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REVIEW ARTICLE

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An overview on systemic lupus erythematosus pregnancy

Abstract A systemic lupus erythematosus (SLE) pregnancy is no longer regarded as unacceptable, with an early diagnosis, a mild disease condition, and good interdisciplinary collaboration ensuring intense surveillance of pregnant SLE patients. The key point is a sufficiently long period of disease quiescence before conception. A low dose of prednisone is preferable during pregnancy. Nevertheless, 20% of disease flare-up still happens interpartum or postpartum, even in such well-planned pregnancies, although usually with only mild severity. Pregnancy during an active disease stage, especially active nephritis, should always be avoided. Substantial renal function damage may occur, and there is a relatively high prevalence of preeclampsia, which may further compromise the mother as well as the fetus. It is well documented that antiphospholipid syndrome and antiphospholipid antibodies are strongly associated with fetal wastage. Low-dose aspirin or heparin is indicated for a favorable fetal outcome. Women with positive anti-SSA and/or anti-SSB should be aware of the danger of congenital heart block in their infants. Cytotoxic drugs applied in the early stage of pregnancy are dangerous to the fetus. A rather long-term follow-up is required to make a precise evaluation of the maternal SLE influence on the offspring.

Key words Fetus · Medication · Pregnancy · Risk · Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus (SLE) is an autoimmune disease which has a high rate of occurrence in women of childbearing age. The prognosis for lupus has been greatly improved in recent years owing to earlier diagnosis and an effective remedy. The problem of SLE pregnancy has received much attention, but still remains controversial in some aspects. More than half a century ago, in the precorticosteriod era, pregnancy in lupus patients was regarded as taboo, for it was frequently fraught with serious outcomes such as disease exacerbation, fetal loss, and even maternal death. The mortality of pregnancy-induced acute SLE exacerbation could be as high as 25%.[1] This idea has gradually changed, for there has been increasing evidence supporting the fact that SLE is not an absolute contraindication for pregnancy provided that the disease has been well controlled, and the patients are closely monitored by a multidisciplinary medical team consisting of physicians, obstetricians, and pediatricians.

Fertility in women with lupus is usually normal except in those with amenorrhea or severe disease activity. Oligomenorrhea and amenorrhea can be the results of severe disease exacerbation, and a side effect of alkylating cytotoxic immunosuppressives with cyclophosphamide is the most frequent cause. Although an SLE pregnancy may have a satisfactory outcome, if not completely normal, pregnant lupus patients are prone to disease flare or exacerbation.

Many papers have been published concerning SLE pregnancy. The results of some clinical studies are listed in Table 1.[2–11] Different maternal–fetal outcomes have been presented, and many of them are retrospective in nature. The differences in the results may come from the patients selected, and the criteria for SLE activity, as well as the nature of the study. We conducted a prospective study on 71 cases of SLE pregnancy from 1988 to 2000. We also carried out some research into SLE placental pathology.

Factors predisposing to SLE flare during pregnancy

There are many physiological changes occurring in pregnant women. Sex-hormone levels, mainly estrogen, progestogen, and prolactin, after the 7th gestational week are increased during pregnancy. The available studies have elucidated the linkage between SLE and gonadal hormones. Doria et al.[12] observed an unexpected lack of estro-

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Table 1. Results of some clinical studies on SLE pregnancy

	NOP	TP	LD	FL	%	PB	IUGR	NL	PD	SLE flare (%)
Moga et al. (1975–1991)[2]	27	35	23	12	34.3	6	NM	0	0	31.4
Julkunen et al. (1993)[3]	16	26	23	3	11.5	7	4	0	1	8.7
Nicklin (1991)[4]	17	42	25	17	40.5	10	4	NM	NM	NM
De-Bandt et al. (1991–1997)[5]	31	59	38	21	35.6	19	11	1	1	20.3
Pajor et al. (1998)[6]	33	75	30	45	60	UM	NM	2	5	NM
Rahman et al. (1970–1995)[7]	73	141	86	55	39	21	6	3	2	NM
Zhang et al. (1988–2000)[8]	71	71	71	1	1.4	22	13	0	0	30.6
Le Thi Huong et al. (1982–1994)[9]	34	58	46	12	20.7	28	1	2	0	27
Le Thi Huong et al. (1987–1992)[10]	103	103	76	27	26.2	48	NM	3	4	45.3
Cortes et al. (1984–1999)[11]	60	103	68	35	34	19	24	1	0	33

NOP, number of patients; TP, total pregnancy; LD, life delivery; FL, fetal loss; PB, premature birth; IUGR, intrauterous growth retardation; NL, neonatal lupus; PD, periperium death; UM, unmentioned

gen serum level increase, and to a lesser extent a progesterone serum level increase, in SLE pregnant women during the second, and even more the third trimester of gestation, which correlated with a decreased disease activity score. He attributed this relative hormone deficiency to placental compromise. Another significant change is the maternal augmentation of circulating blood volume and a higher glomerular filtration rate, which facilitates the onset of lupus nephritis in women with active lupus, resulting from an increased tendency for glomerular deposit of circulating immune complex. It is reported that a high level of anti-dsDNA antibodies correlates the high risk of disease exacerbation and fetal prematurity.[13]

Sex hormone and disease activity

One of the controversial areas of SLE pregnancy comes from the prevailing notion that increased sex hormones during pregnancy may cause SLE flare.

Studies in normal mice showed that estrogen treatment induces polyclonal B cell activation, with the increased expression of autoantibodies characteristic of autoimmune diseases. In addition, sex hormone levels in both humans and experimental models were correlated with the activity of their cytokine-secreting cells.[14] There are specific responses in cells from diseased patients that support the molecular activities of sex hormones on cells, among which is the rise of calcineurin mRNA in SLE T cells in response to estrogen. There is a more estrogenic environment in patients of both sexes with SLE. A preferential hydroxylation of estrone, and an increased oxidation of testosterone in patients with SLE, maximizes the effects of estrogens on T cell functions.[15] Pregnancy induces a shift from TH1 to TH2 immune response, which may trigger SLE manifestations that are dependent on humoral immune responses. The marked increases in estrogen and progesterone during pregnancy seem to enhance some of the manifestations of SLE, but will rarely result in permanent aggravation of the disease. There is no increased maternal–fetal risk in the absence of lupus nephritis, antiphospholipid antibodies, or a previous history of pregnancy loss.[16] Prolactin is another hormone stimulating immune responses which has been found to be elevated in SLE patients of both sexes, and to correlated to disease activity in several studies. It participates in local and generalized immune and inflammatory processes, and acts as a bridge between the neuroendocrine and immune systems in SLE. However, new evidence has shown that usually the hyperprolactinemia (HPRL) in SLE is the result of stimulation to pituitary prolactin (PRL) secretion by cytokines. HPRL seems to influence the postpartum behavior of SLE.[17]

Despite all these adverse influences of increased sex hormone levels on SLE during pregnancy, it should be emphasized that an abnormal hormone level alone will not aggravate the disease condition. More often it may provide the stage for other factors to trigger disease.[15] There are no prospective data that show a deleterious effect of exogenous estrogens on disease activity in human SLE.[18] Limited data from SELENA (Safety of Estrogens Lupus Erythematosus National Assessment), which is still undergoing clinical trials, documented the relative safety of exogenous estrogen to stable lupus patients. This paves the way for giving hormone replacement therapy (HRT) to postmenopausal stable lupus patients to cope with coronary artery disease and osteoporosis. This information is also of benefit in evaluating the maternal risk of SLE pregnancy.

The association between pregnancy outcome and the disease condition before conception

Julkunen[19] claimed that the outlook of pregnancy for women with lupus nephritis is usually favorable if the disease (both renal and nonrenal) has been quiescent for at least 6 months before pregnancy. Hayslett[20] reported that one-third of pregnant SLE patients will have disease activity during pregnancy if they had a disease remission period more than 6 months before conception, while the survival rate of the infants was between 80% and 85%. According to our prospective observation of about 70 cases of SLE pregnancy, disease remission for more than 1 year preceding conception enhanced the maternal–fetal prognosis for as many as 80% of the patients were free from disease flare during the course of the pregnancy. Even so, the majority of those flares are minor, with arthritis and skin rash being

the most prevalent. At the same time, fetal survival rate reached almost 100%. Past SLE visceral involvement is not an additional risk factor predisposing to a poor maternal–fetal outcome if it had been inactive for over a year before gravidity, and without vital organ dysfunction.[8]

Uncontrolled SLE patients, or those having a disease remission period of less than 6 months prior to conception, are at high risk during pregnancy. An active disease condition and/or a substantial renal insufficiency at conception are not only associated with a high risk of maternal complications, but also with high frequencies of fetal loss. There is a much higher probability of disease exacerbation and aggravation in such circumstances compared with the stable patients previously described. Pregnancy can be a profound adverse factor for disease deterioration in such circumstance. Major organ involvement may occur, especially nephritis in those patients who were originally without visceral damage. Strong disease activity in term will lead to increased fetal wastage, which is the term for the sum of spontaneous abortion and stillbirth via placenta vasculopathy, or to a lesser extent will result in intrauterine growth retardation (IUGR) and prematurity. These conditions constitute the fetal risks.[1]

Active lupus nephritis, especially with moderate to severe hypertension, is the main risk factor for maternal–fetal prognosis in SLE pregnancy.[7] This has been confirmed by a number of retrospective and prospective studies.[21] It may progress to more severe clinical manifestations such as massive proteinuria, refractory hypertension, or even renal failure, which is often a life-threatening event. There is an increased prevalence of pregnancy-induced hypertension in SLE pregnancy, with preeclampsia being more frequent in lupus nephritis patients. Active lupus nephritis is also correlated with a high rate of fetal loss together with other fetal complications such as growth retardation and prematurity.[1] These adverse outcomes make uncontrolled nephritis a strong contraindication for pregnancy, especially for patients with increased blood pressure and renal function deterioration. When a pregnant SLE patient presents with symptoms of high blood pressure accompanied by proteinuria, it is of vital importance to differentiate between preeclampsia and active lupus nephritis because of the different principles of management. There might be some difficulty with this differential diagnosis because proteinuria, edema, and hypertension can appear in both of these conditions, and in some cases they can occur simultaneously. Some clues may indicate the activation of lupus nephritis, such as a decreased level of compliment components, especially C3, obvious hematuria/cellular casts in urine analysis, and extrarenal lupus activity. Preeclampsia usually happens after the 24th gestational week, and often involves optic fundi vasospasm and exudates.[22] Renal insufficiency and hypertension are more dangerous than proteinuria. There have been case reports of successful pregnancies after renal transplantation.[23] On the other hand, stable lupus nephritis patients will enjoy a rather uneventful pregnancy, and previous results of renal biopsies cannot be used to evaluate the probability of intrapartum or postpartum disease flare. Renal function is usually not irreversibly affected in these patients.[3] Fetal outcome is no worse than that of other SLE pregnancies.[24] The long-term prognosis for patients with lupus nephritis is not affected by pregnancy if it has been clinically controlled.[25]

Antiphospholipid syndrome

Another important factor responsible for placental injury is antiphospholipid syndrome (APS). Patients with APS usually carry a high titer of antiphospholipid antibodies (aPL). APS and aPL have been widely associated with fetal wastage. aPL can interfere with the production and release of prostacyclin in the placental endothelium, which is a potent inhibitor of platelet aggregation. At the same time, aPL itself directly boosts platelet aggregation and TAX2 production through binding to phospholipid in the platelets. The final result will be a facilitation of intravascular clotting. Normally there is a type of protein, the so-called placental anticoagulant protein 1 (PAP1), on the surface of villus, which has a high affinity to phospholipid in order to inactivate coagulation factors. Patients with APS show a paucity of this protein, leading to an increased tendency for coagulation in placental vessels. This is also part of the pathogenesis of APS. Patients with aPL can be triggered into clinical thrombosis under certain physiological and pathological conditions such as pregnancy, exogenous estrogens, and surgery. APS is usually accompanied by an elevated circulating immunocomplex (CIC) and a low level of complements. The majority of aPL-mediated fetal loss tends to occur after the 12th week of gestation. Anti-DNA antibodies cross-reacting with laminins may play a role in early pregnancy failure in SLE patients by interfering with placental implantation.[26] aPL includes lupus anticoagulant (LAC) and anticardiolipin antibodies (aCL). Patients with double-positive LAC and aCL are more likely to have placental extensive infarction caused by decidual vasculopathy and decidual thrombosis.[27] Anti-β-2GP-1 antibodies may have a significant role in APS diagnosis, especially when there is a lack of positive results from traditional assays for LAC or aCL antibodies. During pregnancy, aPL titers may decrease or disappear after treatment, which correlates with an improved fetal survival.[28] Julkunen et al.[29] reported a case of SLE diagnosed following recurrent miscarriages with a total of 15 spontaneous abortions. The unusual finding was that the woman had a high titer of antithyroid microsomal antibodies, while enzyme-linked immunosorbent assay (ELISA) tests for lupus anticoagulant and anticardiolipin antibodies were repeatedly negative, supporting the similar predictive value of antithyroid antibodies for pregnancy loss. These findings show that the nature of pregnancy loss is an underlying immunological defect associated with the production of antibodies.

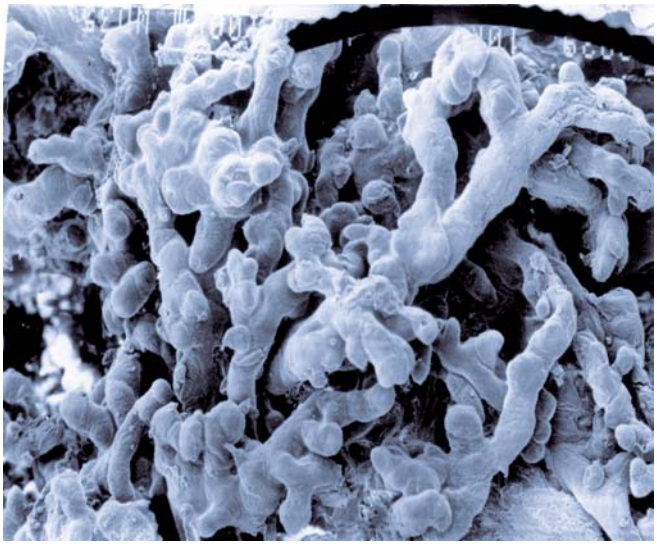

Fig. 1. Electron microscope scanning of villus of normal pregnancy

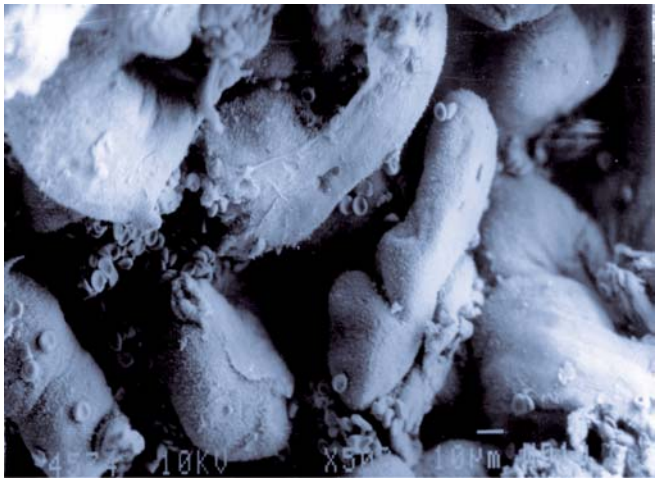

Fig. 3. Electron microscope scanning of villus of SLE pregnancy: there are many eyeholes on the surface

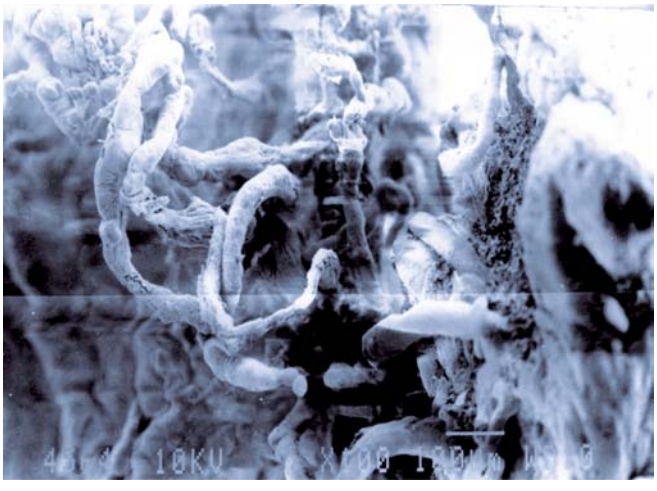

Fig. 2. Electron microscope scanning of villus of SLE pregnancy: thin and slim in appearance, lack of ramification, the peripheral part looks like a bean sprout

Fig. 4. Electron microscope scanning of villus of SLE pregnancy: epithelium cell denudation with a mass of disruption

Placental pathology in SLE pregnancy

In an SLE pregnancy, the placenta had a significantly smaller weight than normal controls in a group of samples. Placental villi are much thinner and slimmer in appearance and scarce in number, with fewer ramifications under electron microscope scanning (Figs. 1–4). Placental villus dysplasia is caused by placental vasculopathy that is autoimmune in nature. Granular IgG, IgA, IgM, and C3, as well as immunocomplex, especially DNA-anti-DNA-Ab complex deposits, can be found on the wall of villus vessels or in trophoblast membranes by immunohistology. Excessive intervillous fibrin deposition and infarction were noted in almost all cases. There is disseminated thickening of the vessel wall, together with a narrowing of lumen, and sometimes even vessel occlusion due to intravascular thrombosis. Chronic villitis is another SLE-related placental risk which is antiphospholipid antibody-independent. All these changes contribute to placental vessel infarcts and fibrinoid necrosis, resulting in a severe ischemic state.[30]

The dysplasia of villus directly impairs the material exchange function of the placenta, resulting in malnutrition of the fetus. This type of placental damage may contribute to an unfavorable fetal outcome such as IUGR, still birth, etc. Fetal wastage is usually the consequence of extensive placental infarction, which is most prominent in APS patients.

Information comparing placental pathological changes correlated with maternal disease activity is not available, but there appears to be a spectrum of severity in patients with different disease conditions. According to our observations, there are more cases of severe placental decidual vasculopathy and infarction in disease-active patients.

Neonatal lupus and anti-Ro/SSA antibodies

Neonatal lupus is actually a syndrome which includes skin rash, congenital heart block (atrial–ventricular), and an abnormal low blood count, such as leucocytopenia, anemia, and thrombocytopenia. The rash can be widespread, not necessarily on the face, and without any specific characteristics. In most cases it totally disappears several weeks after birth, and requires no special management, as do blood count abnormalities. Heart trouble is a rare but serious problem, sometimes needing a pacemaker to restore normal hemodynamics, and a few of the affected infants may die. Neonatal lupus is not closely related to adult lupus. The affected infant will not usually develop lupus while growing up. The known risk for mothers giving birth to a neonatal lupus baby is a special set of autoantibodies called anti-Ro (anti-SSA) and anti-La (anti-SSB).

Anti-Ro/SSA antibodies are believed to be closely related to congenital heart block (CHB) in infants. There are some experimental results indicating that anti-52kd-Ro/SSA antibodies impair the normal function of the sinus and the atrioventricular node by interfering with the calcium channels. This type of antibody can be transmitted to the fetus via the placenta, causing neonatal CHB. Some papers also describe neonatal bradycardia and QT prolongation, in which this special type of autoantibody was incriminated. Some previous retrospective studies estimated that the risk of delivering an affected infant for mothers carrying this type of antibody may be as high as 5%. Antonio et al.[31] conducted a prospective study on 100 cases of anti-Ro/SSA-positive pregnant patients with 118 pregnancies, and reported a probability of 2% risk for CHB in their fetus or neonate. This figure may be even lower in SLE pregnancies because of the fact that anti-60kd is the predominant anti-Ro/SSA specificity in SLE patients. In accordance with this speculation, no SLE mother in Antonio's study got CHB offspring. Anti-52kd-Ro/SSA antibodies are more often seen in patients with primary Sjögren's syndrome (SS) and undifferentiated connective tissue disease (UCTD). Most of the time, we find the mother of a CHB newborn to be anti-Ro positive. Press et al.[32] identified 64 mothers of 64 children with CHB (seen between 1964 and 1993) through the cardiology database of the Hospital for Sick Children, Toronto, Canada. Anti-Ro and/or anti-La antibodies were positive in 32 of 53 (60%) mothers tested. Anti-Ro and/or anti-La antibodies were positive in 12 of 13 mothers tested at the time of delivery. Leu and Lan[33] conducted a survey among 430 pregnancies of 154 SLE patients, and showed that all three infants who suffered congenital heart block/neonatal lupus syndrome were associated with maternal anti-SSA/Ro antibodies. The frequency of congenital heart block/neonatal lupus syndrome was 0.79% (3/379) in live births by all SLE patients, and 1.17% (3/257) in live births by anti-SSA/Ro-positive SLE mothers. Miyagawa et al.[34] analyzed the results of anti-SSA/Ro antibodies tests on 825 patients attending the hospital with clinical signs and symptoms of collagen diseases, and reported that the frequency of female positivity to SSA/Ro was 11.0%, which was significantly higher than that in males (3.2%) ($P < 0.01$). In our study, we found 33 anti-Ro/SSA-positive mothers and 8 cases were both anti-Ro/SSA- and anti-La/SSB-positive, but there were no electrocardiac abnormalities in their infants. There are also reports that female children have an increased risk of CHB. This information is useful for preconception counseling to women with established connective tissue disease carrying anti-Ro/SSA antibodies.

Medication

Corticosteroid therapy has been a major contributing factor in improving the maternal fetal outcome of SLE pregnancy in the past few decades. Different preparations of steroid have different concentrations in the cord because of the variation in the transplacental passage. In the case of maternal administration of prednisone or prednisolone, the fetal blood level is nearly 10% of the maternal level, while that figure for dexamethasone may reach 100%. The reason for this phenomenon is that the placental oxidative enzymes may inactivate the prednisone or prednisolone, but dexamethasone is free from this biochemical inactivation. On the other hand, the fetal liver is not so capable of converting prednisone to its active metabolites.[1] Therefore a low to moderate dose of maternal prednisone administration will not have much influence on the fetus. A low dose of prednisone may have a prophylactic role in preventing maternal SLE flaring up without many side-effects in the fetus. Several previous studies have confirmed this idea. We have also found this in SLE pregnancy. On the other hand, if the target of steroid therapy is the fetus, then dexamethasone should be the drug of choice. There is little evidence of fetal teratogenesis or other serious fetal abnormalities caused by steroids except for sporadic reports of perinatal adrenal insufficiency resulting from large-dose maternal prednisone administration.[35]

Antimalarials are extensively used in the management of SLE. They have several types of pharmacological effect, such as immune modulation, antiplatelet aggregation, and decreasing cholesterol level. Some studies have documented fetal safety in maternal antimalarial therapy during pregnancy, and a survey in 2002 showed that the majority of lupus experts tended to continue this drug during pregnacy.[36,37] Nevertheless the drug can cross the placenta and avidly bind to pigmented tissue, especially the fetal retina. There were some individual reports of neonatal retinal degeneration as a consequence of maternal chloroquine intake for malarial prophylaxis. There are few large samples for a prospective study on this point. As a more cautious strategy, SLE patients should have a stable disease condition, without antimalarials, when preparing for a possible pregnancy. Considering the long half-life of the drug, there should be a period of several months before pregnancy to allow for drug excretion.

Immunosuppressive drugs are another group commonly prescribed for lupus patients. Many of them are known to be teratogenic in humans. Among these, cyclophosphamide

and methotrexate have the greatest potential risk for fetal death or malformation if used in the early trimester of pregnancy. Azathioprine is less toxic to the fetus. Ostensen[38] reported no increased risk of congenital abnormalities with azathioprine used in standard doses. Martinez[39] did not find any macroscopic malformations in live children of women who took azathioprine during pregnancy. Many (30/71) limited case reports have shown the fetal safety of cyclosporin A used for suppressing maternal SLE disease activity. On the whole, it seems less dangerous if these types of drug are applied in a period other than the first trimester of pregnancy.

There is little established information about the use of NSAIDs during pregnancy, except for aspirin and Indomethacin. Aspirin is a drug which is debatable for intrapartum administration. It can strongly inhibit platelet aggregation, and thus facilitate the microcirculation and prevent recurrent fetal loss, and decrease the occurrence of preeclampsia, and to some extent IUGR. It is indispensable in treating pregnant patients with APS. The production of thromboxane is increased in SLE patients, and the presence of APL may promote thromboxane dominance, which possibly contributes to an adverse outcome of pregnancy. Aspirin can eliminate this thromboxane dominance.[40] To date, animal and human studies have testified the teratogenicity of aspirin. It can cause cleft palates, constriction of the ductus arteriosus in utero, and neonatal pulmonary hypertension. Nevertheless, it has a high benefit/risk ratio if prescribed in low dosages, such as 50–60 mg daily. Large anti-inflammatory doses are not suitable because in the early trimester it maybe teratogenic, and later it will lead to a prolonged gestation or labor, as well as maternal fetal bleeding during delivery. Maternal indomethacin therapy is considered to be the cause of primary pulmonary hypertension in the newborn.[1,35]

Management for optimal maternal–fetal survival

SLE women should have detailed preconception medical counseling before pregnancy, and their past obstetric history must be reviewed. Careful assessment of maternal disease activity and severity is essential for maternal–fetal risk evaluation. It is better to conceive after 1 year of disease quiescence without any medication except for a low dose of corticosteroids, i.e., less than 10 mg prednisone per day. Such a dosage should also be prescribed to patients who have already stopped steroid therapy. All SLE pregnancy cases should be regarded as high-risk pregnancies, and require intense fetal–maternal surveillance through interdisciplinary collaboration. Patients with a history of thrombotic events or previous spontaneous abortion should be treated with heparin combined with low-dose aspirin, as well as other necessary medication. Low-dose aspirin should also be prescribed to those who are APL-positive but without a past history of thrombosis or abortion as prophylaxis for potential fetal loss. Some researchers recommend intravenous immunoglobulin (IVIG) infusion therapy for APL-positive patients with recurrent spontaneous abortion to improve the chances of fetal survival.[41]

Postpartum lupus exacerbation cannot be neglected either. Some articles suggested that increasing the corticosteroid dosage during the late stage of gestation may prevent postpartum disease flare. We have given an extra 100 mg intravenous hydrocortison, reduced daily, in the first 3 days immediately after delivery, and then switched to the normal dosage.

There are increased risks for the SLE fetus, as shown by a higher prevalence of spontaneous abortion, stillbirth, intrauterine growth retardation (IUGR), and prematurity. These adverse fetal outcomes are often associated with maternal disease activity, and APS in particular. Maternal active disease activity, positive APL, and anti-Ro/SSA and/or anti-La/SSB antibodies are all fetal risk factors that necessitate periodic monitoring of the fetus as well as of placental function. Nonstress tests (NST) and contraction stress tests (CST) are usually given to evaluate fetal cardiac performance, beginning between the sixteenth and twentieth week of gestation. Some time in the third trimester, if the fetus is compromised by maternal lupus flare or exacerbation, there is often an indication for elective preterm delivery, but the precondition is the relative maturity of the fetal lungs. By analyzing the ratio of lecithin and sphingomyelin in the amniotic fluid, we can estimate the degree of fetal pulmonary maturity. If the ratio is bigger than 1, a Cesarean is indicated, and then the neonate has a better chance of surviving respiratory failure. Dexamethasone therapy, either by maternal intramuscular injection or through amniotic cavity injection, will boost the fetal lung maturity and facilitate early Cesarean delivery.[22]

Heredity

SLE has shown no significant effects on the physical development of the patient's progeny. Most autoimmune antibodies which existed in the umbilical blood were transferred through the placenta during pregnancy, and will disappear within 9 years after birth.[42] Evidence for a genetic susceptibility to SLE can be seen as the high concordance rate observed in identical twins, and the relatively high incidence of familial cases. No definite mode of inheritance has been documented. Petri[43] asserted the hereditary susceptibility of SLE, but denied that it was a disease of inheritance.[43] Michel et al.[44] conducted a survey of 125 lupus multiplex families, and compared their disease characteristics with those of 100 sporadic SLE patients sharing the same French Caucasian origin. The relationships between affected members was 45% siblings, 31% parent–offspring, and 24% second-degree. Although the autosomal dominant mode was strongly suggested in one extended pedigree, with six clinically affected members, and a recessive pattern was suspected in five other families, no obvious mode of inheritance was suggested in most of the remainder. The disease patterns in multiplex families were not significantly different from those of sporadic cases. In our series of stud-

ies, we have found no neonatal SLE, and no SLE disease onset in the offspring of an SLE mother. Recent studies on the identification of susceptibility genes in Chinese lupus patients, suggested the presence of candidate susceptibility genes at 1q23.3 in Chinese SLE patients, and Bcl-2 gene polymorphism is associated with SLE and may be directly involved in linkage disequilibrium with some susceptibility loci nearby.[45] A definite conclusion on parent–offspring inheritance needs further long-term follow-up.

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