Clinical cure of severe, early onset preeclampsia with low molecular weight heparin therapy in primigravida with hyperreactio luteinalis and thrombophilia

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Inherited thrombophilias, suggested to be risk factors for ovarian hyperstimulation syndrome and known to be associated with venous thromboembolism during pregnancy, may also increase the risk for preeclampsia (PE). We describe the case of a 29-year-old woman with primary infertility with no history of thrombosis, hypertension or renal disorders. In her first pregnancy, achieved by frozen embryo transfer, she developed severe early-onset (23rd gestational week) PE with heavy proteinuria, and at the same time was found to have enlarged ovaries with hyperreactio luteinalis. After admission we found that she was a heterozygotic carrier of the factor V Leiden mutation. After administering low molecular weight heparin (LMWH) therapy, her blood pressure normalized, proteinuria diminished and her \( \beta \)-dimer values returned to that of a normal pregnant level. The fetus grew normally. Her ovaries normalized during the pregnancy, as determined by ultrasound examinations. At term she delivered spontaneously a normal weight, healthy girl. Previously, only prophylactic LMWH, in subsequent pregnancy, have been administered in patients with thrombophilia and a history of severe PE. We describe a case of spontaneous hyperreactio luteinalis, where the clinical characteristics of PE improved after beginning LMWH therapy in severe, very early onset PE. Inherited thrombophilia, spontaneous hyperreactio luteinalis and PE may be associated phenomena.

Key words: hyperreactio luteinalis/low molecular weight heparin/preeclampsia/thrombophilia

Introduction

Hyperreactio luteinalis is a rare condition complicating pregnancy. It is characterized by varying degrees of bilateral ovarian enlargement due to theca lutein cyst formation, wherein it mimics ovarian hyperstimulation syndrome (OHSS), which is an iatrogenic complication of ovulation induction. OHSS is typically identified very early during the first trimester, whereas hyperreactio luteinalis often occurs in patients without any precipitating history and during the second or third trimester (Foulk et al., 1997). There is also potential for confusion in diagnosis and even unnecessary surgery. Hyperreactio luteinalis usually complicates those pregnancies in which higher concentrations of maternal serum HCG are found, such as gestational trophoblastic disease, multiple pregnancies, maternal diabetes or rhesus isoimmunization. It has also been described in a rare situation with chronic renal failure, where due to diminished clearance of HCG, the ovaries had been exposed to HCG for a prolonged period. Also, increased ovarian sensitivity to gonadotrophins has been suggested as a mechanism for hyperreactio luteinalis (Schnorr et al., 1996). One recent paper reported that the prevalence of thrombophilia markers is significantly increased in women who develop OHSS after ovulation induction (Dulitzky et al., 2002).

Inherited thrombophilic disorders are associated with an increased risk of venous thromboembolism during pregnancy. Preliminary research suggested that these disorders might also increase the risk for preeclampsia (PE) (Kahn, 1998; Kupferminc et al., 2001). PE is known to be associated with an imbalance in coagulation and fibrinolysis that results in a hypercoagulable state in both maternal and placental circulation (de Boer et al., 1988; Estelles et al., 1991). It has been suggested that the hypercoagulable state in severe PE is strongly related to the onset of intrauterine growth retardation (IUGR) through the deterioration of placental circulation. Furthermore, it has been suggested that patients with severe PE or IUGR and an inherited thrombophilia may benefit from prophylactic treatment with low molecular weight heparin (LMWH), probably combined with aspirin, in subsequent pregnancies (Kupferminc et al., 2001). Previously, heparin or antithrombin (AT) therapy has been given to treat severe, early onset PE for 7 days, but neither treatment was able to postpone the delivery after the 32nd gestational week (Nakabayashi et al., 1999).
Case report

Our patient was a 29-year-old woman with 4 years’ unexplained primary infertility. She did not have any history of renal disease or hypertensive disorder, her blood pressure was 118/70 mmHg. The basic infertility investigations showed ovulatory cycles; however, late ovulation with a short luteal phase was seen infrequently. Transvaginal ultrasound (TVUS) examination revealed normal-sized ovaries, with a few follicles exceeding 7 mm, and a normal uterus. IVF was planned, and during the first cycle 28 mature oocytes were retrieved, but they were not fertilized. The next cycle was carried out after ovarian suppression with GnRH analogue, nafarelin (Synarel®, Syntex Nordica AB, Södertälje, Sweden), commenced during the mid-luteal phase of the previous cycle, and ovarian stimulation was conducted with 100 IU of recombinant FSH (Puregon®, Organon, Oss, The Netherlands) for 10 days. ICSI was performed, resulting in 12 normally cleaving embryos. The first fresh embryo transfer and the first frozen–thawed embryo transfer cycle were unsuccessful. The next frozen–thawed embryo transfer was carried out during the hormone substitution cycle. Estradiol (E2) valerate (4 mg/day) was commenced on period day 1; after 13 days the endometrium was 7-mm thick and the ovaries showed no growing follicles. Intravaginal micronized progesterone (600 mg/day) was given. Three days later, two embryos were transferred, and 12 days later the patient’s serum HCG level was 111.9 IU/l. The first TVUS 5 weeks after embryo transfer showed a normal single intrauterine pregnancy with fetal heartbeat. The ovaries were normal sized. The hormone substitution was given until pregnancy week 10, at which point TVUS still showed normal ovaries and a normally growing fetus.

At gestational age 22 weeks and 5 days the patient was referred to our tertiary clinic because of severe PE [hypertension, proteinuria and extreme oedema in lower extremities (weight gained 8000 g in last 2 weeks)]. The reduced diuresis was normalized after 2 days’ forced oral administration of fluids. On ultrasound examination, the fetus was moving actively, and the measurements of biparietal diameter, abdominal circumference and femur length were all normal according to the gestational age. The amount of amniotic fluid was normal, and the placenta was thick and homogenous. The ultrasound examination revealed large ovaries, both up to 10 × 6 × 7 cm, with multicystic appearance without any solid components.

Because of a manifest severe PE of early onset, extreme oedema, immobilization and high levels of d-dimer (21 mg/l), therapy with LMWH was started at the dose of dalteparin 5000 IU/day at the gestational age of 23 weeks and 1 day. The values of the main parameters followed are shown in Table I.

In laboratory studies, serum transaminases and haptoglobin were repeatedly normal, and lupus anticoagulant and other phospholipid antibodies were negative. There were no signs of either hypo- or hyperthyroidism. Factor V Leiden point mutation was found in coagulation factor V in heterozygotic form. Tests for protein C, protein S, factor II mutation and AT-III showed normal pregnancy-related values. Protein S was also retested post-partum, and was normal. In hormonal analyses, serum HCG was exceptionally high at 153 790 IU/l (expected to be <15 000 IU/l), E2 54.13 nmol/l, progesterone 1257.2 nmol/l, testosterone 6.2 nmol/l and free testosterone 25 pmol/l. Serum FSH was, as expected, <0.10 IU/l, and LH was 38.6 IU/l, as measured by specific immunofluorimetric assays. The level of LH presumably reflected cross-reaction with the high level of HCG. To examine the possible causes of the early onset PE and multicystic ovaries, radiological examinations were also performed. Magnetic resonance imaging of the pituitary gland was normal, as was the ultrasound examination of the liver, pancreas and kidneys. No renal vein thrombosis was shown.

During the next 2 weeks, the patient lost 10 kg in weight, blood pressure was normalized to the level of 130/80 mmHg without any antihypertensives, and proteinuria diminished to the level of 1.3 g/day. The fetus grew as expected, and the mother was free of symptoms. After 4 weeks the patient was discharged from hospital, and the situation was monitored in the out-patient clinic every 10–14 days. In serial ultrasound measurements the fetus grew normally, and cardiotocography tracings and Doppler measurements were normal. The size of the ovaries diminished slowly, being 4 × 5 cm at 37th gestational week. LMWH therapy was continued. Other values are shown in Table I.

At the gestational age of 38 weeks and 6 days the patient had spontaneous deliverery of a healthy girl weighing 3175 g. The delivery was otherwise uneventful, but the placenta had to be removed manually under general anaesthesia and the blood
loss was 1500 ml. Unfortunately, we were unable to retain the placenta for further investigation. LMWH therapy was discontinued 6 weeks after delivery. At that time, the left ovary was normal sized, and the right ovary was enlarged (46 × 31 mm). All anti-DNA antibodies were again negative. Other main values are shown in Table I. Three months later the nephrologist reported normal renal function, with no signs of renal disease.

Discussion

A severe OHSS-like syndrome occurring in a spontaneously conceived pregnancy has been reported in the literature (Lambers and Rosen, 1996; Bidus et al., 2002). Our patient had received ovulation induction during the infertility treatment, but not during the cycle she conceived. Indeed, during that cycle her ovaries were suppressed with exogenous hormones and the pregnancy resulted from transfer of frozen–thawed embryos. We could find only one case report where hyperreactio luteinalis occurred in the first trimester in a similar situation, during frozen–thawed embryo transfer (Check et al., 2000). Both of these cases indicate that hyperreactio luteinalis can develop even without a single corpus luteum of pregnancy, probably because of some intrinsic sensitivity to gonadotrophins (Perez Mayorga et al., 2000).

Many patients with hyperreactio luteinalis have undergone exploratory operations because of ovarian masses, or even oophorectomies during Caesarean sections (Wajda et al., 1989; Schnorr et al., 1996; Bidus et al., 2002). Usually the pregnancies have otherwise been uncomplicated, although predisposition to venous thrombosis has been reported in association with both iatrogenic and spontaneous OHSS (Kaaja et al., 1989; Todros et al., 1999; Dulitzky et al., 2002).

Hormonal changes in OHSS and hyperreactio luteinalis may contribute to alterations in coagulation factors and predispose to thromboembolic complications (Belaen et al., 2001; Delvigne et al., 2002). Todros et al. (1999) reported one case with factor V Leiden mutation and deep venous thromboses with hyperreactio luteinalis, even while administering LMWH. Early severe PE has been diagnosed in a 25-year-old primigravida during gestational week 22, and both her ovaries had been enlarged for 6 weeks. In that case, the pregnancy was terminated due to worsening maternal conditions (Regi et al., 1996). Our case is unique, with a combination of hereditary (factor V Leiden) and acquired (hyperreactio lutealis) thrombophilia, which lead to ‘transient’ PE. We believe that the thrombotic process in the placenta was the key mechanism by which PE developed. The fibrin formation in the placenta was stopped by LMWH, as witnessed by normalization of D-dimer, and the pregnancy continued until term.

PE is most common in primigravidas, and its epidemiology suggests that genetic factors can be important in its pathogenesis (Dekker and Sibai, 1999). It is possible that increased thrombosis in the placenta impairs the normal transformation of spiral arteries, and thus heritable thrombophilias are to blame for at least some of the predisposition to PE. However, the evidence currently available shows no clear association between PE and thrombophilias, other than factor V Leiden in severe PE (Morrison et al., 2002; Walker, 2002).

The incidence of factor V Leiden mutation in Europe is 2–5% in unselected populations and 10–20% in patients with venous thrombosis (Lockwood, 2002). Our patient did not have any previous or actual thrombosis, or any other risk factor for PE other than primigravidity. High D-dimer levels indicated at least subclinical activation of coagulation, and after administering the treatment, D-dimer levels continually decreased with resolving clinical symptoms. One of the major diseases excluded was renal vein thrombosis. Furthermore, no deep venous thrombosis of the legs was shown. One of the suspected sites for thrombosis could have been placenta, and after treatment with LMWH, no IUGR was observed. To our knowledge this is the first case where PE was cured by treatment with LMWH during pregnancy in a patient with inherited thrombophilia.

It has been suggested that screening for thrombophilia might be worthwhile in women with a family history of thrombosis who undergo infertility treatments and in women who develop severe OHSS (Dulitzky et al., 2002). Although in most of the cases this is done to avoid venous thromboembolic complications, in our case the site of thrombosis was placenta, which lead to severe, early onset PE. We would further suggest that women with severe, early onset PE are advised to be tested for both inherited and acquired thrombophilias (phospholipid antibodies), and that randomized controlled trials for LMWH treatment in severe, early onset PE should be conducted.

References


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