Pregnancy of a lupus patient—a challenge to the nephrologist

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with a predilection for women in their reproductive years. The influence of sex hormones on immunity is only beginning to be unravelled, is fascinating and may explain some of the contradictory reports of the effects of pregnancy on SLE and vice versa [1]. Clinical renal involvement occurs in up to 60–80% of lupus patients at some time point in their disease course. In the pre-steroid era, patients with severe lupus nephritis (LN) rarely survived beyond 2 years. With improved therapy of SLE/LN, survival and quality of life for lupus patients have improved vastly. This holds true even for the Asian region [2,3]. Thus, pregnancy and its outcome are a major concern for most SLE/LN patients and their doctors. Indeed, early reports of pregnancy outcome were quite dismal and underscored active disease at conception, hypertension, proteinuria, moderate renal dysfunction and the antiphospholipid syndrome as major risk factors for pregnancy losses, pregnancy-induced hypertension and pre-eclampsia, progressive renal function deterioration and even the occasional maternal death [1,4–8]. Newer issues relate to neonatal lupus, iatrogenic premature ovarian failure and breast feeding in the presence of immunosuppressive and other drug therapy for control of the underlying SLE/LN. All these complex issues pose a real challenge to the clinician and the nephrologist in particular.

Fertility in SLE

SLE patients are as fertile as the general population [7]. However, a pregnancy rate of 2.0–2.4 per patient has been reported not only during disease quiescence but also during active disease [3,4]. However, a lowered fertility rate is seen in patients with active disease when on high dose steroid therapy and in patients with established renal disease and moderate to severe renal failure [8]. The frequency of premature ovarian failure from cyclophosphamide used for the treatment of severe LN in the past two decades ranges from 11 to 59% and its risk is related to the age of the woman at start of therapy, duration and cumulative dose of cyclophosphamide [9–11].

Effect of pregnancy on SLE/LN

Whether lupus flares are more frequent during pregnancy remains controversial. Flares occur during all trimesters and often also occur post-partum. The frequency of flares ranges between 7 and 33% in women who have been in remission for at least 6 months prior to conception, but flares occur in up to 61–67% of patients if the disease was active at conception [4,5,12,13]. Prospective controlled studies have also reported contradictory results. Some authors found no difference in flares when pregnant SLE patients were compared with matched non-pregnant lupus controls [14,15]. Others reported a similar experience in their pregnant patients with inactive LN at conception [16,17]. Petri et al. and Ruiz-Istaroza et al. reported that pregnancy exacerbated lupus activity [18,19]. Overall most studies of patients with LN favour planned conception after 12–18 months of established remission [1,13,16,17]. Patients with anticardiolipin (aCLs) and/or a positive lupus anticoagulant (LA) are also at increased risk for flares [20,21]. Hence, a comprehensive pre-pregnancy screen should include lupus serology, serum complement levels, antiphospholipid antibodies (aPLs) and anti-La/SSB antibodies, and is important in order to enable the nephrologists to provide appropriate prophylaxis.

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Effect of SLE/LN on pregnancy—obstetric and fetal outcome

Historically, lupus pregnancy was associated with a high rate of obstetric and fetal complications. These include spontaneous abortion (20–30% both pre- and post-diagnosis of SLE), late miscarriage, intrauterine growth retardation, intrauterine death, preterm delivery and prematurity, with an overall fetal loss as high as 50% in unplanned pregnancies vs 13% in planned pregnancies [1,12,13,15,16].

Two major SLE complications influence pregnancy outcome, i.e. LN and the antiphospholipid syndrome.

Lupus nephritis

In the presence of LN, in past studies fetal losses ranged from 8 to 36%, miscarriages between 4 and 31%, and stillbirths or neonatal deaths between 4 and 23% [1,4,5,12,13]. The number of therapeutic terminations of pregnancies in these studies ranged from 0 to 19% and contributed to the total fetal wastage mentioned earlier. However, the activity of LN at conception greatly impacted on fetal losses which ranged between 25 and 57% in women with active LN vs 8–12.5% in those with quiescent renal disease [16–19].

How then should renal remission be defined? For the purpose of pregnancy, I believe it should be defined as past LN with stable renal function and with serum creatinine in the normal range or estimated glomerular filtration rate (eGFR) > 60 ml/min/1.73 m², urinary red cells < 5/high-power field, proteinuria < 0.5 g/day and normal (ideally) serum C3 levels for at least 12–18 months and not 6 months only as proposed by others [1,13,16,17,22,23].

Pre-eclampsia vs active lupus nephritis

In patients with lupus, pregnancy is associated with an increased risk of pre-eclampsia of 13–32 vs 3–5% in healthy women [1,12,23–26] and the risk is particularly high if the patient has pre-existing hypertension, active LN or established chronic kidney disease and the antiphospholipid syndrome.

Pre-eclampsia is often difficult to distinguish from active LN. Pre-eclampsia is more likely in patients with antiphospholipid syndrome, past pre-eclampsia or in patients who have hypertension, LN or diabetes mellitus. Both conditions can present with hypertension, proteinuria, oedema and renal function deterioration, and may co-exist in the same patient. The distinction is important as management is vastly different. Active LN is more likely if baseline proteinuria doubles and is associated with active urine sediment (red cells, white cells and cellular casts), low serum complement and increased titres of anti-DNA antibodies [1,12,13,27,28]. Extrarenal lupus manifestations are helpful when present. In contrast, pre-eclampsia is more likely to be associated with thrombocytopenia, elevated serum liver enzymes and uric acid, as well as reduced urinary calcium excretion. Whilst treatment with steroids is mandatory in active LN, steroids will typically aggravate pre-eclampsia.

In contrast to active lupus, proteinuria also declines rapidly with the delivery of the baby in pre-eclampsia.

Other renal risk factors

Apart from active LN and pre-eclampsia, other renal risk factors that impact on fetal outcome include proteinuria, impaired renal function and hypertension. Fetal loss ranged between 36 and 38% in lupus patients with pre-pregnant proteinuria ≥ 0.5 g/day compared with 13% in patients without proteinuria, suggesting that renal lupus should be fully quiescent before pregnancy is advisable [1,8,12,13,16].

Impaired renal function is another strong predictor of poor fetal outcome not only in lupus patients, but also in pregnant women with other renal diseases [1,8,12,13]. In patients on chronic maintenance haemodialysis, the success rate of pregnancy is <50% [29]. Successful pregnancy outcome in female LN patients transplanted for end-stage renal failure is comparable with that of renal recipients with other diagnoses (73% live births in SLE patients vs 76% in controls) [30].

Pre-existing hypertension, whether primary or resulting from steroids (and, recently, cyclosporin A and tacrolimus), past or present LN, as well as the presence of the antiphospholipid syndrome, are risk factors for pre-eclampsia with its attendant morbidity and mortality. Fetal loss occurred in 27% of normotensive women as compared with 70% in hypertensive mothers [6].

In the early 1990s, many studies reported that antiplatelet agents, especially low to moderate doses (75–100 mg) of aspirin, were useful to prevent pre-eclampsia in high-risk pregnancies [31]. Knight et al. reviewed 51 trials involving 36 500 women and showed a 19% reduction in the risk of pre-eclampsia with the use of antiplatelet agents. Overall, there was a 16% reduction in infant deaths and an 8% reduction in the risk of low birth weight babies [31]. Kincaid-Smith et al. reported that low-dose heparin was also useful for pre-eclampsia prophylaxis [32].

Antiphospholipid syndrome

The antiphospholipid syndrome is defined by the presence of aPLs in association with vascular thrombosis (arterial and venous) and/or recurrent abortions in women [33,34]. Other features include thrombocytopenia, neurological disease or livedo reticularis. Three different types of antibodies have been described, i.e. aCLs, circulating lupus anticoagulants and antibodies to the β(2) glycoprotein-1 (anti-β2GP-I).

In a review of some 14,000 women, Kuttet found that the prevalence of aPLs was 5% in normal obstetric patients, 24% in women undergoing in vitro fertilization and 37% in women with SLE [35]. A meta-analysis of 10 studies and 554 patients found that fetal loss was more common in women with than those without
aPLs (38–59 vs 16–20%), LA (36 vs 13%) or aCLs (39 vs 18%) [36]. Although high-titre aPLs are the best immunological predictors of fetal loss in SLE patients, previous fetal loss is an even more powerful predictor [34].

The aPL confers increased risk of thrombosis in the mother and severe early onset of pre-eclampsia. It also causes a placental vasculopathy leading to fetal intrauterine growth retardation and death, although the precise pathogenetic mechanisms have yet to be fully defined [37,38]. Both Kutteh et al. and Rai et al. reported that aPL-positive lupus patients, if left untreated, will only have a live birth rate of 20%. With the use of low-dose aspirin, the live birth rate increased to 42–44%. With combined low-dose aspirin and low-dose low molecular weight heparin (LMWH), live birth rates almost doubled to 71–80% in their respective studies [39,40]. High-dose steroids were of no benefit. [41].

There is a dearth of data concerning Asian lupus patients. Mok et al. from Hong Kong reported a prevalence of 27% (n=18) aPL positivity in their experience with 91 pregnancies in 66 pregnant lupus patients. Positivity for aPL was associated with recurrent miscarriages. The LA was the strongest predictor [odds ratio (OR) = 23.3, P = 0.002] [42]. In our own retrospective review of 197 pregnancies in 82 women, aPL screening was performed in 73 patients. LA was positive in 10 (17%) of 60 patients [23]. aCL, IgG and IgM antibody determinations were performed in all 73 patients, and 19 (26%) patients tested positive. Five patients were positive for all three aPLs; three of these suffered 11 fetal losses between them and one had no living child. Twenty-four (33%) of these aPL-positive patients had the antiphospholipid syndrome. There was a significant association between fetal wastage and aPL (P < 0.0001) and between the aPL and LN (P < 0.02). Thus, our experience concurs with that of most published studies.

Neonatal lupus

Anti-Ro/SSA and anti-La/SSB antibodies are present in some 30–50% of SLE patients in most reported series including our own [43–45]. These IgG antibodies cross the placenta to cause neonatal lupus in 5% of babies born to these mothers. Subsequent children have a 15–25% risk. Anti-Ro antibodies confer a 1–2% risk, whereas anti-La antibodies confer a 5% risk [44]. The majority of the affected babies suffer a transient and often mild lupoid rash lasting 3–6 months. Other clinical manifestations include immune thrombocytopenia, autoimmune haemolytic anaemia and cholestatic hepatitis. The most severe complication is congenital heart block (CHB). CHB is diagnosed by fetal bradycardia at ~18–23 weeks. Some 20% of the affected infants die in the neonatal period and most survivors require permanent pacemakers. Dexamethasone (which crosses the placenta) and plasmapheresis provided short-term benefits only. Intravenous immunoglobulins have been reported to be useful, but numbers are small [44]. Hence, all lupus patients contemplating pregnancy should also have their anti-Ro/SSA and anti-La/SSB status determined. Affected fetuses should be referred to the paediatric cardiologist for close monitoring.

Medications in pregnancy and the puerperium

The goals of therapy are to maintain the mother with SLE/LN in disease remission, provide prophylaxis against the aPL-associated thrombotic complications, prevent and treat hypertension and pre-eclampsia, as well as optimize fetal growth and well being. The mother should be counselled and prepared in advance for pregnancy.

Maintenance hydroxychloroquine at 200 mg daily has been demonstrated to be safe and reduces flares, fetal wastage, intrauterine growth retardation and fetal distress. It is also safe for breast feeding [46–48]. Low to moderate dose aspirin, low-dose or therapeutic dose heparin (LMWH) should be instituted for prophylaxis against pre-eclampsia and thrombosis in the aPL-positive patients and in patients at risk for pre-eclampsia. For past severe LN, the immunosuppressive therapy should be switched in advance to appropriate agents. In particular, azathioprine (1–1.5 mg/kg/day), low-dose cyclosporin A (2 mg/kg/day) and low-dose steroids (7.5–10 mg daily) are safe [13,49,50]. However, except for children of mothers on low-dose steroids (<15 mg/day), breast feeding is inadvisable. Medications must be avoided which can cause birth defects, adverse reactions or are excreted in breast milk. These include cyclophosphamide, methotrexate, mycophenolate mofetil, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, long-acting non-steroidal anti-inflammatory drugs (NSAIDs) and warfarin (first and third trimesters) [13,48–50].

Conclusions

Pregnancy in a lupus patient, especially after severe LN, continues to pose a major challenge to the nephrologist. Albeit fraught with potential risks and complications, current pregnancy outcome is definitely more optimistic and gratifying when planned to occur during disease remission and under close supervision by an experienced, dedicated, multidisciplinary team. Prophylactic measures against the aPL-associated vasculopathy and against pre-eclampsia are available and achieve a high rate of success. Nonetheless, vigilance for disease flares, pregnancy-induced hypertension, pre-eclampsia and the rare fetus with CHB should be maintained, and adequate facilities for the care of preterm babies are crucial.

Conflict of interest statement. None declared.
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