably safe
Anakinra	B	Probably safe	Probably safe
Rituximab	C	Avoid (consider if severe disease)	? (Probably safe)
Abatacept	C	?	? (Probably safe)
Tocilizumab	C	?	? (Probably safe)
Belimumab	C	?	? (Probably safe)
Ustekinumab	B	? (Probably safe)	? (Probably safe)
Intravenous immunoglobulins	C	Safe	Safe
Endothelin receptor antagonists	X	Avoid	Avoid
Phosphodiesterase 5 inhibitors	B	Safe	Safe
Prostaglandin derivatives	B	Safe	Safe
Labetalol	C	Safe	Safe
Methyldopa	B	Safe	Avoid (higher risk of postnatal depression)
Nifedipine/amlodipine	C	Safe	Safe
Hydralazine	C	Safe	Safe
Doxazosin	C	Safe	Safe
Angiotensin-converting enzyme inhibitors	C (during first trimester); D (during second to third trimesters)	Probably safe during first trimester; avoid during second and third trimesters	Safe
Angiotensin receptor blockers	C (during first trimester); D (during second to third trimesters)	Avoid	Probably safe
Heparins	C	Safe	Safe
Vitamin K antagonists	X	Avoid	Safe
Bisphosphonates	C/D	Avoid	Avoid
Statins	X	Avoid	Avoid

COX = cyclooxygenase; FDA = Food and Drug Administration.

death, pre-eclampsia and its complications in women at higher risk,[27,28] and its maximum effect is probably achieved when it is taken during the afternoon or at bedtime.[29] In addition, all women with aPL should take LDA to decrease their risk of miscarriage and late obstetric complications.[30] In high-risk patients and in those with a low calcium diet, the intake of at least 1 g of calcium daily has been shown to dramatically reduce the risk of pre-eclampsia and preterm delivery.[31]

Postpartum

Because of a high risk of disease flare and thrombosis, close surveillance for 2–3 months after delivery is important. All women should have an assessment of their VTE risk and receive thromboprophylaxis postpartum accordingly.[26] Counselling on contraception is important for women with CTD because planned pregnancy is associated with fewer complications and higher pregnancy success rates.

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