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; Ehler-Danlos syndrome; Marfan's syndrome; pregnancy; pruritis; rash; systemic lupus erythematosis

Connective tissue disorders in pregnancy

Introduction

A connective tissue disease (CTD) is any disease that has the connective tissues of the body as the target of pathology. They can be inherited or acquired. Those that are acquired 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, focussing on any associated maternal and/or fetal risks, and how each disorder should be managed in pregnancy.

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

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Case 1: management of heritable connective tissue disorders

A 36 year old primiparous woman presents to your clinic for pre-pregnancy counselling. She has Marfan's Syndrome 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 with her diagnosis and the risks of pregnancy for her fetus. She is also keen to have a natural delivery and would like to discuss the preferred mode of delivery for women with her condition.

Marfan's syndrome 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 Marfan's syndrome. 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 Marfan's. 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.

There's an increased risk of aortic dilation and dissection and therefore require more intensive monitoring. The increased risk may be due to increased arterial wall stress associated with the hypervolemic 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$4 cm (low to moderate risk). This risk increases to approximately 10% in women with an aortic root diameter >4 cm (high risk). Complications can occur at any time during pregnancy but the majority are seen in the second and third trimester.

Effect of Marfan's on pregnancy

One retrospective study of women with Marfan's 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

Some authorities (such as the American College of Cardiology and the American Heart Association 2008 guidelines for the management of valvular heart disease) recommend that any woman with Marfan's should be counselled against pregnancy,

because aortic rupture or dissection can occur at any root size, but this is not universal practice. 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, and if >4.5 cm should be offered aortic root replacement before embarking on pregnancy. Termination of pregnancy may be considered if there is any level of aortic root enlargement (greater than 4.0 cm) 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 labetalol are preferred.

Women should have regular echocardiograms during pregnancy to assess the aortic root size, even if ≤4 cm prior to pregnancy. 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 ≤4 cm) caesarean section is only recommended for obstetric indications. Epidural anaesthesia for pain relief with an assisted second stage to limit maternal effort is recommended. 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.

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 Ehler—Danlos Syndrome and has had two previous second trimester miscarriages.

Ehlers—Danlos syndrome (EDS) is an inherited collagen disorder, with different EDS types affecting different sites in the body, such as joints, skin, heart valves, and organ and arterial walls. For five out of the six types the gene defect is known.

With the classical Ehler—Danlos Syndrome (formerly EDS I and II) a Shirodkar suture may be required to treat cervical incompetence.With vascular (formerly EDS IV) types of EDS, there's an increased risk of uterine rupture, damage to the vagina and perineum, and arterial or intestinal rupture. In other types of EDS pregnancy is generally well tolerated.

Autoimmune connective tissue disorders

These are usually multi-system diseases, with both genetic and environmental factors playing a part in their pathogenesis. As in the majority of autoimmune conditions they are commoner in women. 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.

Immune changes during pregnancy include a switch from a predominantly Th1 (cell-mediated) to a Th2 (humoural) type immune response, which then reverts postpartum. This is probably why autoimmune conditions often improve during pregnancy (not universally), but often relapse immediately postpartum.

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. It is up to nine times more common in women than men and affects black women three times as often as white women. The peak onset is during child-bearing years.

30—40% of women with SLE have antiphospholipid antibodies (aPL). The combination of aPL with one or more of the characteristic clinical features (Table 1) is known as the antiphospholipid syndrome (APS).

Pre-pregnancy care

Pre-pregnancy counselling should reassure patients that fertility is normal and pregnancy outcomes are usually good in mild or stable SLE. However if disease is active, advise that pregnancy should be delayed for at least 6 months post flare.

The following are associated with an increased risk of adverse pregnancy outcomes.

- Hypertension
- Renal involvement
- Active disease at conception
- The presence of aPL and anti-Ro/La antibodies (Table 1)

Pre-existing renal disease may worsen in pregnancy, particularly in patients with heavy proteinuria, hypertension and high baseline serum creatinine concentrations. Women with severe renal impairment (creatinine >250 mmol/l) have a <30% chance of a successful pregnancy.

Pregnancy appears to increase the likelihood of a flare antenatally, and this is obviously more common in women who stop taking maintenance medication, especially hydroxychloroquine (see Table 2). Pharmacological agents should be reviewed, but continued if safe and required for good disease control.

Medical problems such as thrombosis (arterial and venous particularly in the puerperium), autoimmune thrombocytopenia, autoimmune haemolytic anaemia, and pulmonary hypertension may complicate pregnancy further. Pulmonary hypertension, reported in up to 14% of patients with SLE, is associated with a high risk of maternal death.

Maternal and fetal complications

LMWH and aspirin peri-conception may be considered in women with APS and recurrent miscarriage, with one study demonstrating 80% success compared with 44% viable infants if the women were treated with aspirin alone.

The risks of SLE are not confined to the mother. If antibodies to the (eNAs) are present (anti- Ro and/or—La) these may affect the fetus via transplacental passage of antibodies. Cutaneous neonatal lupus occurs in around 5% of babies and usually presents as a rash at approximately 2 weeks of age. It will resolve