Pregnancy Outcome in Juvenile Systemic Lupus Erythematosus: A Brazilian Multicenter Cohort Study

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ABSTRACT. ***Objective.*** To determine pregnancy outcome and fetal loss risk factors in patients with juvenile systemic lupus erythematosus (JSLE).

Methods. A total of 315 female patients with JSLE followed in 12 Brazilian pediatric rheumatology centers were consecutively selected. Menarche was observed in 298 (94.6%) patients. Patients' medical records were reviewed for pregnancy outcomes and demographic, clinical, and therapeutic data.

Results. A total of 24 unplanned pregnancies occurred in 298 (8%) patients. The outcomes were 5 (21%) early fetal losses (prior to 16 wks gestation), 18 (75%) live births, and 1 (4%) death due to preeclampsia and premature birth. The frequencies of active diffuse proliferative glomerulonephritis, proteinuria ≥ 0.5 g/day, and arterial hypertension at the beginning of pregnancy were higher in pregnancies resulting in fetal losses than in live births [60% vs 5% (p = 0.02), 60% vs 5% (p = 0.02), 60% vs 5% (p = 0.02), respectively]. JSLE pregnancies with fetal losses had a significantly higher mean SLE Disease Activity Index 2000 (SLEDAI-2K) at the start of pregnancy compared with those with live births (9.40 ± 7.47 vs 3.94 ± 6.00; p = 0.049). Four pregnancies were inadvertently exposed to intravenous cyclophosphamide therapy for renal involvement despite contraceptive prescriptions, resulting in fetal loss in 3 (p = 0.02). In multivariate analysis only intravenous cyclophosphamide use at start of pregnancy (OR 25.50, 95% CI 1.72–377.93, p = 0.019) remained as an independent risk factor for fetal loss.

Conclusion. We identified immunosuppressive therapy as the major contributing factor for fetal loss in JSLE, reinforcing the importance of contraception. (First Release April 1 2008; J Rheumatol 2008;35:1414–8)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a strong female predominance that commonly affects women of childbearing age, who have generally normal fertility, even during periods of disease exacerbation[1,2]. In spite of better understanding of the disease, novel therapeutic strategies, and advances in obstetric and neonatal medicine, pregnancy in lupus is still considered to be a high risk[3].

Multiple factors have been identified in association with less successful maternal outcome[1-9], including nephritis[3,4,10,11], arterial hypertension[1-4,7,10], and the presence of antiphospholipid antibodies (aPL)[7,11]. In adult lupus, active disease any time during pregnancy is associated with a worse fetal prognosis, with higher rates of fetal loss, premature birth, intrauterine growth retardation (IUGR) and stillbirth[5,7,12-16]. Moreover, preeclampsia, diabetes mellitus, urinary tract infections, and cesarean delivery are significantly increased in lupus patients compared to controls[3]. On the other hand, pregnancies inadvertently exposed to intravenous cyclophosphamide (IVCYC) for severe SLE resulted in a higher rate of fetal losses[17,18] and congenital malformations[6]. Neonatal lupus also adversely affects SLE pregnancy[1,6,19,20].

With regard to pregnancy outcome in juvenile SLE (JSLE) reports are scarce[21,22], despite a known increased risk. Maternal age below 20 years is associated with worse outcome and this group often fails to follow the recommendation of contraception[23].

Our aims in this cross-sectional multicenter study were to evaluate the maternal, fetal, and neonatal outcomes of JSLE pregnancies, and to identify demographic data and clinical and therapy factors that would predict poor fetal outcomes.

MATERIALS AND METHODS

Patients. Between January and December 2005, we retrospectively reviewed the charts of all 4/9 female patients with JSLE (American College of Rheumatology criteria)[24] with disease onset at age ≤ 18 years for pregnancy outcome. They were followed in 12 Brazilian pediatric rheumatology centers (Appendix). All centers are tertiary referral for pediatric rheumatology and are located in the southern or northwest part of the country.

One hundred four patients were excluded: girls without menarche and age ≤ 10 years (n = 99) and patients with amenorrhea not related to pregnancy (n = 35). The remaining 315 were studied. The period of followup of these patients was 6.1 ± 3.5 years (range 0.2–21.3 yrs). The Brazilian national ethics board (CONEP) approved the study at all the centers.

Study procedures. Patients' medical records with JSLE pregnancy were reviewed for pregnancy outcomes, demographic data (age at onset of JSLE, disease duration, age at menarche, age at first sexual intercourse, and age at first pregnancy), and clinical and therapeutic findings.

Pregnancy outcomes. Pregnancy outcomes after JSLE diagnosis were evaluated according to maternal outcome [unplanned pregnancy, lupus flare, preeclampsia, arterial hypertension, gestational diabetes, infections, delivery (premature rupture of membranes and cesarean section), postpartum, and maternal deaths] and fetal and neonatal outcomes (early fetal loss, late fetal loss, live birth, premature birth, IUGR, full-term birth, neonatal death, neonatal lupus, and congenital malformations).

The following definitions were used: arterial hypertension as reported[25], preeclampsia (abrupt onset of hypertension complicated with at least 0.5 g/24 h proteinuria), premature rupture of membranes (spontaneous rupture of membrane before the onset of labor and before 37 weeks' gestation), early fetal loss (termination of pregnancy prior to 16 weeks' gestation), late fetal loss (termination of pregnancy between weeks 16 and 20), IUGR (birthweight < 2.5 kg at term or below the 10th percentile for the stated period of gestation), premature births (termination of pregnancy with a live birth between weeks 21 and 37), full-term births (termination of pregnancy with a live birth between weeks 38 and 40), and neonatal death (death within 30 days of birth)[5,14].

Clinical evaluation, disease activity, disease damage, and treatment. Systematic analysis was performed regarding the presence of JSLE manifestations, prior to and during the pregnancy, including: articular involvement (arthralgia or nonerosive arthritis), cutaneous lesions (malar or discoid rash, oral ulcers, vasculitis, or photosensitivity), cardiopulmonary disease (serositis, myocarditis, restrictive lung disease, pulmonary hypertension), renal involvement (proteinuria ≥ 0.5 g/24 h, presence of cellular casts, persistent hematuria ≥ 10 red blood cells per high power field, or renal failure), and neuropsychiatric disease (seizure, psychosis, depression, or peripheral neuropathy). Antiphospholipid antibody syndrome (APS) was defined according to the classification criteria[26]. aPL (anticardiolipin antibody IgG ≥ 40 GPL, IgM ≥ 40 MPL, and lupus anticoagulant) were measured at pregnancy onset in all patients[26]. SLE disease activity and cumulative damage at start of pregnancy were measured in all patients, using the SLE Disease Activity Index 2000 (SLEDAI-2K)[27] and the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/ACR-DI)[28]. Data concerning medication use in the first month and during the pregnancy were determined.

Statistical analysis. Descriptive statistics as presented are the mean ± standard deviation (SD) for continuous and number (%) for categorical variables. Continuous variables from pregnancies with fetal loss and those with live births were compared by t-tests or by the Mann-Whitney test. Comparisons of categorical variables were assessed by Fisher's exact test. Multivariate analysis (backward stepwise analysis) was done to identify risk factors for fetal loss. Statistical significance was set as $p < 0.05$.

RESULTS

Pregnancy outcomes. From a total of 315 female patients with JSLE with current age ≥ 10 years, 298 (94.6%) postmenarche patients were evaluated for pregnancy outcome. A total of 28 unplanned pregnancies occurred in 24/298 (8%) JSLE patients. Of these 24 patients, 22 women were nulliparous and 2 multiparous. Four pregnancies were excluded since one pregnancy occurred 6 months before diagnosis of lupus and 3 patients were pregnant in the first trimester during the study. In the remaining 24 pregnancies in 23 patients, the mean age at onset of JSLE was 13.4 ± 2.6 years (range 9.0–17.8 yrs), age at menarche was 12.9 ± 1.6 years (10–16 yrs), age at first sexual intercourse was 16.4 ± 1.8 years (13–20.1 yrs), disease duration at the time of pregnancy was 5.3 ± 3.5 years (0.6–10.2 yrs), and age of the first pregnancy was 18.1 ± 1.8 years (14–21.7 yrs). Fourteen patients are still followed at the pediatric/adolescent units and 9 were graduated to adult care at the time of this cross-sectional study.

Maternal outcomes. Disease activity (SLEDAI-2K ≥ 8) was observed at the start of 5/24 (21%) pregnancies: 4 (17%) with active diffuse proliferative glomerulonephritis (2 of them with renal insufficiency) and 1 (4%) with vasculitis, arthritis, and malar rash. During the third trimester, 2 (8%) additional patients became clinically active, with arthritis or cutaneous involvement, which improved with increased prednisone dose (20 and 30 mg, respectively). Only one JSLE pregnancy had urinary tract infection and another one had preeclampsia during the third trimester. No maternal death occurred and no patient had gestational diabetes or premature rupture of membranes. Cesarean section was carried out in 5/19 (26%) live births: 3 dystocia and 2 previous cesarean. No flare was observed in the 3 months following partum.

Fetal and neonatal outcomes. The outcome of the 24 pregnancies was 18 (75%) live births and 6 (25%) deaths. Early fetal losses were observed in 5/24 (21%) JSLE pregnancies and in 3 fetal loss occurred before 10 weeks' gestation. The additional death in 1 (4%) pregnancy was due to preeclampsia and consequent premature birth in week 34. IUGR was observed in 7 (39%) of the 18 live-birth babies. Premature births occurred in 2/18 (11%) during the 36 weeks' gestation and resulted in one low birthweight (2050 g). Full-term births occurred in 16/18 (89%) pregnancies after an average gestation of 38.33 ± 0.82 weeks (38.20–40.30 wks) with a mean birthweight of 2783.92 ± 558.36 g (2025–3850 g). Of note, a case of cutaneous neonatal lupus without heart block and anti-Ro/SSA antibodies was diagnosed in one patient of

this latter group. Neonatal death was observed in one child with Down syndrome and severe heart malformations.

Predictors of fetal loss. Demographic data of 23 JSLE pregnancies, excluding the premature death, resulting in fetal losses or live births is shown in Table 1.

Pregnancy before 18 years of age was identified in 10/23 JSLE patients. The outcomes of this subgroup were 7 (70%) live births and 3 (30%) fetal losses. The frequency of fetal loss was comparable to that observed in the 13 patients with pregnancy after age 18 years (30% vs 15%, respectively; p = 0.617).

Comparison of clinical features, disease activity and damage, and treatment of 23 JSLE pregnancies with fetal losses and live births is shown in Table 2. The frequencies of active diffuse proliferative glomerulonephritis, proteinuria ≥ 0.5 g/day, arterial hypertension, and SLEDAI-2K ≥ 8 at start of pregnancy were higher in pregnancies with fetal losses than in those with live births [60% vs 5% (p = 0.02); 60% vs 5% (p = 0.02); 60% vs 5% (p = 0.02); 60% vs 11% (p = 0.048), respectively]. Further, JSLE pregnancy with fetal loss had a significantly higher mean SLEDAI-2K score at the start of pregnancy compared to SLEDAI-2K in pregnancy with a live birth (9.40 ± 7.47 vs 3.94 ± 6.00, respectively; p = 0.049). The frequency of positive aPL (anticardiolipin antibody IgG ≥ 40 GPL or IgM ≥ 40 MPL or lupus anticoagulant) was similar in pregnancies with fetal loss and in those with live births (40% vs 28%; p = 0.621). The frequency of APS was also comparable (20% vs 0%; p = 0.217; Table 2), with only one patient with APS presenting renal thrombotic microangiopathy and fetal loss.

Table 1. Comparison of demographic data of 23 JSLE pregnancies resulting in fetal loss and live birth.

Variables, yrs	Fetal Loss, n = 5	Live Birth, n = 18	p
Age at onset of JSLE	13.9 ± 2.9 (10.3–17.8)	13.13 ± 2.36 (9.0–16.3)	0.681
Age at menarche	13.6 ± 1.81 (12.0–16.0)	12.6 ± 1.4 (10.0–15.0)	0.286
Age at first sexual intercourse	16.2 ± 1.5 (15.0–18.0)	16.4 ± 2.1 (13.0–20.1)	0.775
Disease duration	4.1 ± 4.2 (0.6–8.7)	5.1 ± 3.3 (0.7–10.2)	0.371
Age at pregnancy	18.0 ± 1.9 (15.0–20.2)	18.3 ± 2.0 (14.0–21.7)	0.654

Values are mean ± standard deviation (range).

Table 2. Clinical features, disease activity and damage, and treatment of 23 JSLE pregnancies resulting in fetal loss and live birth.

Variables	Fetal Loss, n = 5	Live Birth, n = 18	p
Prior clinical features			
Articular	4 (80)	17 (94)	0.395
Cutaneous	4 (80)	15 (83)	1.000
Cardiopulmonary	1 (20)	8 (44)	0.610
Nephritis	5 (100)	10 (55)	0.122
Neuropsychiatry	1 (20)	8 (44)	0.610
Clinical features at start of pregnancy			
Active diffuse proliferative nephritis	3 (60)	1 (5)	0.020
Proteinuria ≥ 0.5 g/day	3 (60)	1 (5)	0.020
Arterial hypertension	3 (60)	1 (5)	0.020
Antiphospholipid syndrome	1 (20)	0 (0)	0.217
Antiphospholipid antibodies	2 (40)	5 (28)	0.621
JSLE activity and damage at start of pregnancy			
SLEDAI-2K	9.40 ± 7.47 (2–20)	3.94 ± 6.00 (0–18)	0.049
SLEDAI-2K ≥ 8	3 (60)	2 (11)	0.048
SLICC/ACR-DI	0.60 ± 1.3 (0–3)	0.28 ± 0.57 (0–2)	0.918
SLICC/ACR-DI ≥ 1	1 (20)	4 (22)	1.000
Treatment at start of pregnancy			
Inadvertently given IVCYC	3 (60)	1 (5)	0.020
Prednisone	5 (100)	18 (100)	—
Azathioprine	2 (40)	5 (28)	0.296
Antimalarial drugs	3 (60)	12 (67)	1.000

Values expressed in n (%) or mean ± standard deviation (range). IVCYC: intravenous cyclophosphamide, SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity 2000, SLICC ACR DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Four pregnancies were inadvertently exposed to IVCYC during the first trimester. The frequency of IVCYC use at start of pregnancy with fetal loss was higher than that in pregnancy with live birth (60% vs 5%; p = 0.020). On the other hand, the frequencies of use of prednisone, azathioprine, and antimalarials at start of pregnancies were similar in the 2 groups (100% vs 100%, 40% vs 28%, p = 0.296; 60% vs 67%, p = 1.0).

Logistic regression analysis was performed and included active diffuse proliferative glomerulonephritis, proteinuria ≥ 0.5 g/day, arterial hypertension, SLEDAI-2K ≥ 8, and IVCYC use at the start of pregnancy. Only IVCYC use at start of pregnancy (OR 25.50, 95% CI 1.72–377.93, p = 0.019) remained as an independent risk factor for fetal loss.

Placental findings. Histological examinations were carried out on 7/23 placentas. No abnormalities were observed in 6 of them. One patient with full-term birth and positive aPL (IgG ≥ 40 GPL) had a placenta with minor-vessel thrombosis. She did not fulfill criteria for APS, and had a subsequent pregnancy after this study with a full-term birth.

DISCUSSION

To our knowledge, our study constitutes the largest available cohort evaluated for pregnancy outcome in juvenile SLE, and it clearly demonstrates that poor fetal outcome is associated with use of IVCYC indicated for active nephritis during the first trimester of pregnancy.

In pregnancies in adults with lupus the rate of pregnancy loss varies between 15% and 59% in different cohorts; most studies report a pregnancy loss rate of 15%–30%[1,2,4-9,14]. Our figure is within this range, in spite of reports suggesting worse pregnancy outcomes in a healthy adolescent population[23,29]. Of note, the majority of pregnancy losses we observed were in the first trimester, as also reported for adults with lupus[1,3].

Although the frequency of live births in our report (78%) was similar to that (72%) of an interview-based household survey of 3 cities in healthy young Brazilian women that terminated pregnancies[30], we have identified IVCYC use for active nephritis at start of pregnancy as an important cause of fetal loss in adolescent lupus.

Studies in adults with SLE disagree on the effect of lupus nephropathy on fetal loss[31,32]; it is accepted, however, that there is a better prognosis if disease has been inactive for 3–6 months before conception[1,6,7]. Indeed, lupus nephritis imposes hemodynamic constrains on the integrity of the uteroplacental unit, particularly in patients with arterial hypertension[7] and proteinuria[14].

On the other hand, a better outcome in JSLE was clearly associated with inactive disease, since the majority of live births were delivered in pregnancies with low mean SLEDAI-2K scores. Similarly, the chance of a successful pregnancy is decreased in adult lupus patients with active disease[4-6,8,10,33]. The risk of lupus activity during pregnancy is controversial and seems to be increased in patients who have active disease at conception[1]. In our group, less than 10% of the patients had mild flares after the onset of pregnancy, which responded to temporary increase in corticosteroid.

Antiphospholipid antibodies are recognized as a valuable serological marker for obstetric complication during pregnancy[26]. In our study, the only patient who fulfilled the criteria for APS had fetal loss.

Pregnancies in healthy Brazilian adolescents have been significantly associated with the risks of IUGR and premature birth[23]. Indeed, 39% of our women with live births experienced IUGR and 11% experienced premature births, and none was attributable to premature rupture of membranes, a major cause of the high rate of preterm deliveries in adult SLE[34].

A study in Brazil demonstrated that 42.5% of young healthy females begin sexual activity before the 18th year[35], an age range also observed in those with JSLE. Despite the strong recommendation for contraceptive use in all female lupus patients, particularly barriers method (male or female condom) and hormonal method (medroxy-progesterone acetate or levonorgestrel), 4 gestations were inadvertently exposed to IVCYC in the first trimester and 3 resulted in fetal losses, as also described by others[17,18].

Of note, cyclophosphamide is particularly harmful for rapidly dividing cells such as those in the developing fetus[36] since it produces DNA-DNA crosslinking, with consequent DNA inactivation. In spite of that, we observed no teratogenesis in the only live birth exposed to this drug, as reported in patients treated for malignancy[37].

We identified immunosuppressive therapy for active nephritis as the major contributing factor for fetal loss in patients with JSLE, reinforcing the importance of contraception. JSLE patients should therefore be supported in preventing pregnancies when they have active nephritis or require IVCYC. Consideration should also be given to supporting young women with JSLE who are in a period of relatively good health to fulfill their desire for a pregnancy at a time when the chance of a good outcome is at its highest.

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APPENDIX

The participating Brazilian pediatric rheumatology centers: University of São Paulo, Federal University of São Paulo, Federal University of Rio de Janeiro, Santa Casa of São Paulo, State University of Rio de Janeiro, State University of Campinas, Santa Casa of Belo Horizonte, Division of Rheumatology, Federal University of Rio de Janeiro, Division of Rheumatology, University of São Paulo, University of São Paulo-Ribeirão Preto, Hospital São Rafael-Bahia, and State University of São Paulo-Botucatu.

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