Original Articles

Reproductive Biology Section

Successful full-term pregnancies with assisted reproduction supported with prednisolone, acetylsalicylic acid and high progesterone doses in a lupus patient

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Summary

We present two rare cases of successful full-term pregnancies in a young woman suffering from lupus erythematosus for two years, who had subfertility problems and two missed abortions, before and after the diagnosis of lupus, with assisted reproduction. She received 10 mg of prednisolone daily from ovulation induction (with recombinant FSH - 50 IU) until delivery, together with acetylsalicylic acid from ovulation induction until the 37th week of gestation and finally progesterone in high doses from the last insemination until the 12th week of gestation.

Key words: Lupus erythematosus; Miscarriage; Pregnancy; Progesterone.

Introduction

Systemic lupus erythematosus (SLE) is expressed clinically with skin lesions in 70% to 80% of the cases, renal complications in 40%, hematological disorders in 50% and cardiovascular complications in 30% to 50% of the cases. The effect of pregnancy in the course of the disease is not clear and appreciable improvement has been observed after therapeutic interruption. Most researchers agree that the best period for a successful pregnancy is the period of quiescence of the disease. Pregnancy complicated with lupus is associated with a 50% to 60% clinical flare up of the disease, with renal or hematological symptoms, usually during the second or third trimester and occasionally in the postpartum period [1, 2]. The risk for the fetus remains high. Fetal loss is common, particularly in patients with a lupus anticoagulant, renal failure, or arterial hypertension. Preterm delivery occurs in 25% to 50% of the cases and intrauterine growth restriction (IUGR) in 30% [1-3].

We present two rare, successful full-term pregnancies in a patient suffering from lupus erythematosus after receiving a combination of prednisolone, acetylsalicylic acid and high doses of progesterone.

Case Report

A young woman aged 26 was diagnosed with lupus two years before presenting with fertility problems. She had a history of two missed abortions. The diagnosis of lupus was established (with a meticulous clinical and laboratory investigation) after a missed abortion in the seventh week. She was treated with 10 mg of prednisolone daily for one year and six months, and after recession of the disease she was referred for another attempt at pregnancy. She had no skin lesions and renal function tests were normal. The patient conceived normally but an ultrasonogram in the seventh week revealed an empty embryonic sac (blighted ovum). After the new miscarriage she again had a meticulous clinical and laboratory investigation but no relapse was detected.

Before another attempt at pregnancy she was treated with 10 mg of prednisone and 80 mg of acetylsalicylic acid daily, and received recombinant FSH (50 IU) daily from the 2nd-13th day of the cycle for ovarian stimulation. On ultrasound, three follicles with a maximum diameter of 20 mm were noted. Serum estradiol was 480 pg/ml and the endometrium measured 11 mm. She was injected with 10,000 IU of hCG and was subjected to intrauterine insemination on days 14 and 16 of the cycle. After the last insemination she received 200 mg po progesterone and 400 mg vaginally, and conception was successful. She had a positive pregnancy test after 14 days. She continued with prednisolone and acetylsalicylic acid until the 37th week. During the first 12 weeks she continued the same dose of progesterone.

The laboratory biochemical follow-up during pregnancy was within normal values. There were no skin lesions, there was no arterial hypertension, renal function was normal, hematocrit was 35%, Hb 11.5% g/dl and platelets ≈ 100,000. The first trimester ultrasound for nuchal translucency was normal, as well as PAPP-A, Fe3 and b-hCG. The fetus showed normal growth and no signs of premature labor were noted throughout gestation. The patient delivered vaginally on the 39th week with epidural anesthesia. The neonate had a normal birth weight of 3,150 g.

The puerperium was normal without complications as bleeding and flare-up of the disease, and the newborn did not present complications such as congenital heart block, that frequently occur in SLE.

Three years after this full-term pregnancy, she was referred for another attempt at pregnancy. The disease was in quiescence and the patient was already receiving 5 mg prednisolone daily.

Revised manuscript accepted for publication May 10, 2007

During one year of free sexual intercourse for conception, pregnancy was not diagnosed. She again received 80 mg acetylsalicylic acid daily and 100 mg clomiphene citrate from the third to seventh day of the cycle for ovarian stimulation. Unfortunately during the next eight months of ovarian stimulation, pregnancy was not diagnosed. The patient again received recombinant FSH (50 IU) from the 2nd-13th day of the cycle for ovarian stimulation. On ultrasound, two follicles with a maximum diameter of 20 mm were noted. Serum estradiol was 320 pg/ml and the endometrium measured 9.4 mm. She was with injected 10,000 IU of hCG and subjected to intrauterine insemination on day 15 of the cycle. After the insemination she received 200 mg progesterone po and 400 mg vaginally, and conception was successful in the second cycle of ovarian stimulation. She had a positive pregnancy test after 14 days. The patient received prednisolone and acetylsalicylic acid until the 37th week. During the first 12 weeks she continued the same dose of progesterone.

During gestation the patient had no clinical and/or biochemical signs of relapse of the disease and controls of the fetus were normal (not only was the estimated risk resulting from nuchal translucency in combination with PAPP-A, Fe3 and β-hCG low, but also the B-mode (22 weeks) ultrasound findings were normal.

She delivered vaginally at the 39th week with epidural anesthesia. The neonate had a normal weight of 2,760 g.

Discussion

Systemic lupus erythematosus is a hormone-dependent disorder predominantly affecting young women in whom changes in hormonal activities affect the course of the disease. During pregnancy the Th_2 cells predominate to prevent rejection of the fetal allograft. They produce increased levels of IL4, IL5, IL6 and IL10 [4]. Unfortunately IL4 and IL10 are also involved in the pathophysiology of SLE and thus, as in rheumatoid arthritis, SLE worsens during pregnancy [5]. Prednisolone administration during pregnancy reduces relapses or flare-ups of the disease. In contrast other potential causes could be involved in hypertensive disease during pregnancy that statistically is increased in pregnant women with SLE. As a result of hypertensive disease in pregnancy, which is present in increased percentages in women with SLE, the percentages of IUGR, premature births and embryonic deaths has increased in patients with SLE. Acetylsalicylic acid in small doses until the 38th week has beneficial effects, protecting from miscarriage, hypertensive disease, IUGR and premature labor. Progesterone, which is produced in the second half of the menstrual cycle from the corpus luteum and later from the placenta, constitutes the hormone key of gestation. This hormone regulates the receptivity of the endometrium for implantation of blastocysts, the differentiation of endometrium for implantation and growth of the fetus, and finally progesterone intervenes in the interaction process of the fetus and uterus. Progesterone has an immune-immunosuppressive role in pregnancy, enhancing Th_2 cell activity and interleukin production aiding in fetal allograft tolerance [6-8]. IL4 and IL6 promote hCG release from the trophoblast and regulate the production of progesterone from the corpus luteum. The predominance of Th_1 inflammatory cells would enhance inflammation with damaging effects on gestation. Also progesterone possesses favorable immunotolerant actions by stimulating the production of progesterone-induced blocking factors against natural killer cells whose activity is crucial to implantation, and the interaction between the conceptus and the host in early pregnancy [9]. In a few randomized controlled trials, the administration of progesterone (intramuscularly or vaginally, from 100 to 400 mg/day) was compared with controls. The results showed a slight but significant efficacy of progesterone administration [10]. Our patient suffered from SLE. She had had one missed abortion before the diagnosis of lupus and the administration of treatment, and also one missed abortion after already receiving treatment with 10 mg prednisolone daily and the disease had been in recession for six months. During her previous conception ultrasound diagnosed a blighted ovum, a pathologic entity frequent in abortions of immunologic etiology. The patient underwent assisted reproduction with a small dose of FSH (50 IU daily), conceived in the first cycle of treatment with intrauterine insemination. The pregnancy was successful and full term with the patient receiving prednisolone, and in addition acetylsalicylic acid and high doses of progesterone (during the first 12 weeks). Complications in the mother and fetus, and relapse of the disorder during pregnancy were not detected. It seems that the immune tolerance (the mechanisms of implantation and protection of early gestation) in this patient was differentiated. She received 10 mg prednisolone daily before the first successful full-term pregnancy, but she again had a missed abortion (the 2nd), with ultrasound findings as in the first missed abortion (blinded ovum). Also in the second successful full-term pregnancy, she was already receiving 5 mg of prednisolone and 80 mg of acetylsalicylic acid daily eight months before but the conception was successful with assisted reproduction using recombinant FSH and high doses of progesterone administration. It seems that the simultaneous administration of prednisolone, acetylsalicylic acid and progesterone vaginally in high doses (in a program of ovarian stimulation), constituted the gold standard in the therapeutic approach to this patient. Further investigation is needed to clearly demonstrate if the previously reported combination of therapy with high doses of progesterone could be beneficial in women suffering from lupus erythematosus or other autoimmune disorders with a history of missed abortions and desire for gestation. The double action of progesterone not only supports the endometrium, the implantation of early gestation and supplements corpus luteum function, it also acts as an immunosuppressant, thus protecting against early immunological-origin abortions.

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