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Severe preeclampsia and fetal virilization in a spontaneous singleton pregnancy complicated by hyperreactio luteinalis

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Abstract. – *Background:* **Hyperreactio luteinalis is a rare condition that stems from theca cell hyperplasia in the ovaries due to a high level of human chorionic gonadotropin during gestation. It occurs commonly in pregnant patients with trophoblastic disease, occasionally in multiple pregnancies, and rarely in normal singleton pregnancy.**

Case Report: **A 24-year-old pregnant woman, G3 P0, who was admitted to the Perinatology Clinic with increasing findings of virilization during pregnancy was presented. The patient had bilaterally enlarged multicystic ovaries on sonographic examination and elevated serum androgen levels She was managed conservatively until 38th week of gestation as a presumptive diagnosis of hyperreactio luteinalis. Elevated blood pressure and prominent proteinuria were detected during the follow-up of the patient and labor was induced. She underwent an emergency caesarean delivery because of fetal distress. During caesarean section, ovarian biopsies were taken and a histopathological diagnosis of hyperreactio luteinalis was determined. The female fetus also presented virilization.**

Conclusion: **Although infrequent, hyperreactio luteinalis with both maternal and fetal virilization can occur in women with spontaneous singleton pregnancies. The clinical manifestations in such women may be complicated by severe preeclampsia.**

Key Words:

Hyperreactio luteinalis, Hyperandrogenemia, Pregnancy, Preeclampsia.

Introduction

Hyperreactio luteinalis (HL) is a benign and rare condition characterized by bilateral multiple theca-lutein cysts that develop due to excess increase of luteinization in the ovaries[1]. The exact etiology of HL is unknown. However, it has been thought that this condition has a connection to exposure of the ovaries to high levels of human chorionic gonadotropin hormone (hCG)[2]. Supporting this hypothesis, HL has generally been encountered in such situations as hydatidiform moles, choriocarcinoma, erythroblastosis fetalis, and multiple gestation, in all of which hCG levels are significantly higher than normal. Most cases are asymptomatic and are discovered via routine obstetrical ultrasonography (USG) or during caesarean section[3]. Acute abdominal findings or abdominal pain related to torsion or rupture of bilateral multiple cysts can be seen. In 15-25% of the cases, maternal virilization related to increased levels of androstenedione and testosterone produced in hyperplasic thecal tissue in the ovaries may occur[1-3]. Due to highly active placental aromatase enzymes, the transmission of increased androgens to female fetuses is largely prevented, and virilization in a female fetus is not generally expected[4].

In this article, we present a case of HL that was recognized via prenatal ultrasonography in a naturally conceived pregnant woman presenting with hyperandrogenemic symptoms such as hirsutism, hair loss, and cystic acne. She subsequently developed severe preeclampsia at 38th week of gestation. We also discuss the topic, along with the relevant literature.

Case Report

The 24-year-old patient, G3 P0, was referred to the Perinatology Clinic with complaints of hirsutism, acne, and progressive hair loss at the 36th gestational week. In taking her medical history, there was nothing noteworthy, except for two

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previous abortions, both in the first trimester. The patient had no history of ovulation induction. During physical examination, hair loss in the bilateral frontotemporal region, cystic acne prominent in the face, and marked hirsutism in the midline were noted. Genital examination of the patient revealed no signs of virilization. With a prediagnosis of hyperandrogenemia, the patient was asked to submit to routine laboratory tests – serum androgen, thyroid stimulating hormone (TSH), steroid hormone binding globulin (SHBG), human Chorionic Gonadotropin (hCG), and levels of tumor markers were measured. Thyroid function tests, routine hemogram and biochemical values were normal. Abnormal values were as follows: hCG: 91373 mIU/ml (2700-78,100); unbound testosterone: 3.72 pg/ml (0.18-2.18); androstenedione: 7.67 ng/ml (0.5-4.7); SHBG: 6.2 nmol/l[13-71]. Obstetrical ultrasonography revealed a single live fetus with slightly decreased amniotic fluid level and normal placental localization, compatible with 35th week developmental stage. In evaluating the adnexa, the diameters of the left ovary were 95 × 83 mm, and the diameters of the right ovary were 78 × 57 mm; both ovaries were in a multicystic condition (Figure 1). Minimal peritoneal fluid was detected in the pouch of Douglas. Her blood pressure on admission was 150/90 mmHg and (2+) proteinuria was detected by routine urinalysis. After a discussion with the patient, whose condition was diagnosed as hyperreactio luteinalis and preeclampsia, was followed up with on these findings. During the period of follow-up, the blood pressure began to show elevations up to 160/110 mmHg values and 5.2 g of protein in a 24-hour urine sample was found. The decision to induce the labor was taken at the 38th gestational week due to the signs of severe preeclampsia. The patient was admitted for vaginal prostaglandin induction. On 5th h of her induction, the patient evolved with acute fetal distress and an emergency cesarean section was indicated. Intraoperatively, both ovaries were seen as multicystic and increased in dimensions (Figure 2). Biopsies were taken from both ovaries for the frozen section to exclude an ovarian malignancy. The operation and postoperative follow-up of the patient were uneventful. During genital examination of the neonate, prominent cliteromegaly and labioscrotal fusion were defined (Figure 3). The karyotype of the neonate, who was followed in the Neonatal Intensive Care Unit, revealed 46 XX. With a prediagnosis of pseudohermaphroditism, the follow-up of the neonate was taken over by a pediatric endocrinologist. In the histopathological analysis of the ovaries, theca-lutein cysts surrounded by luteinised granulosa cells, separated by edematous stromal tissue, and having no neoplastic changes were defined, and a diagnosis of HL was determined (Figure 4). The patient was discharged on the third postoperative day. During the fourth week postoperative control, it was confirmed that the hyperandrogenemia findings were disappearing and the bilateral cysts were retreating. Laboratory tests showed that unbound testosterone and androstenedione levels were in the normal ranges. Her blood pressure was measured in normal ranges, as well.

Discussion

HL is a rare condition complicating pregnancy and has generally been encountered in hydatidi-

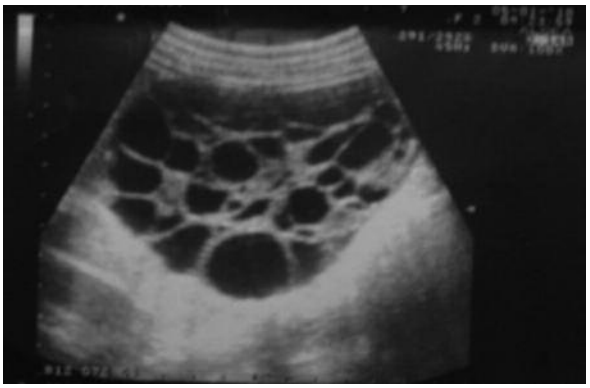

Figure 1. Ultrasound image of multicystic and enlarged ovary (*left*).

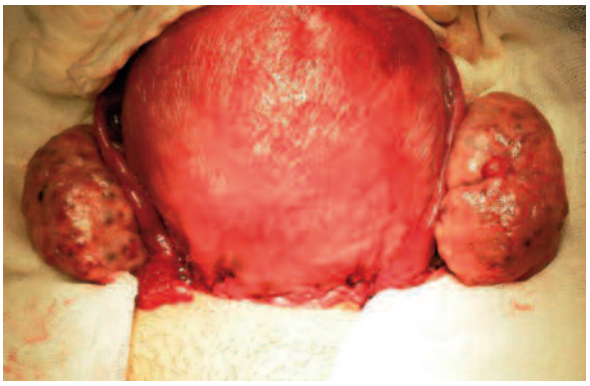

Figure 2. Intraoperative appearance of the ovaries with hyperreactio luteinalis.

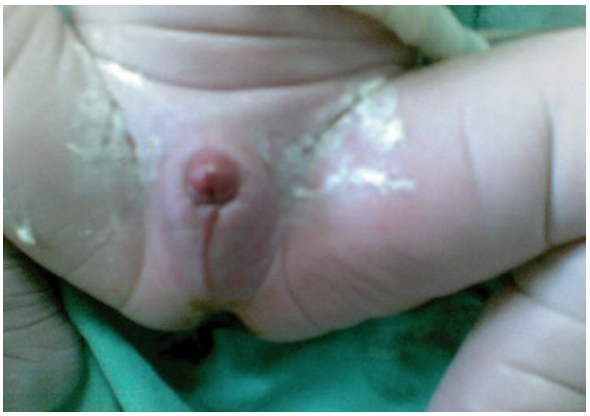

Figure 3. Ambiguous genitalia of the female newborn with prominent cliteromegaly and labioscrotal fusion.

form moles, choriocarcinoma, erythroblastosis fetalis, and multiple gestation, with higher concentrations of maternal serum hCG[3,4]. Although the exact prevalence of the condition is not known, it has been stated that it may be concomitant in 10-22% of trophoblastic diseases[4-6]. Rarely HL occurs in singleton pregnancies. This rare ovarian condition usually proceeds asymptomatically and is found incidentally at the time of cesarean section or imaging, but it sometimes presents as an abdominal mass or acute abdomen. In rare cases, it may lead to maternal and fetal virilization[1,4]. It has been reported that in gestational cases in which virilization is seen, the second most frequent underlying cause is HL, with gestational luteoma being the first[1]. Virilization occurs in 25-35% of mothers with luteoma. The female fetus is afflicted with virilization in two-thirds of virilized mothers[1]. The presenting

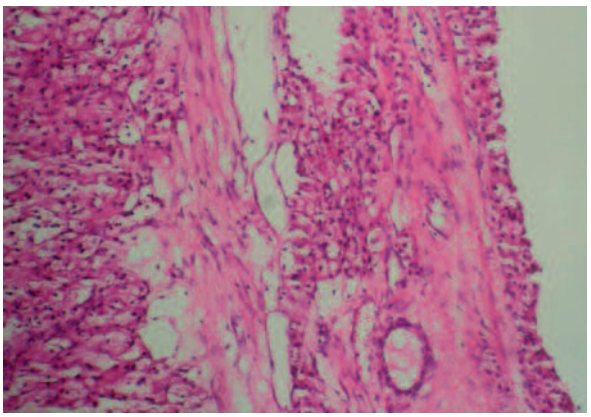

Figure 4. Histopathological diagnosis of hyperreactio luteinalis. Cyst lining consists of thecal cells with prominent luteinization (H&E × 100).

case is a rare example of HL occurring in a singleton pregnancy with both maternal and fetal signs of hyperandrogenemia.

In the literature, it has been reported that some obstetrical and medical complications, such as thyroid dysfunction, hyperemesis gravidarum, intrauterine growth retardation, and hydrops fetalis may be concomitant with HL[5,6]. Recently, the association of HL with hypertensive complications of gestation, preeclampsia, and HELLP (hemolisys, elevated liver enzymes, low platelet count) syndrome has been discussed.

We searched the Pubmed database by using a combination of keywords including ''hyperreactio luteinalis'', ''preeclampsia'' and ''hypertension''. We retrieved 4 cases of HL diagnosed during pregnancy from 1955 to today, except the presenting case[7-10]. High levels of hCG in these cases have been postulated to have a role in the development of hypertensive complications. Masuyama et al[9] reported that preeclamptic complications related with HL might be a consequence of an imbalance of angiogenic factors and hCG levels that were 10 times higher than normal during the first trimester and throughout the pregnancy of these cases. Similarly, in the present case serum level of hCG was significantly higher than expected. Furthermore, Grgic et al[8] have suggested that the abnormally increased level of HCG in first trimester in otherwise normal pregnancy could potentially be a sign of an inadequate placental invasion. The poor placental invasion could give rise to developing of preeclampsia and in minority of cases this could result with severe preeclampsia or HELLP syndrome.

Increased levels of dihydrotestosterone, androstenedione, and free serum testosterone have been present in patients who developed virilization. In our case, serum testosterone and androstenedione levels were increased, as a reflection of hyperandrogenemia, and SHBG levels were decreased. The reason for excessive increase in luteinization in the ovaries has not been exactly determined yet. In these cases, due to its similar effect as LH, hCG signaling has been assumed to cause hyperplasia in thecal cells in the ovary and to lead to increased androgen synthesis. It has been reported that internal thecal cell hyperplasia concomitant with significant luteinization in the ovaries was the most marked histological finding in HL cases. Reubinoff et al[6] have indicated that androgens in these cases increased in cyst fluid as well. In the case presented, similarly, higher hCG values were found respective to the gestational

week. However, androgen levels in thecal lutein cyst fluid could not be investigated. In hyperreactio luteinalis cases, infarct or torsion of the ovary and rupture and hemorrhage of cysts may be seen, but rarely. Other than these rare conditions, it is advised to follow up with HL cases and to avoid unnecessary surgical interventions[3,4]. Shortly after delivery, bilateral cysts regress with the disappearance of hCG signaling. Unless there is a clinical suspicion of a malignancy, torsion or rupture of the cysts, spontaneous follow-up of patients is the appropriate approach. Therefore, it is highly important to distinguish these cases from neoplastic adnexial cysts. Prenatal ultrasonography is the most frequently used technique for diagnosis. In the presence of hyperandrogenemia findings concomitant with multicystic and enlarged appearance of ovaries, as in our case, prediagnosis has been HL. However, in asymptomatic cases, it may not be possible to distinguish hyperluteinized ovaries, especially from mucinous ovarian tumors. In these cases, magnetic resonance imaging (MRI) may provide additional findings. Recently, Takeuchi et al[11] reported on the MRI data of eight HL cases concomitant with gestational trophoblastic diseases. They reported that, according to the data, hyperluteinized ovaries reveal higher diffusion coefficient (ADC) values than mucinous ovary tumors. Therefore, this feature may be useful in the differential diagnosis of HL from ovarian neoplasia. In the presence of multicystic and enlarged ovaries during caesarean section, instead of oophorectomy or cystectomy which could be result with sterilization, histopathological analysis of ovarian biopsies and diagnosis of HL can help avoid unnecessary surgical procedures.

In conclusion, our case is a rare example of HL with both maternal and fetal virilization occurring in a spontaneous singleton pregnancy. Although HL is a benign condition that does not require surgery, for obstetricians it is important to be aware that in such cases, preeclamptic complications can be seen associated with abnormally high levels of hCG.

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