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REVIEW

SLE in pregnancy

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Systemic lupus erythematosus (SLE) is a multisystem disease which is frequently found in young women, causing inflammation of multiple organ systems such as skin, kidneys, nervous system and joints. The American Rheumatism Association (ARA) criteria (table1) is used as a guideline to approach the patients.[1] It was thought to be rare disease in the past. Today, with more sensitive laboratory tests, the aware ness and the use of medications precipitating lupus, the incidence is about 1 in 1,000.[2] The disease tends to effect young women, therefore it is relatively common in pregnancy. The prevalence in childbearing-aged women is about 1 in 500.[2] It is, therefore, the collagen vascular disease most frequently found during pregnancy.[3]

Etiology and pathogenesis

The etiology of disease is still unknown and the pathophysiology is not completely understood. The current concept of pathogenesis is autoantibodies causing cytotoxic damage, i.e. thrombocytopenia and hemolytic anemia, and immune complexes causing inflammation such as nephritis, dermatitis. The mech anism of increasing production of autoantibody and immune complex is still controversial. Current theories suggested that slow virus infection may play an important role.[4-6] Female sex hormones may be another important factor.[7] Ninety percent of patients are female and several male patients have serum estrogen increased.[2] Genetic factors are believed to be an implication because of the high incidence of disease in familial members and twins. Studies showed that the frequency of human leukocyte antigen (HLA) DR 2, 3 and 4 null alleles is increased in SLE patients.[8-10] Medications, such as hydralazine, methyldopa, phenytoin and phenobarbital, can also cause lupus-like syndrome.[11] However, it usually remits after stop the medication.[11]

Diagnosis

SLE manifestations are variable in clinical, laboratory and course of disease. The diagnosis is based on the American Rheumatism Association (ARA) criteria (table 1) and the patient must have at least 4 of them.[1] During pregnancy, diagnosis can be confused with pregnancy induced hypertension (PIH) especially if there is renal involvement which causes proteinuria. Although 80% of SLE patients are diagnosed before pregnancy, the others are diagnosed during pregnancy either in first or in subsequent pregnancies.[12] Careful history taking concerning signs and symptoms before pregnancy may be helpful. Super-imposed PIH usually manifests after 24th weeks of gestation with more acute course. Hypertension is presented before proteinuria and not associated with ARA criteria.[13]

Hematologic and serologic manifestations of

SLE patients are varied. Most patients have anemia, leukopenia and some may have thrombocytopenia.[14,15] Antinuclear antibodies (ANA) are found in almost all patients(95%) while Lupus erythematosus cells (LE cell) are also common(75%).[14,15] The more specific and important autoantibody is anti-DNA antibody because it is usually correlated with activity of the disease especially when the kidney is involved.[3] Seventy five percent of patients have serum complement level of C3 and C4 decreased which usually correlates with activity of the disease.[3,16] Other positive serologic tests such as anticardiolipin antibodies, lupus anticoagulant, rheumatoid factor and a false positive test for syphilis are less commonly found.[17]

Table 1 Criteria for the diagnosis of SLE as suggested by The American Rheumatism Association (1982)

Criteria for diagnosis
1) Malar rash (butterfly distribution)
2) Discoid lupus
3) Photosensitivity
4) Oral or nasopharyngeal ulceration (generally painless)
5) Arthritis (non erosive arthritis involving 2 or more peripheral joints)
6) Serositis (pleurisy or pericarditis)
7) Renal involvement (proteinuria > 0.5 g/day or cellular casts)
8) Neurologic involvement (psychosis or convulsions)
9) Hematologic involvement : one of
hemolytic anemia
leucopenia, wbc < 4000/mm^3 on two or more occasions
lymphopenia < 1500/ mm^3 on two or more occasions
Thrombocytopenia < 100,000/ mm^3
10) Immunological disorders:
Positive LE cell preparation
Antibody to native DNA in abnormal titre
Antibody to SM nuclear antigen
Chronic false positive syphilis serology for 6 months
11) Antinuclear antibody in abnormal titre

For more of 11 criteria should be present either in simultaneously or serially for diagnosis of SLE.

Effect of pregnancy on SLE

SLE itself has a fluctuating course, remitting and relapsing, which makes it difficult to establish the relationship between pregnancy and SLE. However, pregnancy does not affect the long term outcome of the disease.[18] Many studies showed that pregnancy may be associated with flare up especially in the puerperium whether it is postpartum or post abortion.[19-21] Garsenstein(1962) reported that the incidence of flare up was three times in first half of pregnancy, one and a half times in second half of pregnancy and six times during puerperium.[18] However, in the more recent reports, the incidence of flare up has been much less.[12,22,23] Activity of the disease before pregnancy is the main factor in influencing flare up rate. Flare up rate is rare if the disease has been absent for more than 6 months.[12,24]

Maternal morbidity is increased in patients

complicated with renal or central nervous system involvement.[25] Pregnancy may aggravate lupus nephritis especially in the untreated patients.[26] but the prognosis is good in patients with remission of disease at the onset of pregnancy.[27,28] Although pregnancy may worsen SLE, termination of pregnancy is not the treatment of choice because exacerbation may also occur after therapeutic abortion.[24] Preconception counselling, careful monitoring and early treatment of active disease should make successful pregnancy outcome without maternal or fetal complication.

PIH versus SLE

Hypertension and edema especially in the latter half of pregnancy may be difficult to differentiate PIH from the flare up of lupus nephritis which is more serious and needs more aggressive therapy.[17] Diagnosis of PIH is made if there is no sign of SLE or serologic abnormality.[29] The presence of SLE manifestations and serologic abnormalities, i.e. increase ANA titer, decrease complement level, will favor the diagnosis of SLE.[29] However, lupus nephritis rarely occurs in the third trimester. The patients usually have some renal compromise, i.e. elevated serum creatinine, decrease creatinine clearance, from early pregnancy which is contrast to the patients with PIH.[24]

Effect of SLE on pregnancy

Although recent data showed that SLE does not effect fertility rate,[17] it has three main effects on pregnancy. First, SLE increases risk of spontaneous abortion which is different from the usual case of abortion in that because it may occur after 12 weeks and it can occur up to 28 weeks of pregnancy. Secondly, it can cause fetal loss from its complications, such as lupus nephritis, hypertension, and lastly, it has effect on the newborns such as neonatal lupus syndrome, congenital heart block.

The incidence of fetal loss is high in SLE patients due to the greater chance of abortion, prematurity and fetal death.[17,26,27] The factors which may be the cause of fetal loss is decidual vasculitis affecting placental blood supply, antiphospholipid antibodies predisposing to vascular thrombosis, the presence of trophoblast-reactive lymphocytotoxic antibodies and anti-Ro, anti-La associated with congenital heart block.[17]

Spontaneous abortion rate is 20-28 percent which is two times higher than normal.[3] The risk is not clearly related to activity of the disease[30,31] but closely related to the presence of cardiolipin antibodies and lupus anticoagulant.[21,32,33] The level of cardiolipin antibodies, particularly Ig G, is better than lupus anticoagulant for predicting the fetal outcome.[34,35]

SLE can cause poor intrauterine growth especially patient with active disease.[2] There is evidence that glucocorticoids decrease newborn head circumference.[3] Hypertension, renal involvement and placental vasculitis are also effect fetal growth.[36] However, expeditious delivery is the acceptable treatment for IUGR.

Although activity of disease does not strongly correlate with fetal outcome,[26] patients with renal involvement and hypertension have higher risk of fetal morbidity.[36] The chance of live birth is reduced from 90% in inactive SLE to 65% in patient with active disease and drop to 50% if serum creatinine is greater than 1.5 mg/dl.[3] However, the best way is to allow SLE patients to become pregnant only when the disease is under controlled.

Neonatal lupus syndrome is the abnormalities in the newborns which includes lupus dermatitis, hematologic and cardiac abnormalities.[36] The hematological problems, i.e. anemia, leucopenia, throm bocytopenia, are usually transient.[36] Complete heart block is the most common cardiac abnormalities which can be detected antenatally. However, it can also be found in connective tissue disease such as rheumatoid arthritis (26%) but is less common than in SLE

(38%).[37] Anti-Ro has a stronger correlation with heart block than anti-La. However Lockshin[38] reported 91 SLE patients with 23% anti-Ro positive without heart block in their infants. Although most of the babies with heart block survive without need of pacemaker after birth, some of them die during antepartum and labor.[39] There is still unclear why antibodies do not affect mother.

Prognosis of the babies without cardiac complications is usually good. Neonatal skin lesions are usually on face and scalp. It is rarely associated with another organ abnormality.[36] Clinical and serologic abnormalities usually disappear within one year.[3]

Management of SLE in pregnancy

Prepregnancy counselling

The patients with SLE should be treated until the disease becomes inactive at lease 6 months before they are allowed to conceive and should be under the care of both rheumatologist and obstetrician during pregnancy.[3] The effect of the disease on pregnancy and the effect of pregnancy on the disease should be discussed with the couple.

Prenatal care

Pregnant women with SLE should be seen by both obstetrician and rheumatologist throughout the pregnancy. Careful history taking, physical examination and the use of sensitive serologic tests should be carried out to achieve good pregnancy outcome. Although complements are good predictors for detecting flare up of the disease, the levels during pregnancy are higher than normal.[17] Therefore, changing of complement level should be closely monitored.

Fetal surveillance is necessary for evaluate the fetus. Daily fetal movement counts, frequent fetal heart rate monitoring, clinical and sonographic assessment of fetal growth and amniotic fluid volume are recommended.[3] Timing of delivery depends on severity of the condition. If there is no complication, the patients should be delivered at term. Early delivery is needed if severity of hypertension and renal failure increase or there is evidence of fetal compromise.[42]

Paracetamol is the best drug to use as an analgesic. Non-steroidal anti-inflammatory drugs (NSAID) can also be used but they should be avoided in third trimester because they can cause premature closure of ductus arteriosus, leading to neonatal pulmonary hypertension.[16]

Corticosteroid is still the most common medication used for the treatment of pregnant women with SLE.[3] However, the dose should be started as low as possible to control the disease and prevent relapse. Indications for steroid therapy are hemolytic anemia, severe thrombocytopenia, leukopenia, prolong clotting time, lupus nephritis, pericarditis, myocarditis, pleuritis and CNS involvement.[3] The dose varies according to severity and organs involvement. The usual starting dose is 20-40 mg/day.[17] Dose should be increased if patients have active disease with major organs involvement.[40] Risk of preterm birth is incresed in this group of patients.[41] There is no need to increase the dose of steroid in the patients treated before pregnancy unless there is a deterioration of the disease.[17] Fifty percent of prednisolone is inactivated by 11 B dehydrogenase in placenta. Study showed that steroid treatment does not have an effect on fetus and breast-feeding is considered safe.[42]

Azathioprine, purine antimetabolite, should be used only when steroid is ineffective or with life-threat ening condition.[43] Chloroquine and alkylating agents should be avoided during early pregnancy.[44] Breast-feeding is not recommended when the mother is taking cytotoxic agent.

Intrapartum care

The patients should be delivered at term if there is no complication. It may be delivered earlier if the mothers have hypertension or renal involvement. Mode of delivery depends on obstetric indication.[36]

Postpartum care

There is no evidence that breast feeding has any effect on the disease activity but postpartum flare up may occur. The decision should be left to the mothers whether they are fit enough for breast feeding. Prednisolone is considered safe but cytotoxic and antimalarial drugs should be avoided during this period.[17]

Contraception

Barrier methods are recommended for SLE patients and sterilization is the best method when the couple has complete family. Although recent studies did not find the flare up of disease in patients taking oral contraception, it should be avoid in patients with antiphospholipid antibodies because of increasing incidence of thrombosis and vasculitis.[36] There is not enough data on progesterone-only contraceptives, al though it may be safe in these patients.[36] Intrauterine device(IUD) may increase risk of infection especially for those treated with prednisolone and cytotoxic agents.[17]

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