

Conservative Management of Hyperreactio Luteinalis: A Case Report

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Abstract

Hyperreactio luteinalis (HL) is characterized by bilaterally enlarged ovaries containing multiple self-limited theca lutein cysts and is usually associated with increased production of human chorionic gonadotropin in the presence of trophoblastic disease or multiple pregnancies. About 30 cases of HL have been reported in patients with normal singleton pregnancies, and most of these patients required surgical intervention during their first pregnancy because of ovarian torsion or to rule out of ovarian malignancy. However, the accurate diagnosis of HL by means of laboratory tests and magnetic resonance imaging and the exclusion of ovarian malignancy in asymptomatic pregnant woman may avoid unnecessary surgical intervention or termination of pregnancy. The present report describes case of HL in a woman with a normal singleton pregnancy in whom conservative management allowed the preservation of both ovaries.

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Key words: OHSS, FSH receptor, hyperandrogenism, pregnancy

Introduction

Hyperreactio luteinalis (HL) is a rare condition during spontaneous pregnancy and is characterized by multiple cysts and bilateral ovarian enlargement associated with high maternal serum levels of human chorionic gonadotropin (hCG) and a hyperandrogenic state^{1–3}.

Ovarian hyperstimulation syndrome (OHSS) is a well-known complication of the early first trimester of pregnancy and is usually a consequence of iatrogenic ovarian induction, but in rare occasions it can occur spontaneously, particularly in patients with hypothyroidism, a pituitary gonadotropin

(follicle-stimulating hormone [FSH]/luteinizing hormone [LH])-secreting adenoma, polycystic ovary syndrome (PCOS), or mutation of the FSH/LH receptor^{4,5}.

It may be difficult to differentiate severe HL in the first trimester from spontaneous OHSS, but HL may be asymptomatic and only discovered incidentally during routine pelvic ultrasonography or cesarean section.

We recently treated a patient with bilateral ovarian enlargement during the first trimester of pregnancy in whom HL was diagnosed and managed conservatively.

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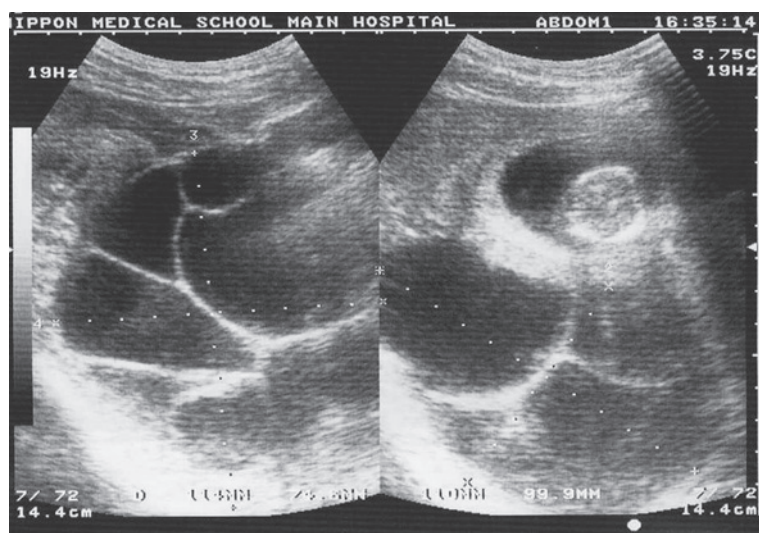


Fig. 1 Transvaginal ultrasonography showed bilateral enlargement of the ovaries (left ovary, 14×11 cm; right ovary, 14×9.9 cm) with multiple anechoic cysts.

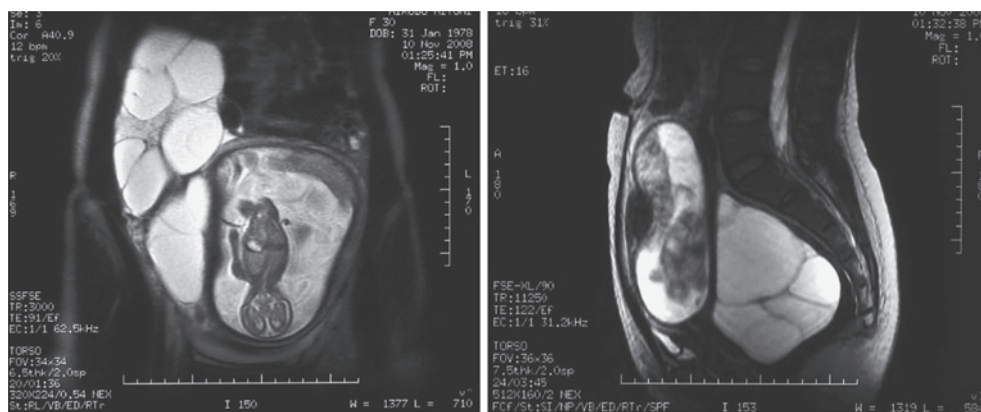


Fig. 2 MRI revealed multiple cystic ovaries (left ovary, 14×10 cm; right ovary, 15×10 cm).

Case Report

A 31-year-old primigravida was referred to our department in the 12th week of pregnancy. The patient had never taken drugs to induce ovulation. Transvaginal ultrasonography showed a normal singleton pregnancy at 12 weeks' gestation and bilateral enlargement of the ovaries (left ovary, 14 × 11 cm; right ovary, 14 × 9.9 cm) with multiple anechoic cysts (**Fig. 1**).

Laboratory results at 12 weeks' gestation included: hematocrit, 39.6% (normal: 33%–43%), liver enzymes and coagulation profiles were normal; blood urea nitrogen, creatinine, and electrolytes were within normal limits; hCG, 104,963 IU/mL; estradiol, 9,599

pg/mL; progesterone, 48.2 ng/mL; FSH, <1.0 mIU/mL; LH, <0.2 mIU/mL; CA125, 23.9 IU/mL (normal, <35); CA19-9, <1.2 (normal, <35); thyroid stimulating hormone, 0.222 IU/mL (normal, <5.00); free thyroxine 4, 1.43 ng/mL (normal, 0.83–1.64, ng/mL); and prolactin, 75.9 ng/mL (normal, 1.4–14.6 ng/mL). Androgen levels were significantly increased: testosterone, 324 µg/mL (normal, 60–150 µg/mL); free testosterone, 2.2 pg/mL, (normal, <1.9 pg/mL); and androstenedione; 24 ng/mL (normal, 0.9–3.5 ng/mL). Possible interventions, such as laparotomy, were discussed with the patient and her husband. On the basis of previous reports of HL, we selected conservative management. Magnetic resonance imaging (MRI) was performed to rule out ovarian malignancy (**Fig. 2**).

At 38 week's gestation, a healthy female neonate (weight, 2,608 g; Apgar score, 8-9) was delivered by means of cesarean section. Because of a swollen right ovary on the Douglas pouch, cesarean section was performed on the basis of a diagnosis of disturbance of the birth canal.

Intraoperative inspection of the abdomen revealed that the ovaries were grossly enlarged and polycystic (**Fig. 3**). The mean diameter of the right ovary was 12 cm and that of the left ovary was 15 cm, with multiple cysts 3 to 4 cm in diameter and filled with yellowish fluid. Samples of the cystic fluid and specimens from wedge resection of both ovaries and the placenta were submitted for pathologic examination. The abdomen was explored, and no other abnormalities were found.



Fig. 3 Both ovaries appeared grossly enlarged and polycystic.

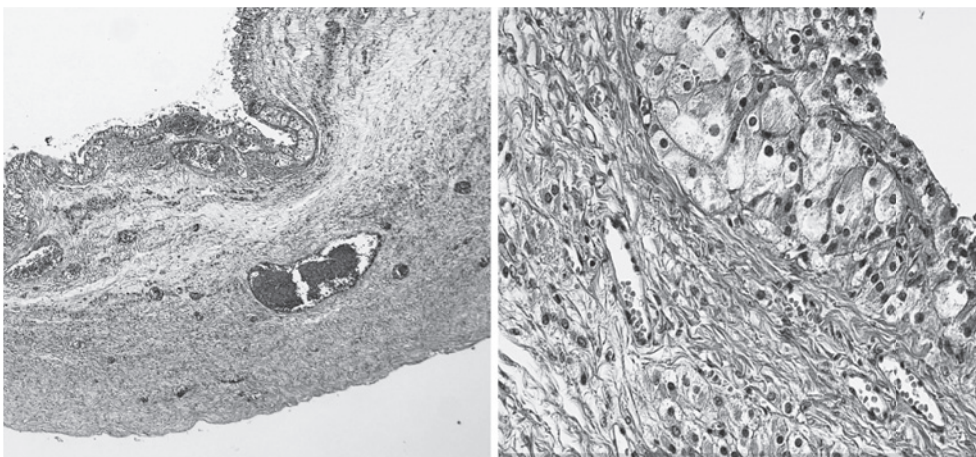
The patient's postoperative course was unremarkable. Ovarian volume decreased slowly and became normal in 4 months. Androgen levels decreased slowly and became normal in 3 months. The female neonate showed no signs of virilization. The pathological diagnosis was hyperreactio luteinalis. The cyst lining comprised granulosa and theca layers, both of which exhibited marked luteinization (**Fig. 4**).

Sequencing analysis of the gene for the FSH receptor was approved by the ethics committee of Nippon Medical School and was performed with the cooperation of Sabine Costagliola, Ph.D., of Brussels, Belgium, after the patient had given written informed consent. However, the gene for the FSH receptor was normal.

Discussion

HL is a rare benign condition, and about 30 cases of HL in normal singleton pregnancies have been reported. Most of the patients required surgical intervention during their first pregnancy because of ovarian torsion or to rule out of ovarian malignancy.

HL is typically a self-limited syndrome with asymptomatic bilateral enlargement of the ovaries containing multiple theca lutein cysts due to excessive hCG stimulation of the ovaries⁶. The hCG is produced by the trophoblast in the first trimester, and its highest median level is 100,000 IU/L in the



HE X4

HE X40

Fig. 4 The cyst lining comprised granulosa and theca layers, both of which exhibit marked luteinization.

9th week of gestation⁶. Abnormally high levels of hCG can be found in molar and multiple pregnancies and in specific ovarian or gestational malignancies, fetal chromosomal abnormality, and HL⁶. On the other hand, the onset of HL is variable⁷⁻⁹, and its relation to the level of hCG is inconsistent^{7,10}. In the present case, levels of hCG were not abnormally elevated.

It is important to differentiate HL from malignant ovarian tumors to avoid unnecessary surgery. The laboratory findings of high levels of hCG, hyperandrogenism, and normal levels of ovarian tumor markers, in combination with such imaging methods as ultrasonography and MRI, help differentiate HL from malignant ovarian masses.

Bilateral multicystic ovarian tumors may also mimic spontaneous OHSS, but pregnant woman with OHSS usually have a history of induction of ovulation. Also, OHSS has been demonstrated to develop with hypothyroidism, PCOS, FSH-secreting adenoma, or mutation of the FSH receptor⁴. Smits et al¹¹ have found that a mutation of the FSH receptor causes hypersensitivity to hCG which can mimic pharmacologically induced OHSS. Our patient had no history of ovulation induction or therapy for PCOS and showed no hypothyroidism, increase in FSH levels, or mutation of the FSH receptor. Therefore, on the basis of these findings, it is still difficult to differentiate severe HL from spontaneous OHSS because the causes of HL and spontaneous OHSS remain unknown.

The diagnosis of HL may be established at any time during gestation. The majority cases (54%) are diagnosed in the third trimester or in the puerperium and present with bilateral enlargement of the ovaries and without other symptoms, whereas 16% are diagnosed in the first trimester¹². More than 37% of cases are diagnosed at the time of cesarean section, because HL is asymptomatic in most patients. In contrast, OHSS presents at the beginning of the first trimester and is associated with more severe symptoms involving acute fluid imbalances (such as massive ascites and hemoconcentration) that impair the natural course of pregnancy. The present case was followed up from the first trimester until delivery.

Symptomatic patients present abdominal discomfort or pain, which is a result of ovarian torsion. HL can be associated with hyperemesis gravidarum, hyperthyroidism, hyperandrogenism, intrauterine growth restriction (IUGR), eclampsia, or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome¹³⁻¹⁶.

Hyperandrogenism is a characteristic of HL, but patients with hyperemesis gravidarum and PCOS also show elevated androgen levels. Hormonal studies in the present case confirmed hyperandrogenemia; thus, maternal virilization was not seen.

The elevated levels of hCG produced by the trophoblast in the first trimester in an otherwise normal pregnancy could be a sign of poor or incomplete placental invasion^{13,14}. The poor placental invasion could lead to preeclampsia, severe IUGR, or HELLP syndrome¹³⁻¹⁶. Because the hCG levels were normal, the present patient was asymptomatic.

In conclusion, we have described a patient with HL presenting as bilateral ovarian enlargement during the first trimester of pregnancy in which conservative management allowed preservation of both ovaries. Although HL is extremely rare in normal singleton pregnancies, it is important to differentiate HL from malignancies to avoid unnecessary surgery.

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