Overview of Systemic Lupus Erythematosus in Hong Kong Chinese: Part 2. Hormones, Pregnancy and Lactation

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Abstract: Systemic lupus erythematosus (SLE) is predominantly a women’s disease. The relative infrequency of the disease in men and in hypoestrogenemic women suggests that endogenous estrogen level may influence the expression of the disorder. A number of animal and in-vitro human studies have investigated the role of estrogens on disease activity of SLE. In the absence of prospective data, it is still unclear whether exogenous estrogens may exacerbate SLE. The relationship between pregnancy and lupus flares is also a subject of controversy but SLE patients should not be discouraged of having children. Lupus pregnancies are high risk pregnancies. Close collaboration with obstetricians and pediatricians is mandatory. A detailed pre-pregnancy counseling on the risk of maternal/fetal complications and congenital heart block should be conducted. Most of the medications used in SLE are excreted in breast milk and extra precautions should be taken. Appropriate contraceptive methods should be advised to lupus couples who do not plan for children.

Keywords: Estrogen, lupus, menopause, pregnancy, prolactin

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by a marked female predominance, through puberty to menarche. Although the female predilection becomes less prominent outside the reproductive age range, female preponderance remains. The overall female to male ratio of the incidence of the disease is around nine to one in all ethnic groups. First onset of SLE manifestations in women before puberty and after the menopausal age is uncommon. The relative infrequency of the disease in men and in women outside the childbearing age suggests that levels of endogenous hormones, particularly estrogens, may be important in the predisposition to the disease.

It is well recognized that SLE may flare during periods of rapid hormonal changes. The classical observation of disease exacerbation in SLE patients during pregnancy and the post-partum period root deeply in the mind of many general physicians and rheumatologists. Moreover, a number of case reports/series have described a temporal relationship between disease onset/flares and administration of exogenous estrogens. Recently, other hormones have also been implicated in lupus activity. One example is prolactin which is found to be immunostimulatory. Hyper-prolactinemia is associated with disease activity in certain subsets of SLE patients and during pregnancy. Although interaction with other endogenous hormones may also be important, hyperprolactinemia may contribute to disease flare in certain individuals.

As most patients with SLE are women of the childbearing age, pregnancy and its influence on disease activity and fetal well-being becomes a concern of many lupus couples. A detailed pre-pregnancy counseling is important in alleviating patient anxiety. Close monitoring of the disease and the status
of the fetus throughout the pregnancy course is mandatory. Whether SLE flares more frequently and more seriously during pregnancy is still controversial. Some of the anti-lupus medications are contraindicated for the pregnant and lactating women.16

In the second part of the review on SLE among southern Chinese in Hong Kong, the clinical relationship between sex hormone, prolactin and activity of lupus, data on SLE flares and fetal outcome during pregnancy, and the safety of various anti-lupus medications during pregnancy and lactation are briefly discussed.

Endogenous Estrogens and SLE

First onset of SLE after the menopausal age is uncommon. Compared with the younger age group, late (age >50 years) onset SLE was associated with a more insidious disease onset and less serious organ involvement, disease activity and flares.4,17,18 SLE patients with low female sex hormone levels at disease onset also appeared to have a lower relative risk of mortality when compared with those with high female sex hormone levels.19 Flares of SLE were also related to the menopausal status. In a study of SLE patients followed from diagnosis to menopause, it was reported that the number of severe disease flares per patient-year declined significantly after menopause.20 SLE patients who developed premature ovarian failure related to the disease itself or the use of cyclophosphamide (CYC) flared less frequently and severely when compared with those still menstruating but having received a not significantly different cumulative dose of CYC.21 However, in these two studies, the effect of age per se on disease activity of SLE could not be easily differentiated from that of the endogenous estrogen levels.

Although female SLE patients have normal estradiol levels, an increase in conversion of estrogens to their active metabolites has been demonstrated.22 Patients with more active disease were associated with higher level of estrogen metabolites. On the other hand, disease exacerbation has been reported in SLE patients who experienced hyperestrogenemia from attempts to enhance fertility such as ovulation induction and in vitro fertilization.23 Thus, the current evidence appears to suggest that a hypoestrogenemic state may protect against the onset of SLE and reduce the risk of severe flares in patients with established SLE, whereas an increase in the level of endogenous estrogens and their metabolites may be associated with disease activity in certain patients.

Exogenous Estrogens and SLE

Although epidemiological studies have shown that the use of exogenous estrogens such as oral contraceptives (OCs) and hormonal replacement therapy (HRT) increases the relative hazard of SLE development in healthy women, the absolute risk is small and should not be the chief deterrent for the prescription of these hormones.24,25 Moreover, the results could not be extrapolated to patients with established SLE.

A number of earlier case reports have linked the use of either OCs or HRT with onset or flares of SLE.6-10 Whether this is related to a publication bias or because of the use of a higher dose of ethinyl estradiol remains to be confirmed. Results from retrospective studies were not consistent.11,26 with one study describing increase in flares in patients with lupus nephritis who used OCs while another study did not report an increase in disease flares in SLE patients who received combined OC pills. In the absence of prospective randomized trial with validated tools to measure disease flares, whether OC pills exacerbate existing SLE remains unclear.

On the other hand, HRT appears to be safe in postmenopausal SLE patients. Three retrospective studies did not report an increase in disease flares in patients receiving HRT when compared with those who were not.27-29 HRT users reported a significant improvement in general well being, libido and depression.27 Although validated measures of disease flares were lacking, these studies suggested that HRT was well tolerated in postmenopausal SLE patients.

A prospective randomized double-blind multicenter study named Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) is going on in the United States.30 It is hoped that more definite data on the relationship between exogenous estrogens and disease activity of SLE will soon become available. Up to this moment, there is still no clinical data regarding the use of the selective estrogen receptor modulators (SERMs) such as raloxifene in patients with SLE.
Recommendations for the Use of Estrogens in SLE

In the absence of prospective data, whether the benefits of estrogen treatment outweigh its possible deleterious effect on disease activity remains elusive. Combined low dose estrogen OC pills may be considered for SLE patients without definite contraindications. Patients with major organ involvement such as active lupus nephritis or positive antiphospholipid antibodies are not candidates for combined OC pills because of the risk of disease exacerbation and thromboembolism. On the contrary, the slight increase in the risk of venous thromboembolism should not be the chief deterrent in the consideration of HRT in postmenopausal SLE patients without the antiphospholipid antibodies, considering its beneficial effects on the general well-being and bone mineral density.31

Pregnancy in SLE

The fertility rate of SLE patients is normal except in situations like uremia or premature ovarian failure related to the disease itself or as a result of cytotoxic therapy. SLE patients should not be discouraged of having babies. With careful pre-pregnancy counseling, choice of optimal timing of conception, identification of high risk patients, collaboration with other specialists and judicious monitoring of the disease, the maternal and fetal outcome of lupus pregnancies have greatly improved in the past decade.

Whether pregnancy is associated with an increased risk of flares in SLE is again controversial. Numerous retrospective and uncontrolled studies reported exacerbation of SLE during pregnancy. Well-designed prospective studies with controlled groups have yielded conflicting results. These studies have been summarized in a recent review article.16 The discrepancy of the findings can be related to the differences in the definition and assessment of lupus flares, selection of patients and controls, the proportion of patients with positive antiphospholipid antibodies and abortion during early pregnancy excluded from analysis, and the use of prophylactic steroids in late pregnancy. Despite the inconsistency, it appears that lupus flares during pregnancy are not uncommon and may occur at any trimester and in the postpartum period. Every pregnant SLE patient should be assumed to have a risk of flare and close monitoring for disease activity is necessary throughout the pregnancy course and the puerperium.

Active SLE at the time of conception was reported to be associated with a higher risk of disease flares during pregnancy.32-34 The incidence of disease flares in patients with lupus nephritis undergoing pregnancies ranges from 7.4% to 63%.16 Renal flares during pregnancy may run an aggressive course and may be fatal. Thus, in SLE patients, pregnancy is best undertaken during disease remission and nephritis, if present, should be in remission for at least six months prior to conception. The longer the patient is in remission at the time of conception, the higher is the chance that she can complete the pregnancy without disease flares.

Obstetric and Fetal Outcome of Lupus Pregnancies

Patients with SLE have an increased risk of pre-eclampsia which may develop in up to one-third of SLE patients with pre-existing nephritis.35 The presence of the antiphospholipid antibodies (aPL) is an additional risk factor.36 Differentiation between pre-eclampsia and nephritic flare during pregnancy can be difficult. Both conditions may coexist in the same patient causing hypertension, proteinuria, edema and worsening renal function. Hypocomplementemia, rising anti-dsDNA titres, active urinary sediments and the presence of other features of active SLE favor disease activity.16

Fetal wastage (abortions and stillbirth), prematurity and intrauterine growth retardation (IUGR) are more common in lupus pregnancies.37 Active lupus nephritis, previous history of fetal death and the presence of the aPL are predictive for fetal wastages.16 Fetal loss related to the antiphospholipid syndrome usually occurs in the second and third trimesters. The presence of both lupus anticoagulant and high titre IgG anticardiolipin antibody (aCL) is associated with the highest risk.38

Clinical trials appeared to suggest that low dose aspirin (75-100 mg/day) and prednisone might improve fetal outcome in aPL-associated recurrent pregnancy loss. However, this combination is no better than a regimen consisting of subcutaneous heparin and aspirin39,40 and the use of
prednisone is associated with pre-clampsia, premature rupture of membranes and pre-term deliveries. Several studies have shown that subcutaneous heparin in addition to aspirin provided a significantly better pregnancy outcome than aspirin alone in aPL-associated recurrent pregnancy loss\textsuperscript{41,42} and a higher dose of heparin is no better than a lower dose.\textsuperscript{43} For primiparous mothers or multiparous SLE patients with low titer IgG or IgM aCL but without a history of fetal loss, usually no specific therapy is recommended. Low dose aspirin should be considered for those patients who have high titre IgG aCL or positive lupus anticoagulant (LAC). High-risk patients such as those with history of recurrent fetal losses should be treated with a combination of low dose aspirin and subcutaneous heparin.

The Neonatal Lupus Erythematosus (NLE) Syndrome

NLE is a syndrome consisting of congenital heart block (CHB), transient cutaneous lupus lesions, cytopenia, hepatic and other systemic manifestations in children borne from mothers with systemic lupus erythematosus, Sjogren’s syndrome or other rheumatic diseases with a positive anti-Ro or anti-La antibodies. The antibodies are usually cleared over weeks and most of the manifestations are mild and transient except for congenital heart block (CHB), which is permanent and carries significant morbidity and mortality to the offspring.\textsuperscript{44} Having SLE \textit{per se} is not an independent risk factor for the development of CHB but rather it depends solely on the presence of anti-SSA/Ro or anti-SSB/La antibodies. For SLE patients with a positive anti-Ro, the risk of CHB is between 1.5-20.5\%, with an average figure of 7.2\% after pooling the data from various studies.\textsuperscript{45} The risk of CHB is higher with the presence of the anti-52 kD SSA/Ro by immunoblot.\textsuperscript{46} The risk of having another child with CHB in those who have already had one child with CHB is around 12\%. This figure is similar to that reported by Buyon et al. in which the recurrence rate of CHB in 49 mothers with subsequent pregnancies was 16\% over a 27-year period.\textsuperscript{47}

Although the anti-ENA antibodies are not essential for routine disease monitoring in SLE, screening for anti-Ro and anti-La antibodies is recommended for SLE patients who plan to be pregnant. Mothers with positive anti-Ro (especially the anti-52kD SSA/Ro) or anti-La antibodies should be counseled for the risk of the NLE syndrome. The fetal heart rate should be monitored and fetal echocardiogram should be done for high-risk mothers during the 16th to 24th week of gestation.

Safety of Lupus Medications during Pregnancy

Use of high dose salicylates during pregnancy has been associated with prolonged gestation and labor, increased bleeding complications during delivery, oligohydramnios, premature closure of the ductus arteriosus and pulmonary hypertension.\textsuperscript{16} However, there is still no evidence that aspirin and other currently available non-steroidal anti-inflammatory drugs (NSAIDs) are teratogenic in human.\textsuperscript{48} High dose aspirin or NSAIDs should be avoided during the last few weeks of pregnancy because of their possible effects on uterine contraction, platelet function and physiological changes that are taking place at and before birth in the fetus such as closure of the ductus arteriosus.

Although cleft palates have been reported with corticosteroid use in pregnant animals, these are rare in human and there is no solid evidence that they are more common than the background incidence of congenital anomalies in normal pregnancies.\textsuperscript{49} No major adverse effects of corticosteroids on babies have been reported in various published series of lupus pregnancies so far.\textsuperscript{16}

Unlike chloroquine in which congenital anomalies have been reported for its use in pregnancy, hydroxychloroquine-induced congenital malformations have not been described.\textsuperscript{90} A recent study of 36 infants from 33 mothers who were taking hydroxychloroquine during pregnancy did not report any congenital anomalies attributable to the drug.\textsuperscript{51} On the contrary, withdrawal of hydroxychloroquine may lead to lupus flares\textsuperscript{52} and the drug should not be discontinued unnecessarily in pregnant SLE patients.

Azathioprine (AZA) is teratogenic in animals. Sporadic congenital anomalies, IUGR, lower birth weights and prematurity have been reported in kidney transplant recipients who received AZA and/or prednisone during pregnancy.\textsuperscript{53,54} Although increases in the rates of birth defects, miscarriages and stillbirths have not been definitely established in association of AZA use, the number of reported cases with adequate follow-up may not be sufficient to detect a small
increase in these rates or to detect late-occurring abnormalities. For patients in whom immunosuppression is absolutely necessary during pregnancy, AZA is a reasonable choice and temporary discontinuation can be considered in the first trimester when the fetus is most vulnerable to the effect of the drug.

Cyclophosphamide (CYC) is teratogenic in animals and in human and is contraindicated in pregnancy. Appropriate advice on contraception should be given to patients during periods of CYC therapy.

Cyclosporin A (CSA) is not an animal teratogen. Increasing data in human pregnancies suggests that there is no increased risk of congenital anomalies in the exposed fetuses. In a large series of 115 renal transplant recipients with 154 pregnancies, CSA was found to be associated with lower birth weights but no malformations were observed. CSA may be considered as an alternative to other cytotoxic agents for the control of severe disease activity in pregnant SLE patients.

**Lactation**

Most drugs used for the treatment of SLE are excreted into breast milk. With immature neonatal metabolism, salicylate intoxication can theoretically occur in infants whose mothers are chronically taking anti-inflammatory doses of aspirin. For this reason, the American Academy of Pediatrics (AAP) recommends that aspirin should be used with caution during breast-feeding and big doses should be avoided.

Most NSAIDs do not achieve high concentration in breast milk. The AAP considers ibuprofen, indomethacin and naprosyn to be safe with breast-feeding. NASIDs that exhibit enterohepatic circulation (eg. sulindac) are better avoided. Moreover, as NSAIDs displace bilirubin, they are contraindicated in jaundiced neonates because of the increased risk of kernicterus. Overall, NSAIDs should be used cautiously in nursing mothers and alternative analgesics such as paracetamol should be considered.

Small amount of corticosteroids can be found in breast milk of women taking these drugs but no adverse reactions have been reported. The AAP considers prednisone and prednisolone compatible with breast-feeding. Low concentration of hydroxychloroquine can be found in breast milk. Although this drug is classified as compatible with breast-feeding, it should be used cautiously because of its slow elimination rate and potential accumulation to toxic amount in the infant.

Cytoxic agents such as CYC, AZA, CSA, methotrexate (MTX) are excreted in breast milk and their use is not recommended in nursing mothers. Breast-feeding should be avoided in patients who require these agents for disease control.

**Prolactin, Anti-prolactin Antibody and SLE**

Prolactin is immunostimulatory. Prolactin level normally rises during the second and third trimester of pregnancy and hyperprolactinemia persists for several months in patients who breast-feed their children. Earlier studies have demonstrated that increased prolactin level in non-pregnant SLE patients was associated with disease activity but later and larger studies did not confirm this result. There is still no data regarding disease flare and breast-feeding in SLE. A SLE patient who had a postpartum relapse of SLE after a period of quiescent disease for more than four years was recently reported. The disease flare was temporally related to breast-feeding with confirmed hyperprolactinemia. As the levels of other hormones were unavailable, the contribution of hyper-prolactinemia per se to this flare could not be ascertained and more cases and controls are needed to confirm this observation.

Anti-PRL antibody was found in about 5% of patients with SLE. The presence of this antibody was associated with a higher prolactin level and hyperprolactinemia in a small subset of SLE patients. However, the exact relationship between hyperprolactinemia and the anti-PRL antibody is still unclear and the significance of the latter warrants further studies.

**Contraception**

For young (≤35 years of age), non-smoking and normotensive SLE patients without a personal/family history of estrogen dependent tumors and thrombotic risk factors such as positive antiphospholipid antibodies, and with stable disease for a considerable period of time, low dose estrogen-containing...
combined OC pills are not contraindicated. For patients who are not candidates for OC pills, progestogens such as progestogen-only pills and depot progestogens (e.g. ®Depot Provera) are alternatives. Intrauterine contraceptive device is associated with increase incidence of infection and is not usually recommended for SLE patients who are receiving immunosuppressive therapy. Mechanical barrier methods such as condom with spermicides and diaphragms are safe and effective and may be suitable for those patients who are contraindicated for contraceptive methods described above.

Conclusion

Although estrogens exhibit a number of deleterious in-vitro effect on SLE and exacerbate the disease in animal models, whether clinical administration of exogenous estrogens in human SLE patients is associated with disease flares remains controversial. SLE patients should not be discouraged of having children. A thorough discussion with the lupus couples regarding the risk of disease flares, optimal timing of conception, possible maternal and fetal complications during pregnancy and their consequences is essential. Pregnancy is best undertaken when the disease, especially lupus nephritis, is in clinical remission for at least six months. Appropriate counseling for the risk of neonatal lupus syndrome should also be given to those patients with positive anti-Ro or anti-La antibodies. Aspirin and/or subcutaneous heparin should be considered for those who have recurrent miscarriages and positive antiphospholipid antibodies. Lupus pregnancy is a high-risk pregnancy and judicious monitoring for disease flares and thromboembolic phenomena during the pregnancy course and the puerperal period is mandatory. Regular surveillance for the well being of the fetus should be performed. Fetal ultrasonography/echocardiography is useful in picking up congenital heart block during the second trimester of pregnancy and monitoring for progress.

References