Review Article

Pregnancy Luteoma: Pathophysiology and Clinical Concern

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Luteoma is a benign ovarian neoplasm, usually incidentally found during pregnancy. It can produce androgenic hormones. Most cases are asymptomatic, while a few present with maternal and/or neonatal virilization. Its etiology is still unclear and may relate to human chorionic gonadotropin (hCG) stimulation. Pregnancy luteoma will resolve spontaneously after childbirth. The early recognition and prompt diagnosis can save the ovary from unnecessary surgery.

Keywords: Pregnancy; Luteoma; Pathophysiology; Virilization

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Luteoma is a rare solid ovarian neoplasm found during pregnancy. It is a benign disease first described in 1996 by Sternberg and Barclay[1]. Less than 200 cases were reported from previous literatures[1,2]. It is one of the two common androgen-producing neoplasms or gestational hyperandrogenism[3]. The incidence of pregnancy luteoma is still unknown[1,4]. Age incidence ranges from 15 to 44 years old[5].

Pathophysiology

The ovaries consist of the outer cortex and inner medulla. The ovarian cortex contains oocytes and developing follicles and is surrounded by stromal cells. Each follicle consists of three cell types: germ, theca, and granulosa cells that are surrounded by support structures. The theca cells around ovarian follicles can produce androgen, which is a substrate for aromatization.

Pregnancy luteoma is a hyperplastic tumor-like lesion of the ovary[6]. Even though the true etiology of this tumor is unclear[4,7], it may be related to human chorionic gonadotropin (hCG) stimulation during pregnancy[1]. The hCG shares a common biochemical structure (alpha-subunit) with luteinizing hormone (LH), follicle stimulating hormone (FSH), and thyroid stimulating hormone (TSH) which can bind to the LH-hCG receptor. This benign ovarian tumor arises from stromal cell proliferation[8]. The luteinized stromal cells then stimulate cell function and cell proliferation resulting in androgen production. The pathophysiology of pregnancy luteoma was shown in Figure 1.

Some literatures stated that hCG was only an accelerator but not a causative agent[9]. Because pregnancy luteoma was not found in high hCG circumstances, namely gestational trophoblastic disease, multiple pregnancies or at the moment of hCG peak level in early pregnancy[1]. It was believed to have existed before pregnancy and was stimulated by high levels of hCG in an unusual manner during pregnancy[4]. Further study also found that some part of pregnancy luteoma is hormonally inactive[10].

With regards to pregnancy luteoma, testosterone level can be abnormally high concomitant with increasing androgenic activity during pregnancy. Normally, testosterone will increase progressively during pregnancy and return to baseline after delivery[11]. There are three mechanisms that can reduce hyperandrogenic state during pregnancy[10]. First, the greater plasma sex-hormone binding globulin (SHBG) retards the testosterone effect. Second, trophoblastic cells in the placenta convert testosterone into estradiol in placental aromatization. The converted estradiol entered the fetal circulation and was metabolized by the fetal liver. This is a protective mechanism for fetus from maternal hyperandrogenism. Third, high level of progesterone reduces clinical manifestations of hyperandrogenism[11,12]. In women with pregnancy luteoma, the remnant of the corpus luteum can produce testosterone apart from normal physiology, resulting in hyperandrogenism[11].

After delivery, the decrease of testosterone level makes pregnancy luteoma regress. The regression starts within days after delivery[7]. The symptoms of virilization will disappear after the decreasing of androgen level, usually during the first two weeks after delivery[6,7,9].

Pregnancy luteoma rarely affects the female fetus. Most cases were usually asymptomatic. None or only little of the maternal testosterone enters fetal circulations. This is the result of testosterone conversion to estradiol by a trophoblastic cell and increasing testosterone clearance even with high maternal testosterone secreting from pregnancy luteoma[9]. The concentration of testosterone in umbilical cord blood is unlikely be detected, but sometimes could, in rare cases, be detectable.

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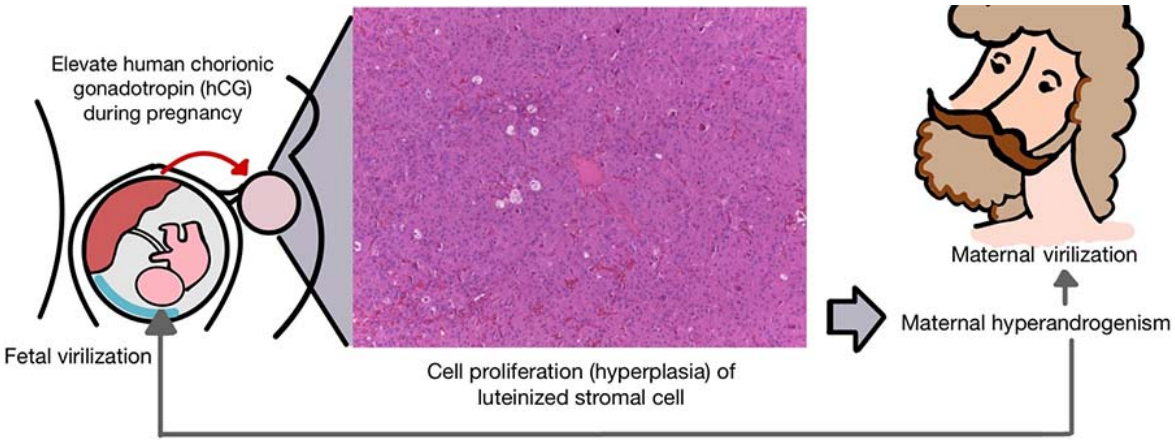

Figure 1. Mechanism of androgen excess in pregnancy luteoma.

The effect to the fetus depends on their gestational age, the onset of hyperandrogenism, which is highest in the first trimester, placental aromatase function[4], and duration/timing of the androgen exposure. During 7 to 12 weeks of gestation, which is time for external genitalia differentiation, a high level of testosterone could cause ambiguous genitalia, partial or complete labial fusion, clitoromegaly, and sometimes pseudo-hermaphrodite[1,3,11]. Male fetuses and neonates are not affected by this hormone[4,13].

Clinical presentation

Most cases are asymptomatic and usually found incidentally during antenatal care imaging, cesarean delivery, or postpartum tubal sterilization[1] at term or near term[5]. More than 80 percent of pregnancy luteoma cases were found in multiparous pregnancies, especially in African-American women[3,13]. The predisposing factors were polycystic ovarian syndrome (PCOS) and advanced maternal age. Women with previous luteoma also increased the risk of recurrent in the next pregnancy[13], which resulted from incomplete resolution after delivery[1,14]. There was no association with toxemia, erythroblastosis, or multiple gestations.

Even though pregnancy luteoma is an androgen-secreting ovarian neoplasm, only 25 to 30% of women have hyperandrogenism. Hyperandrogenic symptoms found during pregnancy are not different from those who are not pregnant. Among women with pregnancy luteoma, virilization varies from 10 to 50 percent[4,9,12,13]. The clinical presentation of virilization is summarized in Table 1. Hirsutism is found in androgen-dependent areas of predilection such as the face (upper lip, chin), chest, abdomen (linea alba), groin, thigh, and lower extremities[10]. Ferriman and Gallwey's score can be used to evaluate hirsutism in pregnancy. Some women experience hair thinning in the temporoparietal area[10]. Acne can be found on the face and other parts of the body such as the shoulder, back, and chest. Clitoromegaly and deepening voice are masculine symptoms that can be found in women with pregnancy luteoma. These symptoms can worsen during pregnancy[4].

Table 1. Clinical presentation of pregnancy luteoma

Virilization
Hirsutism
Acne
Frontal baldness
Deepening voice
Clitoromegaly
Abdominal pain
Abdominal discomfort
Palpable abdominal mass
Ascites

Some pregnant women may present with ovarian enlargement or ovarian tumors without virilization. The ovarian tumor should also be suspected in women with uterine size over date. The luteoma continues growing, causing abdominal discomfort or being palpated as an abdominal mass. If a tumor is large enough, it can cause pressure effects to adjacent organs. Obstructive uropathy and hydronephrosis were also reported[1].

The most concern of this ovarian tumor was acute complications such as rupture, hemorrhage, or torsion, which usually presented with acute abdominal pain. Incidences of these complications were between 3 and 15 percent[1]. It was a life-threatening condition and should be concerned in pregnant women with acute abdomen. The incidentally finding of pregnancy luteoma during rupture tubal pregnancy surgery was reported[15].

Although we know that pregnancy luteoma is a benign condition. Sometimes it can mimic malignant ovarian tumor[1], so the prompt evaluation should be made to exclude malignancy. The nature of pregnancy luteoma is a solid tumor, so it is difficult to differentiate from other solid ovarian

neoplasms by only imaging. The differential diagnosis for this benign tumor were luteinized thecoma and Leydig cell tumor. Malignant ovarian tumors such as granulosa cell tumor, Sertoli-Leydig cell tumor, and nonfunctioning Krukenberg tumor were reported to cause virilization[1,9,13,16]. For the physician, when pregnant women present with bilateral ovarian mass, ovarian neoplasm must be ruled out[17].

During pregnancy, the hCG had a pivotal role in pregnancy luteoma function. After birth, it usually decreases in size, concomitant with testosterone level declines. It usually regresses within 2 to 3 weeks after delivery[1,2,6,8,18] which corresponds to the testosterone level that returns to the normal range[19]. Any ovarian tumors that do not regress after delivery should be suspected of malignancy. Even though pregnancy luteoma may persist for up to 3 months to years[1,3,4], tissue diagnosis can help to exclude malignant ovarian tumors. The differential diagnosis of pregnancy luteoma is shown in Table 2.

Massive ascites and elevated cancer antigen 125 (CA 125) level is a phenomenon rarely reported in pregnancy luteoma and can mimic malignant ovarian tumor or ovarian hyperstimulation syndrome in in vitro fertilization (IVF) patients[6].

Hyperreactio luteinalis is the other common cause of gestational hyperandrogenism[8]. It is also stimulated by high levels of hCG. It is usually present with enlarged bilateral ovarian mass, caused by numerous luteinized follicular cysts[9]. Only 20 percent of women with hyperreactio luteinalis present with maternal virilization while fetal virilization has not been reported[8]. So from the clinical point of view, if pregnant women presented with signs of virilization and adnexal mass, they should be evaluated using ultrasonography, serum testosterone, and serum CA 125 level[12].

Laboratory evaluation

The blood test in women with pregnancy luteoma shows elevated testosterone levels. Due to physiological changes, testosterone level increases from the first to the third trimester of pregnancy. The normal testosterone level in the first, second, and third trimester was 25.7 to 211.4 ng/dL, 34.3 to 242.9 ng/dL, and 62.9 to 308.6 ng/dL, respectively[12], while the concentration of adrenal androgen (dehydroepiandrosterone sulfate) remains unchanged[20]. Elevated serum CA125 can be found due to mesothelial cell stimulation[6].

Table 2. Differential diagnosis of pregnancy luteoma

Benign
Corpus luteum of pregnancy
Hyperreactio luteinalis
Luteinized thecoma
Stromal luteoma
Stromal hyperthecosis
Malignant
Granulosa cell tumor
Sertoli-Leydig cell tumor
Non-functioning Krukenberg tumor
Steroid cell tumor
Melanoma

Diagnosis

During cesarean delivery, gross inspection of pregnancy luteoma is solid ovarian mass, usually soft consistency and multi-nodular appearance (Figure 2, 3). One-third to 50 percent of it was bilateral[7-9,21]. Its size varies from microscopic to more than 20 cm in diameter[9,13].

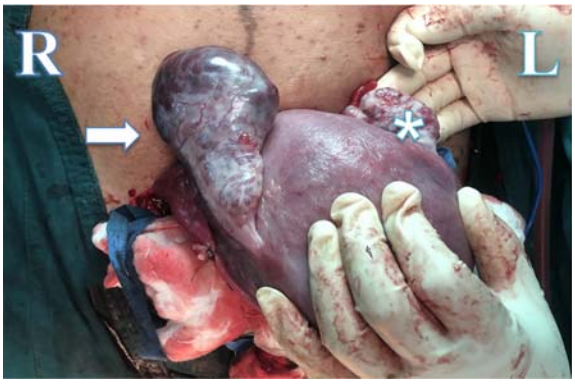

Figure 2. Solid right ovarian mass (arrow) incidental found during cesarean with normal appearance of left ovary (asterisk).

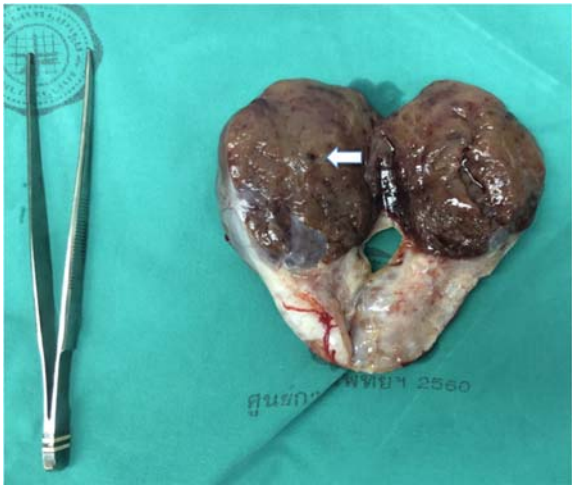

Figure 3. Cut surface of the specimen shows soft, brownish flesh color, well circumscribed, round nodule with hemorrhagic foci (arrow).

Typically, the cut surface shows a yellow to tan color[3,13]. It can also be gray, red to brown flesh color with hemorrhagic foci[9,13,14,21]. The recognition of gross morphology of pregnancy luteoma during surgery is important to avoid unnecessary oophorectomy[22].

A pathological diagnosis of pregnancy luteoma is needed[5]. Histologic findings are sharply circumscribed nodules composed of polygonal cells (Figure 4, 5). The cells arrange in small clusters, sheets, cords or form follicles containing colloid-like material or pale fluid. The nuclei may be pleomorphic, central round, regular and prominent nuclei. Mitosis can be seen in up to 7/10 high power fields. The cytoplasm is abundant with eosinophilic and fine granules.

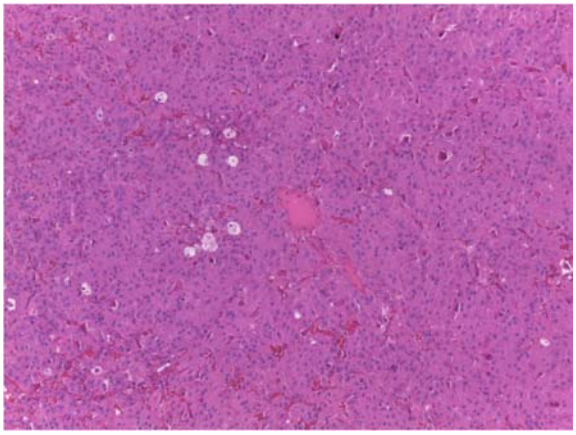

Figure 4. The section reveals polygonal cells arranged in cords, H&E staining 100x magnification.

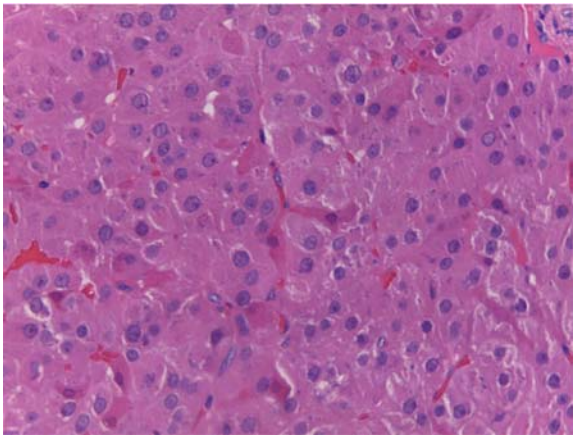

Figure 5. The tumor cells contain abundant pink cytoplasm, round nuclei with small nucleoli (resembling corpus luteum). There is no nuclear dysplasia, H&E staining 400x magnification.

Part of necrosis and degenerative changes may be seen. The immunohistochemistry features of pregnancy luteoma are positive for inhibin and calnetinin[13,21]. The presence of Reinke's crystals during microscopic examination indicates a diagnosis of Leydig cell tumor or steroid cell tumor. In the absence of Reinke's crystals, pregnancy luteoma was diagnosed[22]. However, pathologists who are unfamiliar with this disease may find it difficult to differentiate pregnancy luteoma with luteinized granulosa cell tumor[23].

Placental aromatization is a protective effect to prevent virilization in the fetus[19]. However, two cases of complete virilization in a neonate associated with pregnancy luteoma were reported[24]. One of these two cases was dichorionic diamniotic twin pregnancy conceived via IVF, and had undergone fetal reduction of triplet pregnancy for better outcomes. Whether the IVF or the fetal reductive procedure may disrupt normal aromatization of the placenta and increase the risk of fetal virilization is still questionable[24].

Neonatal virilization is found in 50 to 80 percent in maternal virilization[3,4,7,12]. It reflects placental aromatization defect, or high androgen level exceeding placental aromatization capacity[25]. Physical examination of external genitalia, including posterior labial fusion or clitoromegaly, can be found. Because there are other common etiologies of neonatal virilization than pregnancy luteoma, all neonates who have virilization should be investigated to exclude those etiologies[1]. Some authors mention that intrauterine exposure to elevated androgens levels may lead to an increased risk of mental retardation and hypogonadism[4]. The testosterone level in neonates can reach a peak at the time of delivery and decrease over time. The follow-up can be done at the outpatient department. Clitoromegaly can spontaneously decrease in size as time passes. Ambiguous genitalia in cases of severe virilization (Prader degree III-V) should be surgical corrected[25,26]. During surgery, introitoplasty of common urogenital sinus could be performed[27].

After delivery, pregnancy luteoma usually resolved spontaneously along with symptoms of hyperandrogenism. However, not all symptoms are completely reversed. Acne and hair loss can be fully reversible, while hirsutism, deepening voice, and clitoromegaly may only partially reverse[10].

Imaging

Pregnancy luteoma is a benign tumor. Diagnosis and follow-up should be done with a noninvasive technique[4]. It can be found incidentally in asymptomatic women. Pelvic ultrasonography and magnetic resonance imaging (MRI) are considered safe methods during pregnancy. These methods can help to distinguish pregnancy luteoma from other pelvic mass and differential diagnosis for ovarian neoplasm.

Ultrasonography

Most common adnexal mass during pregnancy is corpus luteal cysts which usually resolve by 14 weeks of gestation. Further investigation should be done in suspicious adnexal mass, e.g. persistent mass with a size of 5 cm in the second and third trimester, growing adnexal mass, mass with

septation, solid part, multicystic or projections in ultrasound findings[18].

There is no specific ultrasound feature and timing for diagnosing pregnancy luteoma. The findings include heterogeneous echogenic[22] solid parts with some cystic area, multiloculated, highly vascular ovarian mass[1]. The solid part is usually hypoechoic compared with a normal ovary, while the cystic part is caused by necrosis. High vasculature can be demonstrated by using a color Doppler, which shows abundant blood vessels within and/or at the periphery of the ovarian mass[19]. It can be a bilateral or unilateral lesion[7,21] and may have multiple lesions on one side of the ovary. The gravid uterus may obscure ultrasound detection of ovarian mass[17].

Magnetic resonance imaging

The findings of pregnancy luteoma from MRI and ultrasonography are similar[18]. Its findings are similar to other ovarian tumors in pregnancy, so it may not be helpful[1,6]. Even though there is no evidence to support the superiority of MRI over ultrasound to diagnose pregnancy luteoma, MRI can be used as an adjunctive modality just in case of inadequate ultrasound from enlarging uterus. It helps to differentiate malignant ovarian neoplasms and avoid unnecessary surgery[9].

With pregnancy luteoma, MRI shows intermediate-high or high signal intensity on T1-weighted images and low signal intensity on T2-weighted images[9]. Meanwhile, some authors report opposite findings, with predominant high-signal intensity on T2-weighted images and low signal intensity on T1-weighted images and fat-saturated T1-weighted sequences[1,18,19]. Contrast enhancement can indicate hypervascularity, which is the nature of this ovarian neoplasm. Due to pregnancy, most MRIs are performed without contrast administration.

It is impossible to differentiate pregnancy luteoma from other solid ovarian tumors based on imaging, but multi nodularity and bilaterality is more common in luteomas[13].

Management

The management of pregnant women with pregnancy luteoma should be counseled with the patient and her family upon clinical symptoms and personal condition[6]. There is conservative treatment and surgical treatment. Because of its benign nature that can resolve postpartum spontaneously, most physicians usually choose conservative treatment in incidentally found asymptomatic pregnancy luteoma[4,6]. Unnecessary surgery such as oophorectomy should be avoided[20].

The surgical intervention is usually reserved for acute complications such as ovarian cyst rupture, hemorrhage or torsion[9,12]. In a severe symptomatic case, surgical treatment may be a good choice in pregnant women in early second trimester[6]. A unilateral salpingo-oophorectomy is the most frequent surgical performed[7]. No further therapy is required[21]. Some authors recommend ovarian biopsy as a correct surgical intervention in pregnancy luteoma[1,7]. A frozen section can be done to confirm the diagnosis[21] and allow preservation of the ovary[22].

In the postpartum period, lactation usually occurs within 30 to 40 hours after delivery. Women with pregnancy luteoma may experience the delay of lactation for a week to a month[27]. The delay is the secondary inhibitory effect from high levels of maternal androgen to mammary glands. Mothers should be encouraged for nipple stimulation, breast pumping and infant suckling[28]. Lactation will eventually occur when serum testosterone falls down below 300 ng/dL[27].

In women with persistent symptoms of hyperandrogenism after delivery such as hirsutism and deepening voice, surgery can be done to remove the cause of hyperandrogenism. After that, laser therapy is used to treat hirsutism. The vocal cords operation can be done to rectify a deep voice[10].

Conclusion

Pregnancy luteoma is a rare benign ovarian neoplasm found during pregnancy. It is usually asymptomatic, incidentally found, and resolved spontaneously after delivery. Conservative treatment is the preferred choice of treatment.

What is already known on this topic?

Pregnancy luteoma is a rare ovarian neoplasm in pregnancy, usually found incidentally during surgery or antenatal imaging. It can resolve spontaneously after delivery.

What this study adds?

Review the pathophysiology of the pregnancy luteoma and also the clinical concerns of this disease. In addition, the study also helps obstetricians to recognize this condition early and avoid unnecessary surgery.

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Potential conflicts of interest

The authors declare no conflict of interest.

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