Connective tissue and dermatological disorders in pregnancy

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Abstract

Connective tissue disorders, particularly those that are autoimmune, are being seen with increasing frequency in the pregnant population. The care of these patients in pregnancy ranges from the routine to the complicated, with some of the conditions posing significant risks both to the mother and the fetus. Dermatological conditions are often encountered in pregnancy, and again range from the benign to those resulting in serious fetal and maternal morbidity, with a number being specific to pregnancy. An important issue for both groups of disorders is the use of particular medications during pregnancy. Those with pre-existing disease should ideally be counselled pre-pregnancy to optimize treatment and adjust medication as appropriate. During pregnancy, frequency of review and degree of treatment will depend on the severity of the condition, and may require multidisciplinary team involvement to optimize both maternal and fetal outcome, including obstetric physicians, obstetricians, anaesthetists, neonatologists, and geneticists.

Keywords autoimmune; connective tissue disease; Ehlers-Danlos syndrome; Marfan syndrome; pregnancy; pruritus; rash; systemic lupus erythematosis

CONNECTIVE TISSUE DISORDERS IN PREGNANCY

Introduction

Connective tissue disorders (CTD) are a group of systemic disorders which involve tissues of the body containing collagen or elastin. They can be inherited or acquired. Acquired CTDs feature abnormal immune system activity directed against the body's own tissues (autoimmunity), resulting in an inflammatory response in tissues.

The impact of pregnancy varies considerably according to the type of disease. Both inherited and acquired CTDs will be discussed in this review, focusing on any associated maternal and/or fetal risks, and how each disorder should be managed in pregnancy.

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Because of the multisystem nature of many of these conditions, a multidisciplinary team approach is recommended, including maternal medicine physicians, obstetricians, anaesthetists, neonatologists, and geneticists.

Case 1: management of heritable connective tissue disorders

A 36 year old primiparous woman presents to your clinic for preconceptual counselling. She has Marfan syndrome (MFS) with pronounced kyphosis and aortic root dilatation and is attending a cardiologist and rheumatologist for annual review. Her most recent echocardiograph, 6 months ago, showed an aortic root diameter of 4 cm. She is eager to know the risks of pregnancy for her and for a foetus. She is also keen to have a natural delivery and would like to discuss the preferred mode of delivery for women with her condition.

MFS is one of the most common inherited disorders of connective tissue, autosomal dominant in inheritance, affecting 1 in 3000–5000 individuals. It occurs predominantly secondary to mutations of the fibrillin-1 gene (FBN1), resulting in the abnormal production of fibrillin which is an important component of both elastic and non-elastic connective tissues.

There is a variable phenotypic expression in people with MFS. The main features include cardiovascular pathology (see risk factors in pregnancy) increased height, arm span exceeding height, reduced upper to lower body segment ratio, arachnodactyly of fingers and toes, scoliosis or kyphosis, depression or protrusion of the sternum, high arched palate, and lens dislocation.

Aggressive medical and surgical treatment has resulted in a markedly improved prognosis for patients with MFS. Aortic root disease, leading to aneurysmal dilatation, aortic regurgitation, and dissection, is the main cause of morbidity and mortality in these patients.

Risk factors for pregnancy

The major concern regarding pregnancy are the cardiovascular manifestations, occurring in 80%, including dilation of the aortic root, mitral valve prolapse and mitral regurgitation.

The risk of aortic dilation and dissection is substantially increased during pregnancy and the postpartum period and therefore these women require more intensive monitoring. The increased risk may be due to increased arterial wall stress associated with the hypervolaemic and hyperdynamic circulatory state and/or hormonal effects on aortic wall composition.

The risk of dissection or other serious complications such as endocarditis or heart failure has been estimated to be approximately 1% in women with an aortic root diameter $\leq$40 mm (low to moderate risk). This risk increases to approximately 10% in women with an aortic root diameter >40 mm (high risk). Complications can occur at any time during pregnancy but the majority are seen in the second and third trimester.

Effect of MFS on pregnancy

One retrospective study of women with MFS has shown an increased risk of preterm premature rupture of membranes and cervical incompetence, leading to a higher rate of preterm

delivery (15%), as well as an increase in perinatal and neonatal mortality (7.1%).

Management during pregnancy

The European Society of Cardiology 2011 guidelines recommend that women with an aortic root diameter of >45 mm be offered prophylactic elective surgery if they are considering pregnancy, while the American College of Cardiology 2010 guidelines recommend surgery at a more conservative limit of 40 mm. Family history of dissection or aortic rupture may indicate an increased risk, but all patients should ideally have transthoracic echocardiography performed prior to pregnancy to assess the aortic root. Women should have regular echocardiograms during pregnancy to assess the aortic root size, even if ≤40 mm prior to pregnancy. Termination of pregnancy may be considered if there is any level of progressive aortic root enlargement during pregnancy (greater than 5 mm) followed by prompt aortic repair.

Prophylactic treatment with beta blockers decreases myocardial contractility and pulse pressure and may also improve the elastic properties of the aorta. They should be used in pregnancy if there is evidence of aortic dilatation or hypertension. There has been concern about an increased risk of intrauterine growth restriction with long-term use of high-dose atenolol in pregnancy, so metoprolol or labetolol are preferred.

They should also have monitoring of maternal heart rate and blood pressure to ensure optimal beta blocker control.

For low to moderate risk patients (root ≤40 mm) caesarean section is only recommended for obstetric indications. Anaesthetic review prior to delivery is recommended, as up to 70% of those with MFS have some level of lumbosacral dural ectasia, and so careful planning of anaesthesia is required. Epidural anaesthesia for pain relief with an assisted second stage to limit maternal effort is recommended. Postpartum haemorrhage should be anticipated in those with MFS. For high risk patients caesarean section is the recommended mode of delivery. Antibiotic prophylaxis against endocarditis to cover labour and delivery is no longer recommended.

Follow up of patients post partum should continue for 3–6 months, with echocardiogram, continuation of beta blocker therapy, and contraception advice.

Case 2: management of heritable connective tissue disorders

A 40 year old woman presents to your antenatal clinic at 10 weeks gestation for management of her pregnancy. She has Ehlers-Danlos syndrome (EDS) and has had two previous second trimester miscarriages.

EDS is an inherited collagen disorder. There are six known subtypes, and different types affect different sites in the body, such as the joints, skin, heart valves, and organ and arterial walls. Table 1 describes the various subtypes and the complications of pregnancy associated with each.

With the classical Ehlers-Danlos syndrome (formerly EDS I and II) cervical cerclage was previously recommended to treat cervical incompetence, however this approach is no longer recommended. Vascular EDS is associated with a significant risk of maternal mortality. In other types of EDS pregnancy is generally well tolerated. In this woman's case, further investigation into her specific subtype of EDS, and previous investigations (if any) for her two previous second trimester miscarriages should be explored, to provide her with as much information and necessary support for this pregnancy.

Autoimmune connective tissue disorders

These are usually multi-system diseases, with both genetic and environmental factors playing a part in their pathogenesis. They are characterized as a group by the presence of non-organ-specific autoantibodies in the circulation. Although each have particular clinical features and typical blood test abnormalities and antibody patterns, the initial presentation can be subtle and non-specific.

The relationship between autoimmune CDs and reproduction is bidirectional. Immune changes during pregnancy include a switch from a predominantly Th1 (cell-mediated) to a Th2 (humoral) type immune response, which then reverts post-partum. This may explain why some auto-immune conditions (such as RA) associated with a pathogenic Th1 (cell-mediated) response often improve during pregnancy but often relapse immediately post-partum, whilst those associated with a Th2 (humoral) immune response (such as SLE) may be more likely to flare during pregnancy.

Case 3: management of systemic lupus erythematosus

A 31 year old woman with severe SLE presents to your antenatal clinic to have pre-conceptual counselling. She is ANA and anti-dsDNA positive, but antiphospholipid antibody negative. She had a normal full blood count and renal profile at her last outpatient appointment. Her last flare up was a month ago and she is on Hydroxychloroquine and recently finished a tapering dose of prednisolone. She wishes to know the teratogenic potential effects of these medications. She is also concerned that she is at risk of recurrent miscarriage and has been researching the topic on the internet prior to her clinic appointment.

Systemic lupus erythematosus (SLE) is a multisystemic relapsing and remitting autoimmune disease. The prevalence in the UK is 97/100,000; the rate in women is six times higher than that in men. The highest prevalence has been observed in the Black Caribbean population.

30–40% of women with SLE have antiphospholipid antibodies (aPL). The combination of aPL with one or more of the characteristic clinical features (Table 2) is known as antiphospholipid syndrome (APS).

Pre-pregnancy care

A recent review of the management of SLE in pregnancy stratified women with SLE into three groups: 1) SLE in remission or stable low disease activity; 2) SLE at an early stage following recent diagnosis or active disease; 3) Severe organ impairment. Pre-pregnancy counselling should reassure patients in Group 1 pregnancy outcomes are usually good. Patients in Group 2 should ideally wait until their disease is stabilized or remits prior