Pregnancy outcome in connective tissue diseases

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ABSTRACT

Objective: To describe the pregnancy outcome in women with systemic lupus erythematosus and other connective tissue diseases attending a specialized high risk clinic at the Royal London Hospital.

Methods: Retrospective review of 30 patients seen over a 30-month period. Diagnoses included 18 patients with lupus and 5 with mixed connective tissue disease. Patients were evaluated following a standardized protocol.

Results: For all patients there were 28 (93%) live births and 2 spontaneous abortions. Of the live births, 6 (21%) were preterms and 5 (17%) were small for gestational age. For the 18-lupus patients there were 17 (94%) live births and one spontaneous abortion. Of the live births, 3 (18%) were preterm, 25% were small for gestational age and one had neonatal lupus erythematosus. Nine patients (30%) were positive for anti Sjogren's syndrome A antibodies: 7 systemic lupus erythematosus patients (39%) and 2 mixed connective tissue disease patients. Eight patients were positive for anti-phospholipid antibodies: 5 for anti-cardiolipin and 3 patients for lupus anticoagulant.

Conclusion: Most pregnancies complicated by lupus do well with no maternal or neonatal deaths in a multidisciplinary high-risk clinic. However a high rate of prematurity and small gestational age remains a problem.

Keywords: Pregnancy outcome, connective tissue diseases, lupus.

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Studies in pregnant patients with systemic lupus erythematosus (SLE), both retrospective and prospective have identified substantial fetal, neonatal, and maternal risks for pregnant women with lupus.[1-2] These include an increased incidence of spontaneous abortion, prematurity, small for gestational age (SGA), neonatal lupus syndrome and higher perinatal mortality.[3] The observed incidence of these outcomes has varied widely, reflecting advances in obstetric and neonatal care in recent years. However prematurity remains a problem even in planned pregnancies in SLE patients.[4] Neonatal lupus erythematosus (NLE), a disease of the newborn defined by the presence of maternal auto-antibodies and characteristic clinical features in the neonatal period,[5] occurs in 1-4% of pregnancies.[6] Typical features include lupus dermatitis, congenital complete heart block, thrombocytopenia or cholestatic jaundice and these clinical features are likely to result from fetal or neonatal tissue damage caused by maternally transmitted immunoglobulin G (lgG) autoantibodies (anti Sjogren's syndrome A antibodies (anti-SSA/Ro) and anti Sjogren's syndrome B antibodies (anti-SSB/La)).[7-9] Other specific autoantibodies confer a high risk of fetal loss or SGA (for example, anticardiolipin antibodies and lupus anticoagulant antibodies).[10] Predictive factors for adverse fetal outcomes include maternal renal disease, hypertension and active disease at the time of conception.[3] Other connective tissue diseases have a variable affect on the pregnancy.[11] Pregnancy is associated with improvement in the clinical signs

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and symptoms of rheumatoid arthritis in more than 70% of patients.[11] It carries higher risks for both mother and baby in scleroderma[12] while, pregnancy outcome is generally good in Behcet's patients.[13] In January 1998, we established a high-risk clinic to look after pregnant women with connective tissue diseases (CTD). The aim of this study is to describe the neonatal outcome in CTD patients particularly lupus patients who were followed up in this clinic until June 2000 (30 months).

Methods. ***Entry criteria.*** All pregnant patients who had been seen in the combined CTD/antenatal clinic at the Royal London were included in the study. Patients who fulfilled the 1982 American College of Rheumatology classification criteria for SLE[14] were labelled as lupus patients and studied separately.

Management policy. Patients were counselled before pregnancy and advised to plan pregnancy when the disease was inactive. The patients were booked to the combined clinic within 2 weeks of their first positive pregnancy test. They were reviewed frequently by the rheumatologist/ obstetrician team, monthly for the first trimester, fortnightly during the 2nd trimester and then weekly until delivery. Lupus patients had their disease activity assessed at each visit using the European Consensus Lupus Activity Measurement (ECLAM),[15-16] which, gave objective serial evaluations of maternal disease activity. All the pregnancies were evaluated with sequential ultrasonographic and Doppler examinations. Patients with positive antiphospholipid antibodies and previous fetal losses received low dose aspirin before conception and throughout pregnancy, together with low molecular weight heparin (LMW) throughout pregnancy. Patients previously on warfarin were converted to therapeutic doses of LMW heparin with monitoring by anti coagulation factor Xa (anti Xa) levels for the whole pregnancy.

Data collection. The following information was obtained from the patients records: the time of CTD diagnosis (before or during pregnancy), gestation at booking, immunological markers particularly maternal antibodies to SSA/Ro-SSB/La and antibodies to phospholipids (APA), cardiolipin (aCL) and lupus anticoagulant, markers of lupus activity (plasma creatinine, complement level, anti deoxyribonucleic acid (DNA) antibody levels, degree of proteinuria and blood pressure), treatment received during pregnancy, number of antenatal visits in each trimester, gestation at delivery, outcome of delivery (live birth, stillbirth or abortion), onset of labor (spontaneous or induced) and mode of delivery (vaginal, instrumental or cesarean section). The following data was obtained from the babies' records: birth weight, presence of neonatal lupus (congenital heart block, skin manifestations, thrombocytopenia, hepatitis and cholestatic jaundice).

Terms. Spontaneous abortion was defined as a spontaneous pregnancy loss at less than 24 weeks gestation; premature birth was a live birth less than 37 weeks gestation and SGA as sex-specific birth weight below the 10th centile of standard population charts, which is the recommendation from a World Health Organization (WHO) Expert Committee.[17]

Statistical analysis. Each pregnancy was treated as a separate observation. Descriptive statistics were used in the analysis for the whole group and for lupus patients separately.

Results. A total of 30 women were seen in the clinic between January 1998 and May 2000. Their median (range) age was 31 (20-40) years. Fifteen women were Caucasian, 8 Black, 6 Asians and one Moroccan. Diagnoses were: SLE (Number = 18, one patient had lupus and Sjgren's syndrome), SLE like illness (2), MCTD (5), primary anti-phospholipid syndrome (APS) (1), polyarteritis nodosa (PAN) (1), Behcet's disease (BD) (1), rheumatoid arthritis (1) and systemic sclerosis (scleroderma) (1). For lupus patients: median (range) age was 30 (22-40) years, 3 patients (20%) were diagnosed during pregnancy and the rest were diagnosed before pregnancy. All other patients, CTDs were diagnosed before pregnancy. The median (range) gestation at the first clinic visit for all patients was 8 (5-22) weeks and for SLE patients was 7 (5-18) weeks. The median (range) number of antenatal visit during the 1st trimester was 3 (0-5) visits for all patients and 4 (0-5) for SLE patients; during the 2nd trimester was 3 (1-6) visits for all patients and 3.5 (1-6) for SLE patients; during the 3rd trimester was 4.5 (2-8) visits for all patients and 4 (2-7) for SLE patients. Six lupus patients had a renal involvement with significant proteinuria and one patient had a lupus exacerbation during the pregnancy. Medication received singly or in-combination during pregnancy was 12 (9 SLE) patients had prednisolone, 9 (6 SLE) azathioprine, 12 (6 SLE) aspirin, 9 (8 SLE) heparin and 6 (4 SLE) hydroxychloroquine. One patient required insulin for gestational/steroids associated diabetes.

Auto-antibodies: Anti-SSA/Ro. Nine patients (30%) were positive for anti-SSA/Ro: 7 SLE patients (39%) and 2 MCTD. One of the lupus patients had cesarean section (CS) at 31 weeks for SGA and heavy proteinuria and generalized edema related to an exacerbation of lupus + pre-eclampsia, and another patient had a baby with neonatal lupus characterized by dermatitis (born at 36 weeks). The rest had normal babies including one lupus patient with a history of neonatal death of a previous pre-term baby (27 weeks gestation) because of congenital heart block.

Anti-phospholipid antibodies. Eight patients were positive for anti-phospholipid antibodies, 5 for anti-cardiolipin and 3 patients for lupus anticoagulant.

They were treated with: aspirin (N=4), heparin (2) or aspirin and heparin (2).

Only one patient had a miscarriage at 6 weeks gestation. A further patient had a pre-term delivery at 36 weeks, having had a previous intrauterine death at 33 weeks GA. She subsequently suffered from a full thickness anterior myocardial infarction one-year later when she was 23 years old and had high titre IgG anti-cardiolipin antibodies (>1000/ml). Her pregnancy was complicated with ventricular ectopics and episodes of chest pain despite therapeutic doses of LMW heparin, though she had an uneventful CS. The rest of the patients had full term normal deliveries. Three patients had both APA and anti SSA/RO antibodies, they had normal babies at term.

Outcome. Of the 30 pregnancies, 28 (93%) resulted in a live birth and 2 in spontaneous abortions (one SLE who had APS at 6 weeks gestation and the other one Behcet's patient at 9 weeks). Therefore the live birth rate for lupus pregnancies was 94%. Median (range) gestation of the 28 live births was 37 (27-43) weeks, for the 17-lupus pregnancies 37 (31-43) weeks. Seven babies were born prematurely (21%) at median (range) 36 (27-36) weeks: 3 to lupus mothers (18%), 2 (twins) systemic sclerosis, one MCTD and one primary APS. Two lupus patients had an emergency CS at 31 weeks gestation: one for pre-eclampsia and another one for SGA and heavy proteinuria and generalized edema related to a flare of lupus + pre-eclampsia. The 3rd patient with anti-phospholipid syndrome had a planned CS at 36 weeks gestation. One patient with systemic sclerosis had a spontaneous pre-term delivery at 27 weeks of twins who had a prolonged admission to the special care baby unit and both were discharged in good condition. For the 23 live births for whom accurate birth weights were available, median (range) birth weight was 2.9 (0.76- 4.7) kg, for the 12 babies of SLE patients 2.9 (1.17-4.7) kg. The mean weight standard deviation (SD) was -0.9 +/- 1.793 and -0.67 +/- 2.02 subsequently. Five babies were SGA 17% (3 to SLE patients 25%). Two patients had evidence of lupus nephritis at the time of conception: one of them had quiescent disease throughout pregnancy and had a full term healthy baby; the 2nd one had a flare up of the disease during pregnancy with evidence of growth retardation. Therefore she had a CS at 31 weeks gestation. Another patient had a mild flare up of her SLE during pregnancy. However, she had a full term baby with no complications. None of the patients were hypertensive during pregnancy, except one who had pre-eclampsia and required emergency CS at 31 weeks gestation. Lupus patients who developed the disease during pregnancy: 2 had full term babies, but the 3rd one had SGA and developed cutaneous neonatal lupus, which resolved by 8 weeks of age.

Neonatal lupus erythematosus (NLE). Only one baby had neonatal lupus manifested by skin rash after 2 weeks from birth and improved gradually. Another baby had transient elevation of liver enzymes. No cardiac or hematological manifestations were observed.

Discussion. Our study focused on fetal outcome in pregnancy complicated by maternal lupus, monitored closely in a special clinic. We also report our observations in patients with other connective tissue diseases. Various complications had been reported previously in lupus pregnancy.[1,6,7] Recently a reduction in fetal complications has been observed. Le Huong et al reported an improvement in fetal loss from 18%[18] to 4%[4] in planned lupus pregnancies. However, a high percentage of preterm delivery remained a problem. Ninety four percent of our lupus pregnancies resulted in a successful outcome. This is a similar to the recent results of Le Huong et al[18] of 96%. However, others reported a lower successful rate: Rahman et al[3] of 60%; Petri et al[19] 60% and Lima et al[20] 82%. There was a high percentage of fetal loss (spontaneous or therapeutic abortion and still birth) in previous studies.[3,18-21] Only one patient had a fetal loss in our cohort, however the numbers were small. Eighteen percent of our lupus patients had pre-term delivery, which is better than the high prevalence reported in previous studies ranging from 24%-43%.[3-4,19-21]

Twenty five percent of lupus patients had babies who were SGA, which is similar to previous reports: Le Huong et al of 29%,[18] Lima et al of 18% and Aggarwal et al 40%.[22] However, others reported a lower incidence of SGA: Rahman et al 8%[3] and Julkunen et al 13%[21] but this was dependant on groups studied. Small gestational age in those babies is most likely secondary to growth restriction as none of the babies exhibited congenital abnormalities and they cannot be classified as normal small babies.[23] Established lupus before pregnancy carries a poorer fetal outcome than when it develops during pregnancy.[1] All 3 patients who developed lupus during pregnancy in our cohort had live birth babies. Other clinical predictors for poor outcome include active renal disease, hypertension[3] and proteinuria during pregnancy.[18] In our study the only hypertensive patient and the patient with renal involvement with a lupus flare up required pre-term delivery. Anti-phospholipid syndrome is a unique subset of SLE, which carries a poor fetal prognosis[24-26] and higher incidence of IUGR.[27] All 8 patients in our cohort except one managed to have normal full term babies on the now established treatment of aspirin and LMW heparin.[28] A previous pilot study of intravenous immunoglobulin did not show improvement in obstetric or neonatal outcomes beyond those achieved with a heparin and low-dose aspirin regimen.[29] There was no congenital abnormalities observed, although Rahman et al reported a 2% incidence of congenital abnormalities, particularly cleft lip, which was thought to be secondary to treatment such as prednisolone. Of the 30 patients reported, 9 mothers were on azathioprine and 6 on hydroxychloroquine throughout pregnancy without fetal or maternal adverse effects. Only one infant of anti-Ro positive mother was diagnosed as a neonatal lupus (6%). Rahman et al reported an incidence of 3.5%,[3] Le Huong et al 4% and Lima et al 10%. Neonatal lupus erythematosus presents with either transit cutaneous manifestations like our case or with more permanent manifestations of congenital heart block, hepatic or hematological presentation.[30] As mentioned before, it is related to trans-placental transfer of IgG anti-Ro antibodies,[5] however it had been reported in anti RO negative mothers.[31] In our cohort one of the anti-RO negative mother's baby had a transient elevation of liver enzymes. The number of women affected with other connective tissue diseases who were seen in the clinic is small, but the overall outcome was good, and better than previous studies.

In conclusion, the live birth rate in this series was 94%. There was an increase in SGA and prematurity and the incidence of NLE is in keeping with previously published figures. Our study confirms the value of (a) Pre-pregnancy counselling, (b) Maintenance of disease remission before and during pregnancy with immuno-suppressive therapy where necessary, (c) Close and frequent monitoring throughout pregnancy in high risk CTD/pregnancy clinic, (d) Close co-operation of a multidisciplinary team which give an obstetrician the confidence to allow the pregnancy to proceed to a greater gestation, partly because of the stabilization of the disease and partly because the availability of the input of a rheumatologist to optimize the control of CTD activity and (e) Readily available excellent neonatal care.

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