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Fetal outcome and recommendations of pregnancies in lupus nephritis in the 21st century. A prospective multicenter study

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ABSTRACT

The aim of this multicenter study was to assess the present risk of fetal complications and the inherent risk factors in pregnant women with lupus nephritis.

Seventy-one pregnancies in 61women (59 Caucasians and 2 Asians) with lupus nephritis were prospectively followed between October 2006 and December 2013. All patients received a counselling visit within 3 months before the beginning of pregnancy and were followed by a multidisciplinary team. At baseline mild active nephritis was present in 15 cases (21.1%).

Six pregnancies (8.4%) resulted in fetal loss. Arterial hypertension at baseline ($P = 0.003$), positivity for lupus anticoagulant ($P = 0.001$), anticardiolipin IgG antibodies ($P = 0.007$), antibeta2 IgG ($P = 0.018$) and the triple positivity for antiphospholipid antibodies ($P = 0.004$) predicted fetal loss.

Twenty pregnancies (28.2%) ended pre-term and 12 newborns (16.4%) were small for gestational age. Among the characteristics at baseline, high SLE disease activity index (SLEDAI) score ($P = 0.027$), proteinuria ($P = 0.045$), history of renal flares ($P = 0.004$), arterial hypertension ($P = 0.009$) and active lupus nephritis ($P = 0.000$) increased the probability of preterm delivery. Odds for preterm delivery increased by 60% for each quarterly unit increase in SLEDAI and by 15% for each quarterly increase in proteinuria by 1 g per day. The probability of having a small for gestational age baby was reduced by 85% in women who received hydroxychloroquine therapy ($P = 0.023$).

In this study, the rate of fetal loss was low and mainly associated with the presence of antiphospholipid antibodies. Preterm delivery remains a frequent complication of pregnancies in lupus. SLE and lupus nephritis activity are the main risk factors for premature birth. Arterial hypertension predicted both fetal loss and preterm delivery.

Based on our results the key for a successful pregnancy in lupus nephritis is a multidisciplinary approach with close medical, obstetric and neonatal monitoring. This entails: a) a preconception

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evaluation to establish and inform women about pregnancy risks; b) planning pregnancy during inactive lupus nephritis, maintained inactive with the lowest possible dosage of allowed drugs; c) adequate treatment of known risk factors (arterial hypertension, antiphospholipid and antibodies); d) close monitoring during and after pregnancy to rapidly identify and treat SLE flares and obstetric complications.

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1. Introduction

For many years, pregnancy has been discouraged in women with lupus and renal disease due to the high risk of maternal and fetal complications [1–4]. However, pregnancy outcome has improved dramatically over time and today pregnancy is no longer considered contraindicated for many women with lupus nephritis. A number of studies have shown that maternal outcome is relatively safe if renal disease is inactive and kidney function is preserved [5–7]. The risk of fetal loss has decreased over the past 40 years as well. The rate of fetal loss in lupus pregnancy was on average 43% in 1960–1965 and was reduced to about 17% in 2000–2003 [8]. Improved renal prognosis, preconception counselling, and intensive perinatal monitoring contributed to improved fetal outcome. Nonetheless, the rate of fetal loss is still higher than in pregnancies of healthy women. Moreover, lupus can complicate pregnancy with an increased risk of stillbirths, premature deliveries, intrauterine growth retardations and heart problems in the newborn [2,5,9,10]. A systematic review of 37 studies, that included 2751 pregnancy outcomes in 1842 women with lupus nephritis, reported an induced abortion rate of 5.9%. Apart from induced abortion, fetal complications included miscarriages (16.0%), stillbirth (3.6%), neonatal deaths (2.5%), and intrauterine growth retardation (12.7%). The unsuccessful pregnancy rate was 23.4%, and premature birth rate was 39.4% [11].

A number of predictors of fetal complications has been identified. Lupus activity at conception or during pregnancy [12] and renal activity in particular [13–15] were the strongest predictors. Independently of clinical activity, hypocomplementemia or anti-dsDNA antibodies positivity in the second trimester are associated with a higher rate of pregnancy loss and preterm birth [16,17]. Another important risk factor for fetal outcome is represented by antiphospholipid antibodies (aPL) positivity [18–22]. Women with a combination of high clinical activity and serological markers of SLE are a higher risk of poor pregnancy outcome. The risk is more elevated in the presence of triple aPL positivity and hypocomplementemia [23].

Nonetheless, the present knowledge of the rate and predictors of fetal complications in lupus nephritis is based on retrospective data collected over a long period of time, during which, the treatments of lupus nephritis were heterogeneous, pre-conception counselling was used sporadically, and many patients became pregnant during a period of lupus activity [5,9,10,24,25].

We report here the results of a multicenter, prospective, observational study designed by “The Pregnancy Study Group” of the Italian Society of Nephrology. The aim of the study was to assess the actual rate of maternal and fetal complications and the risk factors for these events in pregnant women with a history of lupus nephritis closely monitored by a multidisciplinary team. The results of maternal complications have been reported in a previous paper [26].

2. Patients and methods

2.1. Patients

The complete protocol of the study has been reported elsewhere [26]. In brief, patients with lupus nephritis that became pregnant between October 2006 and December 2013 and who met the following criteria were enrolled in this study: i) SLE diagnosis according to the ACR criteria [27]; ii) lupus nephritis diagnosed either by renal biopsy or on clinical ground; iii) a counselling visit within 3 months before the beginning of pregnancy; iv) signed informed consent.

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

During pregnancies patients were followed by a multidisciplinary team that included obstetricians, nephrologists and rheumatologists. Women were seen at least once a month up to the 24th week of gestation and every two weeks from the 24th week up to delivery. Newborn weight and Apgar index to summarize the health of newborns were regularly collected [28].

Demographic characteristics and data about history and therapy of SLE, lupus nephritis, and previous pregnancies were recorded from medical records. Complete blood count, urinalysis, lupus anticoagulant, C3 and C4 complement components were tested at screening visit and regularly checked during pregnancy and at delivery. At baseline and at each trimester, a panel of immunological tests were centrally performed, including anti-dsDNA antibodies, anti-C1q antibodies, anticardiolipin IgG and IgM antibodies, anti Beta2 IgG and IgM antibodies.

2.2. Definitions

The following definitions were used. *Fetal loss*: fetal that does not result in a live infant beyond 28 days after delivery. *Miscarriage*: spontaneous fetal loss <20 weeks' gestation. *Stillbirth*: spontaneous death of fetus >20 weeks' gestation. *Neonatal death*: death within 28 days from birth. *Full-term birth*: termination of pregnancy with a live birth after 37 weeks gestation. *Preterm birth*: delivery prior to 37 weeks gestation. *Small for gestational age (SGA)*: <10 percentile according to customized charts. *Low birthweight and very low birth weight*: <2500 and < 1500 g respectively. *Premature rupture of membranes (PROM)*: the spontaneous rupture of membrane before labor. *Preeclampsia*: new onset of hypertension and either proteinuria or end-organ dysfunction or both after 20 weeks of gestation in a previously normotensive woman [29] *HELLP syndrome*: Hemolysis, Elevated Liver enzymes, Low Platelet [30]. *SLE activity*: A change of greater than or equal to 1.0 of the SLEDAI, in the physician's global assessment of disease activity (measured on a 0–3 scale) from the previous visit or from a visit within the last 93 days [31]. *Inactive lupus nephritis*: proteinuria <0.5 g/24 h, inactive urinary sediment and estimated creatinine clearance (Cr·Cl) $\geq$ 60 ml/min/1.73 m.^{2} evaluated with Cockcroft and Gault formula. *Active lupus nephritis*: proteinuria $\geq$0.5 g/day or Cr·CL.< 60 ml/min/1.73 m^2 with active urinary sediment. *Adverse maternal outcome*: a) the occurrence of SLE flares during pregnancy or in the post-partum: b) the development of pre-eclampsia or HELLP syndrome.