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Hyperreactio luteinalis could be an early sign of HELLP syndrome: case report

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Capsule

Hyperreactio luteinalis due to the high level of HCG in first trimester could be a consequence of inappropriate trophoblast invasion, and sign of subsequently developing preeclampsia, eclampsia or HELLP syndrome.

Abstract

Objective: To report a unique case of hyperreactio luteinalis in pregnancy associated with ovarian torsion and subsequently developing of HELLP syndrome.

Design: Case report.

Setting: University medical center.

Patient: A 34-year-old primigravida with ovarian torsion in 13 weeks of pregnancy and subsequently developed intra-uterine growth restriction (IUGR) and HELLP syndrome.

Interventions: Laparoscopic salpingo-oophorectomy due to the ovarian torsion and cesarean section (CS) due to the developing of HELLP syndrome.

Main Outcome Measure: HELLP syndrome

Results: In first trimester our patient had symptoms of acute abdomen due to the ovarian torsion. Both ovaries were enlarged and multicystic. Hormonal studies confirmed abnormally elevated level of HCG (200 000 IU/L), mild hyperthireosis and hyperandrogenemia. Laparoscopic salpingo-oophorectomy was performed. At 30 weeks of pregnancy clinically and ultrasonography IUGR was confirmed, and at 33 weeks severe preeclampsia were developed. One week later HELLP syndrome was occurred. Emergency CS was preformed, and she delivered female newborn weighting 1640 grams. Seven days after delivery blood pressure and abnormal hormonal status were returned to normal.

Conclusion: Hyperreactio luteinalis due to the abnormally high level of HCG in first trimester could be a consequence of inappropriate trophoblast invasion, and early sign of subsequently developing preeclampsia, eclampsia or HELLP syndrome.

Key Words: hyperreactio luteinalis, elevated HCG, ovarian torsion, trophoblast invasion, IUGR, eclampsia, HELLP syndrome.

Introduction

Hyperreactio luteinalis (HL) is a rare benign condition that is characterized by multicystic and bilateral ovarian enlargement in pregnancy and regression after delivery caused by increased production of human chorionic gonadotropin (HCG) [1].

Only 30 cases of HL associated with normal singleton pregnancies are reported in the literature so far, and greatness of them are discovered in last trimester of pregnancy [2,3].

Majority of pregnant women with HL are asymptomatic, and enlarged ovaries are usually accidentally discovered at routine ultrasound examination. This benign condition may imitate enlarged ovaries in ovarian hyperstimulation syndrome (OHSS) and ovarian malignancy. OHSS is usually consequence of iatrogenic ovarian induction but in the rare occasions it can occur spontaneously particularly in hypothyroidism, pituitary gonadotrophin (FSH/LH) secreting adenoma, pregnant women with polycystic ovarian syndrome (PCOS), or mutation in FSH/LH receptors [4,5].

However, proper diagnosis of HL with laboratory tests and imaging techniques and exclusion of ovarian malignancy in asymptomatic pregnant woman may avoid surgical intervention or termination of pregnancy [6,7].

Symptomatic pregnant women may have abdominal discomfort or pain which is a result of ovarian torsion and in some cases HL could be associated with hyperemesis gravidarum, hyperthyroidism, hyperandrogenism and hirsutism, intra-uterine growth restriction (IUGR) and eclampsia [2, 8-11].

We present a unique case of HL complicated with ovarian torsion in early pregnancy that is managed by laparoscopic salpingo-oophorectomy and subsequently development of IUGR and finally hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome.

Case report

A healthy 34-year-old primigravida came to our emergency gynecologic ambulance at 13+2 weeks because of colicky pain in the right low abdominal quadrant and nausea. The pain started two hours before admittance. She had a naturally conceived and normally developing singleton pregnancy and denied using drugs for ovulation induction.

Her medical and gynecologic histories were unremarkable, except she had appendectomy 17 years ago. She had no signs of thyroid disorder, hyperandrogenism or peritoneal irritation.

On admission her vital signs were stable (blood pressure (BP), 110/70 mmHg; pulse rate, 70 beats per min; body temperature, 36.5 C; and respiration rate, 14/min).

A large pelvic masses extending to the abdomen were felt on examination. Two separate cysts were found on the lumbar regions bilaterally. The right mass was 4 cm and the left one was 2 cm below the level of the umbilicus.

Vaginal ultrasonography (US) showed a single live intrauterine 13 weeks gestation (crown–rump length 6.9 cm, biparietal diameter 2.9 cm) with bilateral enlarged multicystic ovaries (right ovary: 10.4 × 9.1 × 9.2 cm, left ovary: 12 × 10.1× 10.2 cm) without ascites (Figure 1). Doppler ultrasonographic study results were normal.

Initial laboratory testing confirmed normal erythrocyte (E) $4.35 \times l0^{12}$ l, leukocyte (L) 12 $\times 10^9$ l and platelet (PL) 244 $\times 10^9$ l count and normal levels of hemoglobin (Hb) 123 g/l, hematocrit (HTC) 36.5 %, blood urea nitrogen (BUN) 3.2 mmol/l, creatinine (54 mmol/l), acidum uricum (AU) 154 µmol/l, aspartate transaminase (AST) 25 U/L, alanine transaminase (ALT) 20 U/L, alkaline phosphatase (AP) 154 U/L, gamma glutamyl transpeptidase (GGT) 14 U/L. The C reactive protein (CRP) level was slightly increased (8.8 mg/l), fibrinogen level was increased (8.1 g/L) and the serum levels of b-HCG was increased almost double above the standard limits (192 000 IU/l). The prothrombin time

(1.21), active partial thrombin time (25.2 s), thrombin time (14.2 s) and electrolytes (Na 134 mmol/l, K 3.8 mmol/l and Cl 95 mmol/l) were within normal limits. Ovarian tumor marker CA 125 was normal and urine culture was sterile. The hormonal status during pregnancy was shown in Table 1.

On the second day after admission to the hospital, the abdominal pain increased especially on the right side. She developed clinical signs of acute abdomen with increasing in the L count (17.1×10^9 L) and CRP level (26 mg/l) and we decided to perform laparoscopic procedure for diagnosis and treatment.

During the procedure, the double torsion and ischemic changes of the right ovary was found. The ovarian vessels and right fallopian tube was two times rounded over the adhesion from the previously appendectomy 17 years ago. Both ovaries were mulycystic and oedematous. There were no ischemic changes in the left ovary, and the uterus was 13 weeks gestation in size. The right side salpingo-oophorectomy was performed, and the material was sent to the pathology. The pathologist's report confirmed the diagnosis of the infarction of the right ovary. In the remaining ovarian tissue pathologist's found multiple areas of hypertrophic luteinised cells that are the major pathologic finding in this syndrome. The US after the procedure shown enlarged left ovary 10 x 10.2 x 9.5 cm and normal biometric measures for 14/15 weeks gestation.

After the procedure, the clinical and laboratory findings were unremarkable, and she was discharged home on the seventh postoperative day. The routine obstetrics and US controls were normal, except of the last US control at 30 weeks of pregnancy. On that US control the biometric measures were lower (biparietal diameter 7.4 cm, abdominal circumference 20.3 cm, femur length 5.1 cm) for 2 weeks in comparison to the anamnestic data of the last menstrual period, and the IUGR was suspected.

On the next regular control at the 33 weeks of pregnancy her BP was increased to 150/90 and had 3+ protinuria on urinalysis. She was hospitalized for further analysis and treatment. Laboratory testing confirmed normal E ($4.17 \times l0^{12}$ l), L (8.3×10^9 l) and PL (203 x 10^9 l) count and normal levels of Hb (121 g/l), HTC (35.8 %), BUN (3.8 mmol/l), creatinine (64 mmol/l), AU (391 µmol/l), AST (30 U/L), ALT (16 U/L), AP (182 U/L), GGT (16 U/L). The CRP level was slightly increased (9.1 mg/l), fibrinogen level was increased (7.6 g/L) and d dimmers were normal (248 ng/ml). Methyldopa (per os) 4 x 500 per day was administrated and the BP in the next few days was within normal limits. Prophylactic dexamathasone 2 x 12 mg i.m. was given for fetal lung maturity. Clinical examination and US confirmed the diagnosis of IUGR, and the estimated fetal weight was 1700 grams. Three days after admission she had two episodes of elevated BP up to170/110 associated with the epigastic pain, and the laboratory findings of the elevated liver enzymes (AST 197 U/L, ALT 122 U/L, AP 259 U/L) and low PL level (85 x 10^9 l) – HELLP syndrome..

The emergency cesarean section was performed under the general anesthetic, and she delivered a female baby weighing 1640 g, Apgar score 7/9 and pH form the umbilical vein 7.17. Left ovary was enlarged, multycystic and fixed to the posterior side of the uterus. Placental histology showed evidence of under perfusion but without evidence of infection or trophoblastic abnormalities. Seven days after delivery blood pressure and abnormal hormonal status were returned to normal.

Discussion

As a part of our investigation we performed a MEDLINE search of the literature from 1966 to April 2008 using the key words: hyperreactio luteinalis, intrauterine growth restriction, preeclampsia and eclampsia. We found only one case of HL and subsequentialy developing of thrombosis and severe preeclampsia, one case of IUGR and one case of eclampsia but none of the previously reported cases of HL had presented with subsequently developing of HELLP syndrome [8-10].

Hyperreactio luteinalis is very rare benign condition in pregnancy and in the most of the described cases it is associated with asymptomatic bilateral ovarian enlargement due to theca lutein cysts resulting from excessive HCG stimulation of the ovaries. Human chorionic gonadotropin is a glycoprotein produced by the trophoblast in the first trimester and its highest level is around 100 000 IU/l at the 9^{th} week of gestation [1]. Abnormally high levels of HCG could be found in molar and multiple gestation and in specific ovarian or gestational malignancies, fetal chromosomal abnormality and finally in HL [1].

For obstetricians it is important to be aware of this condition which is benign and self limitated, and to differentiate it from malignant ovarian tumors in pregnancy [7]. The laboratory findings in HL as combination of high level of HCG, hyperandrogenism and hyperthyroidism in combination with MRI help to detach HL from malignant ovarian mass. The ovaries in HL are symmetrical with uniform size of theca lutein cysts [6].

Multycystic and enlarged ovaries may also mimic OHSS but pregnant women with OHSS usually have a history of induction of ovulation, although this condition may develop spontaneously like in unrecognized hypothyroidism, pituitary FSH/LH secreting adenoma, pregnant women with PCOS or mutation in FSH/LH receptors [4, 5].

The majority of pregnant women with HL have been discovered in the last trimester or in the puerperium (70 %) with bilateral enlargement of the ovaries and without other symptoms. Only 20% were initially seen in the first trimester, and our case is completely followed up during the whole pregnancy [3]. The most common symptom in pregnant women with HL is abdominal discomfort or pain which is a result of ovarian torsion. In rare cases HL could be associated with hyperemesis gravidarum, hyperthyroidism, hyperandrogenism and hirsutism, IUGR, eclampsia and finally HELLP syndrome [2, 8-10]. Our patient was symptomatic and developed signs of acute abdomen due to the ovarian torsion in first trimester. Hormonal studies confirmed abnormally elevated level of HCG (200 000 IU/L), mild hyperthireosis and hyperandrogenemia.

The elevated level of HCG produced by the trophoblast in first trimester in otherwise normal pregnancy could potentially be a sign of a poor or incomplete placental invasion. Subsequenty poor placental invasion could lead to developing of preeclampsia and in minority of cases this could end with severe IUGR, ecamptic seizure or HELLP syndrome. This report may have implications for better understanding of uterine physiology in pregnancy, and elevaterd level of HCG could be a sign of poor placental invasion in early pregnancy.

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Table 1. Hormonal status throughout pregnancy

GW[a]	13	23	31	7 days AD[b]	NR[c]
HCG (IU/l)	192 000	61 000	77 500	1454	
PROGESTERONE (nmol/l)	434	637	377	421	
TESTOSTERONE (nmol/l)	6.0	4.4	5.0	2.3	0.2-2.6
TESTESTERONE FREE (pmol/l)	39	35	32.5	2.2	3.5-30
ANDROSTENDIONE (nmol/l)	6.4	7.5	8.3	6.6	1-12
LH (IU/l)	2.3	1.6	2.9	1.7	
FSH (IU/l)	2.6	1.8	4.1	3.5	
PROLACTIN (µg/l)	212.1	232.4	281.4	197.3	4-23
THS (m IU/l)	2.4	2.6	1.9	1.6	0.4-4.2
T4 (nmol/l)	167.1	129.6	163.1	132.2	70-165
T3 (nmol/l)	4.5	3.9	4.3	2.1	1.3-2.5

Footnotes: GW – gestational weeks, AD- after delivery, NR – normal range for our laboratory

Figure 1. Ultrasound picture of enlarged and multicystic ovary