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Successful outcome from empirical use of heparin and aspirin in unexplained pregnancy loss

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ABSTRACT

Success in pregnancy of a 42-years old woman with a history of unexplained recurrent miscarriages is described. She had a sub-septate uterus with free spillage bilaterally, based on hysterosalpingogram, and it was corrected by hysteroscopy in October 2009, which was followed by transcervical septal resection (TCRS). Clomiphene citrate was given ovulation. She was treated with folic acid supplementation, aspirin 75 mg, micronized progesterone 400 mg/d, and low molecular heparin 2500 IU/d, from the diagnosis of pregnancy at 5 weeks, until the delivery. However, at 28 weeks glucose tolerance test with 100 g glucose revealed mild derangement in first (159 mg/dL) and second (164 mg/dL) hour values; metformin was given for the control of sugar. Heparin injections were given to the patient continuously during the antenatal period. No major bleeding episode was noted during pregnancy or delivery. A male child weighing 3.2 kg with a good APGAR score was delivered at the end of the term. Both anatomical abnormality and advanced maternal age had determinative role in pregnancy loss, but TCRS and antithrombotic heparin and aspirin treatment had the blithesome effect.

1. Introduction

The loss of two or more pregnancies, before 20 weeks gestational age is taken as the recurrent pregnancy loss (RPL). Known causes of RPL include parental genetic factors, anatomical abnormalities, presence of antiphospholipid antibodies (APA), and more controversial causes would be endocrine disorders[1] and excess thrombophilia[2]; but, standard evaluations for RPL are unavailable[3]. Maternal age is a well-known risk factor for sporadic miscarriage[4,5], and is likely a risk factor for RPL as well. Women over the age of 35 years are considered as at advanced maternal age (AMA), which causes an increased rate of meiotic errors in oocyte development, embarking increased embryonic aneuploidy[6]. Quite simply in a report, the reported miscarriage rate among women under 35 years of age is recorded at 14% compared with 40% for women over 40-years old in a study[7]. So, one would expect the RPL rate to be more than in women over 40, compared with women under 35 years of age (0.403 vs 0.143). Controversy exists over whether recurrent aneuploidy is a major cause of RPL [8]. In one study, the incidence of embryonic abnormalities was recorded as increasing with age, entailing both sporadic and recurrent miscarriages [9]; aneuploidy in 23%-51% of products of conception in RPL patients too were recorded[10].

Antiphospholipid syndrome (APS) is a prothrombotic state that is seen in approximately 20% of women with RPL[11]. In untreated cases, the likelihood of a subsequent live-birth may be 10%[12], but treatment with a combination of aspirin and heparin has been shown to reduce the miscarriage rate, significantly[13]. The mechanism by which, APS leads to pregnancy loss is still unclear. One hypothesis is that the syndrome adversely affects trophoblast function in early pregnancy[14], resulting in thrombosis of placental vessels later in the second and third trimesters of pregnancy[15]. There is increasing evidence suggesting that these antibodies derange the normal biology of trophoblast, leading to inhibition of trophoblast invasion[16], and starting an inflammatory response that may lead to miscarriage[17]. Heparin, in addition to its antithrombotic action, inhibits the binding of antiphospholipid antibodies (IGG and IGM) to the trophoblast[18], and heparin treatment produces a rise in serum activin concentration[19], which might induce improvements in trophoblast function early in pregnancy. It has long been known that human chorionic gonadotropin (hCG) is produced by trophoblast early in pregnancy even before zygote implantation[20]. The hCG rescues the corpus luteum with continued production of progesterone, allowing pregnancy to continue[21]. Further, women with antiphospholipid syndrome are given aspirin intake, preconceptually; by the by, low-molecular weight

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heparin therapy (clexane) was commenced (20 mg/d), when the result of the second blood test (14 d after ovulation) confirmed that hCG was > 25 IU/L, cognitively. This report records a case of RPL due to anatomical abnormality, a sub-septate uterus with free spillage bilaterally that was corrected, as well as role of heparin and aspirin as remedial measures in the woman of AMA, without any apparent extra APA, causing a success in pregnancy.

2. Case report

2.1. Case history

A 42-years old woman married since 4 years, appeared at our Infertility Unit, in early 2010. She presented a history of recurrent miscarriage and secondary infertility. She conceived spontaneously in 2008, and had the abortion at 7 weeks. She had a hysterosalpingogram (HSG), based on which a sub-septate uterus with free spillage bilaterally was revealed, and that was corrected by hysteroscopy in October 2009, which was followed by transcervical septal resection in November 2009. She again conceived spontaneously in late 2009, and she was on medication with progesterone; but, at 12 weeks she had lower abdominal pain and loss of conception. Other routine investigation for fasting blood sugar, thyroid function test, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, liver function test, urea, and creatinine were within normal limits. She had no other obvious/known adverse causal factor for RPL.

In 2010, when the couple attended infertility clinic in our hospital, a semen test was conducted on her, 46-years old partner and semen parameters were found normal according to WHO criteria. She had 2 cycles of ovulation induction with clomiphene citrate 100 mg, with a positive effect on follicular monitoring. She conceived after 2 cycles of infertility treatment in October 2010. Nevertheless, with complete bed rest, progesterone supplementation, and the cervical encirclage at 10 weeks of gestation, she had spontaneous abortion at 12 weeks in January 2011. Later on, a few other tests were conducted. Antiphospholipid antibodies and lupus anticoagulant were found at normal limits. She conceived after the first cycle of treatment with clomiphene citrate 100 mg for ovulation induction and injection lupride 1 mg, for triggering luteinising hormone (LH), in October 2011.

2.2. Examination and treatment

The urine pregnancy test was positive at 35 d of amenorrhea; she was advised complete bed rest, folic acid supplementation, aspirin 75 mg, micronized progesterone 400 mg/d injection and low molecular heparin 2 500 IU/d empirically, despite she was seronegative for APA. An intrauterine embryo of gestational age 6 weeks 6 d was evident on a scan. Further, supplementation of L-thyroxine 25 mcg was started (TSH =4.26 μIU/mL, FT4=0.9 ng/dL). Aspirin and heparin (20 mg/d) were given and no major side effect thereof was evident; thus, heparin injections were administered throughout the antenatal period. The woman had normal platelet counts (100 000/mL) through the pregnancy period. It is our routine protocol to supplement all pregnant women using heparin with calcium (600 mg orally twice daily). A cervical encirclage was too given at 11 weeks of gestation. Triple tests were done at 16 week of pregnancy were negative.

A scan after 20 weeks ruled out major congenital malformations. Pregnancy continued uneventfully up to 28 weeks. However, at 28 weeks glucose tolerance (GTT) test with 100 g glucose showed mild derangement in first (159 mg/dL) and second (164 mg/dL) hour values. She was referred to the endocrinologist. A diet control schedule was planned with 1 600 kcal/d and she was started on metformin (500 mg/d) sustained release tablets, for the control of blood sugar level. Regular antenatal check-up including blood pressure, weight and abdominal examination were conducted. At 34 weeks, a scan revealed a single healthy foetus weighing 2.5 kg, in cephalic presentation, foetal umbilical artery, middle cerebral artery doppler index showed normal spectral flow, amniotic fluid index was 12 cm and placental status was of grade II maturity. The patient was hospitalized at 35 weeks, and daily cardiotocography (CTG) and twice weekly doppler and foetal biophysical profile were monitored. At completion of 36 weeks, elective caesarean section was planned; moratorium of heparin injection and metformin intake were done, 24 h prior to surgery. A male child weighing 3.2 kg with a good APGAR score was delivered in July 2012. There was no major intra-operative or post-operative haemorrhage or other complication.

3. Discussion

APS has been encountered in most areas of clinical medicine because of the wide spectrum of its symptoms and associated comorbidities, and its cardinal obstetric manifestation is RPL[22]. Management of APS during pregnancy has included the use of a bandwagon of antithrombotics, heparin, aspirin, prednisone, and intravenous gamma globulin or aspirin alone; however, the combination of subcutaneous heparin and a low-dose aspirin had provided the highest success rates compared with other treatments, with a low occurrence of side effects, elsewhere [23]. and herein too. The rationale for heparin-use has been its anticoagulant activity that overrides the problems caused by APA binding to phospholipids, 2-glycoprotein 1, or other cross-reactive substances[24]. Recent studies have indicated that defective endovascular trophoblast invasion rather than excessive intervillous thrombosis was the most frequent histologic abnormality in APA-associated RPL[25]; APA had been known to inhibit the differentiation of extravillous trophoblasts[26]. Low-molecular-weight heparin treatment has been extensively used for the prevention and treatment of deep venous thrombosis during pregnancy[27]. Low-dose aspirin treatment has been an effective therapy for women with APS related miscarriages[28]. Several studies have comparative accounts of patients with APA seropositivity, who were receiving heparin and aspirin with untreated seronegative patients; high fecundity rates after IVF-ET in APA-seropositive women treated with heparin and aspirin were recorded[28]. Indeed, several substances such as collagen, thrombin, thromboxane A2 (TXA2), adenosine diphosphate (ADP), and dense and alpha granules from the platelets produce platelet activation. Activated platelets release calcium from the dense granules into the cytoplasm. Moreover, calcium causes platelet contraction with a further release of serotonin, ADP, and arachidonate; the later is converted into TXA2 by the cyclooxygenase enzyme. When this enzyme is irreversibly inhibited by low-dose aspirin treatment, vasoconstriction and platelet aggregation may be avoided[29], which in turn should improve folliculogenesis and implantation subsequently.

Pregnancy is an acquired hyper-coagulable state in which successful foetal outcome is dependent on adequate placental circulation[30]. Abnormalities of placental vasculature may result in a number of gestational pathologies, including pregnancy loss, intrauterine foetal demise (IUFD), intrauterine growth restriction, placental abruption, and preeclampsia[31]. Recurrent pregnancy wastage is a major health problem that affects up to 5% of women of reproductive age. Known etiologic factors including chromosomal aberrations, uterine abnormalities, endocrine dysfunction such as hypothyroidism, luteal phase inadequacy, and infectious disorders account for only about one-third of all foetal wastage[32]. Antiphospholipid syndrome, an acquired thrombophilic state, is a well-established cause of pregnancy loss[33]. A number of observations over the

past 3 years suggest that inherited thrombophilia may be associated with pregnancy loss. Studies performed on cohorts of thrombophilic women have shown an increased prevalence of pregnancy loss in women with antithrombin III, protein C, and protein S deficiencies[34], as well as in women with factor V Leiden mutation[35]. The present case with APA seronegativity with empirical use of low molecular weight heparin and aspirin demonstrated continuation of pregnancy until the term, without any sequel.

Conflict of interest statement

We declare that we have no conflict of interest.

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