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Maternal outcome in pregnant women with lupus nephritis. A prospective multicenter study

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ABSTRACT

Retrospective studies reported a high incidence of maternal complications in pregnant women with lupus. In this paper we prospectively assessed the rate of risk and the risk factors of maternal outcome in women with stable lupus nephritis who received pre-pregnancy counseling.

This prospective multicenter study includes 71 pregnancies in 61 women with lupus nephritis who became pregnant between 2006 and 2013. Complete renal remission was present before pregnancy in 56 cases (78.9%) and mild active nephritis in 15 cases. All women underwent a screening visit before pregnancy and were closely monitored by a multidisciplinary team. Lupus anticoagulant, serum C3 and C4 complement fractions, anti-DNA antibodies, anti-C1q antibodies, anticardiolipin IgG and IgM antibodies, anti-beta2 IgG and IgM antibodies were tested at screening visit, at first, second, third trimester of pregnancy, and one year after delivery. Renal flares of lupus during or after pregnancy, pre-eclampsia, and HELLP syndrome were defined as adverse maternal outcomes.

Fourteen flares (19.7%), six cases of pre-eclampsia (8.4%) and two cases of HELLP (2.8%) occurred during the study period. All flares responded to therapy and the manifestations of pre-eclampsia and HELLP were promptly reversible. Low C3, high anti-DNA antibodies and predicted all renal flares. High anti-C1q antibodies and low C4 predicted early flares. The body mass index (BMI) was associated with increased risk of late flares. History of previous renal flares and the presence of clinically active lupus nephritis at conception did not increase the risk of renal flares during pregnancy. History of renal flares before pregnancy, arterial hypertension, and longer disease predicted pre-eclampsia/HELLP.

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In pregnant women with lupus nephritis adverse maternal outcomes were relatively common but proved to be reversible when promptly diagnosed and treated. Immunological activity, arterial hypertension and BMI may predispose to maternal complications.

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1. Introduction

According to the Nationwide Inpatient Sample, maternal mortality is 20-fold higher in pregnant women with systemic lupus erythematosus (SLE) than in those without. Preterm labor, pre-eclampsia, and serious medical complications are also more frequent in women with lupus [1]. Among other risk factors, lupus nephritis, particularly in its active phase, is a well-recognized predictor of poor maternal and pregnancy outcome [2–9]. However, our knowledge of the rate and predictors of maternal complications in lupus nephritis is based on retrospective studies. Available information on pregnancy outcome in women with lupus nephritis was typically collected over a long period of time during which treatments of the disease were heterogeneous and pre-pregnancy counseling was sporadically used [2,10–13].

This multicenter prospective observational study was designed by "The Pregnancy Study Group" of the Italian Society of Nephrology with the aim of assessing the present rate risk and the risk factors for severe maternal complications in pregnant women with a history of lupus nephritis who were closely monitored by a multidisciplinary team.

2. Material and methods

2.1. Patients

Four Renal Units and four Rheumatology Units participated in the study. To be enrolled, patients had to meet the following inclusion criteria: i) SLE diagnosis according to the ACR criteria [14]; ii) lupus nephritis diagnosed either by renal biopsy or on clinical grounds; iii) pregnancy between October 2006 and December 2013; iv) a counseling visit within 3 months before the beginning of pregnancy; v) signed informed consent.

The protocol was not submitted to the Ethic Committee as the collected data were derived from routine clinical practice, no additional testing was requested to the patients and analysis was performed as aggregate data.

After the beginning of pregnancy, all patients were monitored by a multidisciplinary team, including gynecologists, nephrologists and rheumatologists. Patients were seen at least once a month up to the 24th week of gestation, every two weeks from the 24th week up to delivery and at month 1,3,6 12 after delivery.

Demographic characteristics and data about history of SLE, renal disease, previous pregnancies, and treatment were recorded from medical records. Complete blood count and urinalysis, lupus anticoagulant, C3 and C4 complement fractions were tested at screening visit and regularly checked both during pregnancy and after delivery. At each evaluation, a panel of immunological tests had to be performed, including anti-DNA antibodies, anti-C1q antibodies, anticardiolipin IgG and IgM antibodies, anti Beta2 IgG and IgM antibodies. Pregnant women who did not match the basic criteria of inclusion, those evaluated before the opening of the study or after its closing, those who could not be followed regularly by participating Units or missed two or more biological tests were not included in the study (Fig. 1).

2.2. Definitions

Adverse maternal outcome was defined by: a) the occurrence of renal flares during pregnancy or in the post-partum; b) the development of pre-eclampsia or HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome.

SLE activity was measured by the SLEDAI score [15].

Inactive lupus nephritis: proteinuria <0.5 g/24 h, inactive urinary sediment (<5 red blood cells/high power field (hpf), <5 white blood cells/hpf, no cellular casts), and estimated creatinine clearance (Cr.Cl) > 60 ml/min/1.73 m^2 evaluated with Cockcroft and Gault formula.

Active lupus nephritis: proteinuria > 0.5 g/day or Cr.CL. < 60 ml/min/1.73 m^2 with active urinary sediment.

Arterial hypertension: systolic blood pressure > 140 mm/Hg and/or diastolic blood pressure >90 mm/Hg in sitting position in three consecutive measurements or use of antihypertensive therapy.

Renal flares were subdivided into proteinuric or nephritic flares. *Proteinuric flares* were defined by stable renal function and increase in proteinuria of at least 1 g/day in patients with complete renal remission or increase of ≥2 g/day in women with active nephritis. *Nephritic flares* were defined by an increase in serum creatinine of at least 30% over the basal value associated or not with an increase in proteinuria [16]. Flares were further divided into: "*early flares*" if they developed in the first or second trimester, and "*late flares*" if developed in the third trimester or in the post partum period.

Preeclampsia was defined by i) new onset hypertension and proteinuria >300 mg/day after 20 weeks of gestation in women without proteinuria and hypertension, ii) new onset of hypertension and doubling of proteinuria in those with proteinuria but no hypertension, iii) worsening of hypertension (increase of systolic or diastolic blood pressure of 15 mmHg or more) and doubling of proteinuria in women with both proteinuria and hypertension [17].

HELLP syndrome was defined by hemolysis, aspartate aminotransferase >70 U/l, lactate dehydrogenase >600 U/l, and platelets <100.000 per cubic millimeter, and sometimes hypertension [18].

2.3. Laboratory assays

Serum anti-C1q levels were assessed by a commercial enzyme-linked immunosorbent assay (ELISA) kit (QUANTA Lite™ Anti-C1q ELISA, INOVA Diagnostics, San Diego) [19]. Anti-dsDNA antibodies were tested by a fluoroenzyme-immunoassay method (EliA dsDNA, Phadia/Thermoscientific, Germany). anti-cardiolipin antibodies and anti-Beta 2 antibodies were assessed by homemade assays [20].

2.4. Statistical analysis

We used mean and standard deviation to summarize quantitative variables, and absolute and relative frequencies for qualitative variables. We used multinomial logistic regression to model maternal outcomes as a function of each predictor described above. We categorized maternal outcomes in three levels: absence of complications (reference category), renal flare and pre-eclampsia/HELLP. To distinguish between early and late flares we added a