Spontaneous ovarian hyperstimulation syndrome in four consecutive pregnancies

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Summary: *Background*: Ovarian hyperstimulation syndrome (OHSS) is almost exclusively associated with ovulation induction with gonadotropins or occasionally, clomiphene citrate. Severe ovarian hyperstimulation associated with a spontaneously conceived pregnancy is rare with only two previous reports. Misdiagnosis as a neoplastic process may result in inappropriate intervention.

Case: A patient with polycystic ovarian disease experienced severe spontaneous OHSS in four consecutive singleton pregnancies. Serial color and pulsed Doppler ultrasonographic imaging facilitated adequate evaluation of the patient and permitted conservative therapy. She achieved live births in two of the pregnancies. This is the third reported case of spontaneous OHSS associated with pregnancy and the first to result in live births. In one previous report, misdiagnosis resulted in inadvertent castration.

Conclusions: Spontaneous ovarian hyperstimulation syndrome and pregnancy may occur in patients with polycystic ovarian disease. Color Doppler ultrasonography is a useful aid in the diagnosis and management of this rare complication, and in avoiding inappropriate intervention.

Key words: Pregnancy; Spontaneous ovarian hyperstimulation syndrome; Color Doppler ultrasonography.

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is almost exclusively associated with ovulation induction, with gonadotropins or occasionally, clomiphene citrate. In its most severe form (grades four and five) ([1]), there is a tremendous increase in ovarian size (greater than 10 cm diameter), with attendant abdominal distention, ascites, pleural effusion and decreased intravascular volume. This can lead to sludging and thromboembolic phenomena. Severe ovarian hyperstimulation associated with a spontaneously conceived singleton pregnancy is rare.

A review of the literature revealed only two previous reports of spontaneous OHSS associated with pregnancy ([2, 3]). We describe the first case of severe spontaneous ovarian hyperstimulation syndrome in four consecutive pregnancies in a woman with polycystic ovarian disease. Two of the four pregnancies in our patient resulted in live births unlike in the

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two previous reports that resulted in therapeutic abortions.

Misdiagnosis of spontaneous ovarian hyperstimulation in one previous report also resulted in inappropriate castration ([3]). Our case also illustrates the usefulness of serial color and pulsed Doppler ultrasonography in the evaluation and management of patients with this unusual pregnancy complication.

CASE REPORT

A 31-year-old Caucasian woman, para 2-0-1-1, sought consultation at our institution for secondary infertility. She had regular monthly menses lasting 3-4 days. The patient's past obstetric history was remarkable for the diagnoses of ovarian hyperstimulation syndrome during her three previous consecutive pregnancies (see below). Her medical history (with special regard to factor influencing fertility) and a review of systems was unremarkable.

During her first pregnancy, which occurred spontaneously in 1987, transabdominal ultrasonography revealed bilaterally enlarged ovaries at 13 weeks' gestation (Table 1). Her obstetrician reassured her of the benign nature of the cysts, based on the ultrasonographic appearance resembling theca lutein cysts. She experienced acne and increased abdominal hair growth. Her plasma ovarian and adrenal androgen levels were normal. She had an uneventful pregnancy and term vaginal delivery a normal 2635 g. female infant. The ovaries regressed in size postpartum.

Her second spontaneous pregnancy in 1989 was uneventful until ultrasonographic evaluation for dating again displayed bilateral hyperstimulation ovaries at 14 weeks' gestation (Table 1). Throughout her prenatal outpatient care, there was no clinical or ultrasonographic evidence of ovarian accidents or impairerd fetal development. The fetus was found dead in utero,

Table 1. — *Review of gravidas with spontaneous OHSS.***

Source	Maternal history	Management	Maternal outcome	Fetal outcome
Rosen *et al.* ([2]) (1991)	Gravida 1, para 0, no preexisting disorder 11 wks gestation grade 2 OHSS	Observation sonographic evaluation	No complications	Therapeutic abortion
Zalel *et al.* ([3]) (1992)	Gravida 2, para 1, PCO** 10 wks gestation grade 2 OHSS	Observation sonographic evaluation	No complications	Therapeutic abortion
Present case (1987)	Gravida 1, para 0, PCO 13 wks gestation grade 2 OHSS	Observation sonographic evaluation	No complications	Term live birth
(1989)	Gravida 2, para 1, PCO 14 wks gestation grade 2 OHSS	Observation sonographic	No complications	Term stillbirth
(1990)	Gravida 3, para 2, PCO 9 wks gestation grade 4 OHSS	Repeated abdominal paracentesis sonographic evaluation	No complications	Missed abortion
(1994)	Gravida 4, para 2 abortion 1, PCO 8 wks gestation grade 4 OHSS	Observation sonographic evaluation	No complications	Term live birth

* OHSS = ovarian hyperstimulation syndrome ** PCO = polycystic ovaries

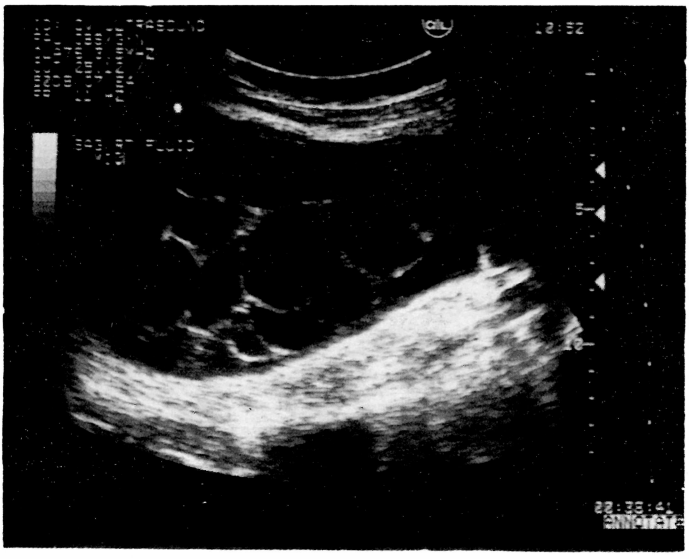

Fig. 1. — Image representative of severe spontaneous ovarian hyperstimulation syndrome (OHSS). Note the tremendous enlargement of the ovary, multiple cystic structures, and copious free fluid.

during admission for a scheduled induction of labor at 41.5 weeks. She delivered a 2800 g stillborn female infant, vaginally. Postmortem examination revealed no abnormality. An attempt to karyotype fetal fibroblasts was unsuccessful. Follow-up ultrasonography showed profound polycistic pattern ovaries, presumably the cause of her OHSS.

In 1992 during her third pregnancy, the patient was admitted by her physician as an emergency at nine weeks gestation, because of dyspnea and painful abdominal distention. Physical examination showed hydrothorax, tense abdominal distention with ascites; and ultrasonographic examination showed grade IV ovarian hyperstimulation syndrome (Fig. 1), and a viable 9-week intrauterine gestation (Table 1). A complete blood count and coagulation studies revealed a hemoglobin and hematocrit of 13.7 g/dL and 39%, respectively, and the platelet count was 133,000/uL; prothrombin time (PT) of 13.1 seconds; and a partial thromboplastin time (PTT) of 32.5 seconds. The patient accepted the option of abdominal paracentesis. Five liters of ascitic fluid was removed. An additional 6 liters of ascitic fluid drained during the subsequent week with only minimal clinical improvement. Repeat ultrasonography at 10 3/7 weeks gestation revealed a nonviable fetus. The patient underwent a suction dilatation and curettage, with rapid improvement in her clinical and hematologic indices.

Postoperative evaluation with ultrasonography showed comlete resolution of ascites and the ovaries had regressed in size. Parental chromosomes yelded normal results. A screen for maternal antiphospholipid and antinuclear antibodies was negative.

At referral, the patient was 1.52 meters tall and weighed 69 kg. Her physical and pelvic examinations were normal. Transvaginal ultrasonography showed typical polycystic morphology of the ovaries (Fig. 2). She had normal basal thyroid and adrenal function, and normal serum prolactin. The serum testosterone concentration was 1.5 nmol/L; serum luteinizing hormone (LH) 39 IU/L; follicle-stimulating hormone (FSH) 7 IU/L; and serum estradiol concentration was 1800 pmol/L. While undergoing infertility evaluation, she readily conceived the present pregnancy without drug therapy. Transvaginal ultrasonography confirmed the presence of grade IV OHSS and a viable, eight-week, intrauterine, singleton pregnancy and bilaterally hyperstimulated ovaries measuring approximately 14 × 16 cm (Fig. 3). Conservative therapy was adopted, and over the next 12 weeks, the patient was followed closely in the fetal assessment unit. She had serial pelvic and abdominal color Doppler ultrasonographic evaluation using an ATL Ultramark-9 (HDI) unit (Advanced Technology Laboratories, Bothel, WA). The technique provided rapid noninvasive, visual

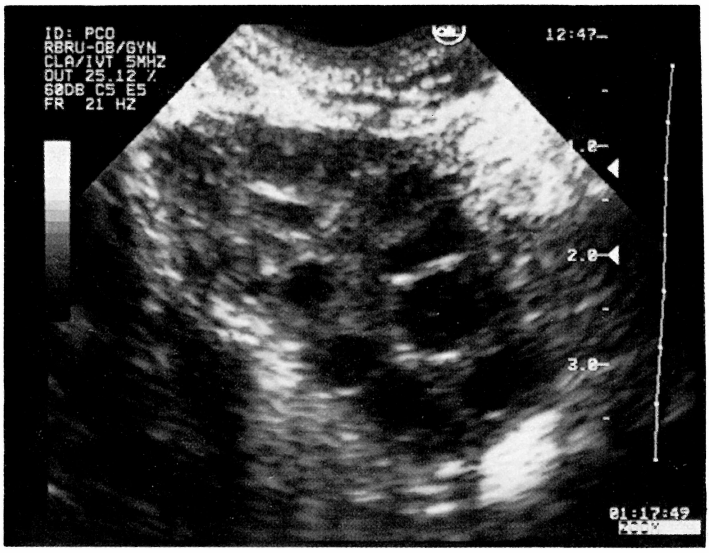

Fig. 2. — Ultrasonographic image of an ovary with characteristics of polycystic ovarian syndrome.

acces to the morphologic, physiologic, and vascular status of both the ovaries and developing fetus. Serial examinations revealed normal color Doppler signals in both the feto-placental unit as well as the ovarian the ovarian vessels indicative of uncompromized blood flow to both ovaries. The pregnancy progressed to term with delivery of a 2860 gm male infant. Examination at eight weeks postpartum showed both ovaries to be of normal size.

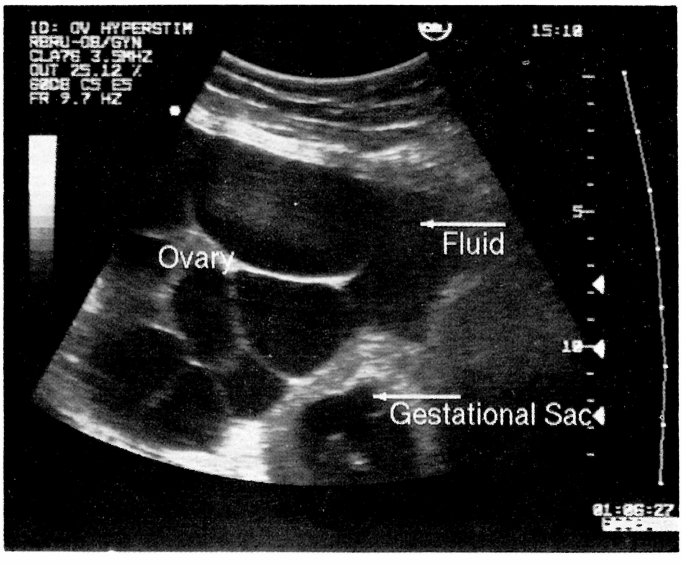

Fig. 3. — Ultrasonographic image of spontaneous ovarian hyperstimulation syndrome at 8 weeks gestation.

DISCUSSION

The syndrome of ovarian hyperstimulation is a serious complication of induction of ovulation with gonadotropins. It is rare in unstimulated ovaries. To our knowledge, there have been only three cases of spontaneous OHSS in the English literature ([1-4]), (two cases associated with pregnancy, Table 2); this being the first documented case of recurrent spontaneous ovarian hyperstimulation syndrome associated with pregnancy. Information on the pathophysiology of OHSS has only recently begun to emerge.

Several mechanisms may be involved. These include an underlying polycystic ovary syndrome ([5]), and high endogenous gonadotropin levels ([6]). Palumbo *et al.* ([7]) postulated that patients with polycystic ovary syndrome have abnormally high concentrations of angiotensin II-like substance. This substance produces angiogenesis, increases capillary permeability, and causes rapid third space fluid accumulation.

Relatively high early follicular-stage estradiol levels, high androgen levels and dyssynchrony in follicular recruitment and maturation are found in patients with polycystic ovary syndrome ([5, 8]). These findings have been proposed as additional factors predisposing to ovarian hyperstimulation, when administering gonadotropins for ovulation induction. It is possible that rare occurrence of a spontaneous luteinizing hormone surge and ovulation in an unstimulated cycle may, by a similar mechanism, lead to ovarian hyperstimulation syndrome, especially if pregnancy results. Similar to two of the three cases described in the literature, our patient showed clinical and laboratory characteristics of polycystic ovary syndrome. This case provides compelling evidence that polycystic ovarian disease is a risk factor for ovarian hyperstimulation syndrome, and suggests that this complication can occur spontaneously without ovulation induction. Clinicians should include discussion of this potential complication in the preconception counselling of appropriate patients.

There is a vast body of literature on the management of ovarian hyperstimulation syndrome and pregnancy ([9]). Treatment is conservative, and aimed at maintaining the intravascular volume, preventing hemoconcentration, hypovolemia and their adverse consequences on coagulation, and kidney function. There is proven beneficial effect of abdominal paracentesis in relieving respiratory distress. Surgical intervention is rarely indicated unless ovarian torsion or rupture occurs. Both of the two previously reported patients with spontaneous OHSS decided for elective pregnancy termination, making the present case the first with a term pregnancy and delivery. Our patient had two successful pregnancies, although she experienced one fetal loss and one spontaneous abortion. This finding would suggest that ovarian hyperstimulation syndrome may be associated with increased pregnancy loss.

Our case emphasizes two points: the importance of a thorough evaluation of all women with ovarian masses complicating pregnancy, and the diagnostic value of transvaginal color Doppler and pulsed ultrasonography in this setting. The recognition of spontaneous OHSS is important as its misdiagnosis as a neoplastic process may results in unnecessary, drastic and sometimes mutilating interventions ([1, 10]). The differential diagnosis includes disorders such as hyperreactio luteinalis, luteomas of pregnancy and recurrent theca lutein cysts. Although our patient experienced increased acne and abdominal hair growth during her first pregnancy, the findings of sudden third space fluid shifts, rapid enlargement and tenderness of the ovaries, and normal serum androgen levels, supported a diagnosis of ovarian hyperstimulation syndrome.

Transvaginal color Doppler imaging aided the diagnosis of OHSS in our patient, and is the procedure of choice in pregnancy. It is non-invasive and carries little risk of ovarian rupture. It allows for better evaluation of complex intraovarian structures that may suggest further complications or a neoplastic process. The absence of intraovarian color flow mapping may also indicate rare ovarian torsion or infarction found in some cases of severe ovarian hyperstimulation. In addition, when abdominal paracentesis is necessary, it is best performed under transabdominal ultrasonographic guidance.

In this rare case of spontaneous ovarian hyperstimulation syndrome we have demonstrated the value of accurate diagnosis and monitoring using transvaginal ultrasonographic imaging. On site imaging facilities permitted noninvasive conservative therapy thereby avoiding inappropriate intervention.

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