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CASE REPORT

Ovarian Hyperstimulation and Maternal Virilisation with Successful Pregnancy Outcome

A case report

Istaqlal S.H. Al Ghaithi,[1] *Jayasree Santhosh,[2] Thuria Al Rawahi,[2] Maryam S. Al Shabibi,[2] Najat R. Al Harthy,[3] Jokha Al Kalbani,[4] Maisa S.S. Al Hanashi[4]

ABSTRACT: Hyperreactio luteinalis (HL) and ovarian hyperstimulation syndrome during pregnancy are both benign conditions where the ovaries are enlarged with presence of multiple thin-walled cysts. The differential diagnosis is ovarian malignancy. Hyperandrogenism with resultant maternal virilisation could be seen in some cases of HL as well as in androgen secreting tumours. We report a 41-year-old female patient who underwent ovulation induction due to secondary infertility at a high-risk pregnancy unit in Muscat, Oman, in 2022. She had recurrent hospital admission with abdominal pain and large multicystic enlargement of both ovaries. She developed virilisation features by 35 weeks of pregnancy. Lower segment caesarean section was done at 36 weeks gestation for breech presentation with intra-uterine growth restriction. Magnetic resonance imaging confirmed the benign nature of the cysts. Ovarian cysts and hyperandrogenism gradually resolved 3-months post-delivery. Awareness, judicious imaging and close monitoring in such cases can result in live birth and avoid oophorectomies.

Keywords: Hyperandrogenism; Hirsuitism; Virilism; Polycystic Ovary Syndrome; Ovarian Hyperstimulation Syndrome; Ovulation Induction; Ovarian Cysts; Case Report; Oman.

Hyperreactio luteinalis (HL) in pregnancy is a benign condition where the ovaries are enlarged with presence of multiple thin walled cysts. This occurs as a result of hypersensitivity of ovarian tissue to human chorionic gonadotropin.[1] A similar clinical presentation occurs in ovarian hyperstimulation syndrome (OHSS) which is characterised by a cystic enlargement of the ovaries, associated with shifting of body fluid into third compartment, due to the over-production of vascular endothelial growth factor and inflammatory factors.[2] Usually, it is a complication of assisted reproductive technology (ART).[3] Both conditions result in a complicated pregnancy (preterm labour, pregnancy induced hypertension/preeclampsia and intra-uterine growth restriction).[4,5] Bilateral large ovarian enlargement can be mistaken with malignancy which may result in oophorectomies.[6]

Elevated serum testosterone can be physiological in pregnancy.[7] Luteinic cysts, androgen secreting tumours of adrenal and ovaries, 21 hydroxylase deficiency and Cushing syndrome can cause virilisation in pregnancy.[8]

We report the case of a patient who underwent ART, developed large multicystic ovaries with virilisation in pregnancy and was conservatively managed resulting in live birth and preserved ovaries.

Case Report

A 41-year-old female patient was referred to a high risk pregnancy unit in Muscat, Oman, in 2022 with a viable 14 weeks pregnancy and bilateral large hyper stimulated ovaries. This was her fifth pregnancy. She had had 3 previous normal deliveries, all conceived with ovulation induction. She was attending a fertility clinic for secondary infertility for 7 years. She was diagnosed with polycystic ovarian syndrome with poor ovarian response, consuming high doses of gonadotropins. The patient conceived after 4 cycles of letrozole with follicular stimulating hormone at 150 IU and human menopausal gonadotropin at 150 IU. She was started on low molecular weight heparin for thromboprophylaxis, low dose aspirin and folic acid.

First trimester ultrasonography showed enlarged ovaries with multiples large thin walled clear cysts (left ovary dimensions = 21 × 18 cm, right ovary dimensions = 16 × 13 cm). An anatomy scan at 22 weeks showed no fetal structural defects. Left ovarian size and morphology remained the same but right ovary had decreased in size to 8 × 5 cm [Figure 1]. There was no ascites.

She was admitted multiple times with abdominal pain, nausea and occasional vomiting. Ascites or pleural effusion were not detected on ultrasonography. There was no evidence of ovarian torsion. She remained haemodynamically stable. Serum electrolytes, aminotransferases, creatinine and haematological parameters all were within the reference range. The patient was conservatively managed with analgesics, antiemetics and thromboprophylaxis.

Her last admission was at 35 weeks with abdominal pain. Sonographic examination revealed

[1]*Department of Obstetrics and Gynaecology, Oman Medical Specialty Board, Muscat, Oman; Departments of* [2]*Obstetrics & Gynaecology,* [3]*Endocrinology and* [4]*Radiology, The Royal Hospital, Muscat, Oman.*
**Corresponding Author's E-mail: santhosh.jayasree@hotmail.co.uk*

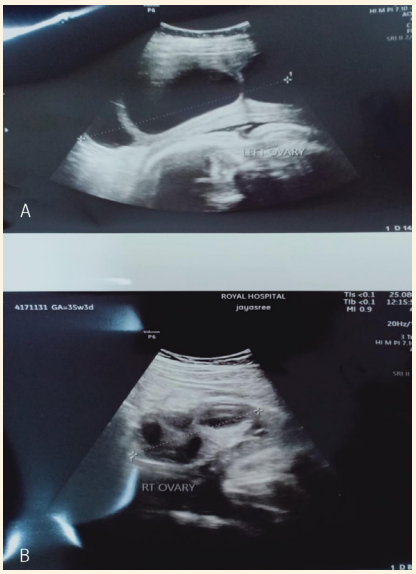

Figure 1: Ultrasound scan of the ovaries of a 41-year-old female patient showing (**A**) left and (**B**) right large ovarian cysts.

a single live breech fetus with an estimated weight of 1.9 kg, abdominal circumference of less than first percentile, the placenta was anterior high, liquor normal, umbilical artery doppler pulsatility index was 1.13. Both ovaries had large multiple thin-walled cysts. Right and left ovary measured 8.5 cm and more than 15 cm, respectively, with normal colour flow. There was no evidence of ascites. She was planned for fetal monitoring and delivery at 37 weeks.

At that time, it was noticed that the patient's voice was becoming hoarse and deep; hirsutism was noted on her abdomen and chest. Serum testosterone was sent and found to be high (24 mmol/L). This case was discussed with the gynae-oncology team and radiologist in view of a rare possibility of androgen secreting tumour. She was planned for a postnatal magnetic resonance imaging (MRI) scan in view of the late gestation and technical difficulties in proper imaging. The couple were informed of the clinical situation and that if the MRI revealed an androgen secreting tumour, the patient would require relaparotomy with staging.

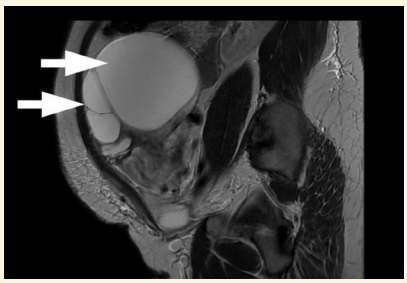

Figure 2: Axial T2 weighted magnetic resonance imaging scan showing simple looking cysts in left ovary

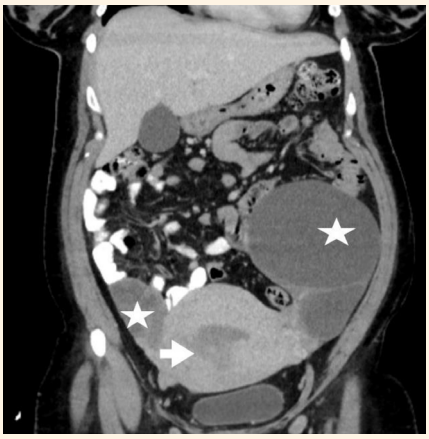

Figure 3: Axial computed tomography image with contrast showing bilateral ovarian cyst.
Stars - bilateral ovarian cysts; Arrow - haemorrhagic contents in postpartum uterus

The patient underwent elective lower segment caesarean section (CS) at 36 weeks for breech presentation and abnormal doppler parameters 1 week after admission. A female baby, weighing 2.2 kg was delivered with good Apgar score. The baby did not show any evidence of virilisation. The CS was performed through a Pfannenstiel incision with minimum trauma to the enlarged ovaries; an intra-operative photograph could not be taken. Peritoneal washing was done during the CS surgery and was later reported as negative for malignancy.

An MRI scan was done 2 days post-CS; multicystic appearance of both ovaries (ovarian hyperstimulation or benign cysts) was seen. The MRI was chosen as there is a chance that an ultrasound scan alone, as an imaging modality, might miss a small solid lesion in a large ovary in a postpartum patient with thick abdominal wall and enlarged uterus. The MRI was performed after discussion with the gynae-oncologist and consultant radiologist. The patient's left ovary measured 15 × 10 cm; the largest cyst measured 11 × 10 cm showed a thin wall and no solid enhancement and no diffusion restriction. Her right ovary measured 6 × 7 cm with multiple cysts, the largest cyst measured

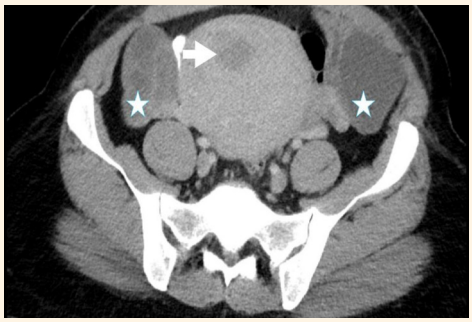

Figure 4: Axial computed tomography image with contrast showing bilateral ovarian cyst.
Stars - bilateral ovarian cysts; Arrow - haemorrhagic contents in postpartum uterus

3.2 × 3 cm and showed irregular wall features, however there was no solid enhancement or diffusion restriction [Figure 2]. She underwent computed tomography (CT) examination of her chest, abdomen and pelvis which did not reveal any significant abnormality other than bilateral cystically enlarged ovaries [Figures 3 and 4]. Endometrial cavity was distended in both CT and MRI scans due to her post-partum status.

The patient and baby were discharged on the fifth postoperative day; both were well. After 2 months she was reviewed in the gynae-endocrine clinic. Her investigations revealed a decrease in serum testosterone (11 mmol), 17-hydroxyprogesterone was 18.1 mmol/L, alpha fetoprotein was 108 μg/L and other tumour markers were all within normal range. Transvaginal sonography revealed thin endometrium, her left ovary with large cyst was 8 × 10 cm and her right ovary was normal. She was followed-up for 6 months postpartum. Testosterone levels returned to normal and growth hormone, insulin-like growth factor-1 and dexamethasone suppression test, thyroid function test and haemoglobin A1C were normal. Her last follow-up in 2023 showed further regression of bilateral cysts.

Patient consent was obtained for clinical photography and publication of this case report.

Discussion

OHSS is an iatrogenic complication of assisted reproductive technology cycles, estimated at approximately 20–33% in its mild form and 3–8% in its moderate or severe form.[9] Risk factors of developing OHSS are an age of less than 35 years, low body weight, hypothyroidism, ovulation stimulation protocols, high oestradiol levels, rapid elevation in oestradiol levels, number of the stimulated follicles, number of the removed oocytes, pregnancy and the presence of polycystic ovaries.[10,11] According to Royal College of Obstetricians and Gynaecologists classifications of OHSS severity (severe cases: ovarian size is usually >12 cm and associated with fluid shift to third space and biochemical abnormalities).[12] HL is a benign bilateral cystic enlargement of the ovaries, due to ovarian stimulation by beta human chorionic gonadotropin in spontaneous cycles.[13] The current patient presented in the first trimester with a history of ART with bilateral large multicystic ovaries. She was initially diagnosed with OHSS even though she had none of the other risk factors associated with OHSS. Despite recurrent admissions with abdominal pain, she never had biochemical abnormalities or fluid shift to third space which raised suspicions of an alternative diagnosis of HL. The cause of her ovarian multicystic enlargement may not have been due to the hormonal treatment but to a hypersensitivity of ovarian stroma to human chorionic gonadotrophin (hCG) which is said to be the cause of HL.[14] HL usually manifests in primigravida, present in the second and third trimester in spontaneously conceived pregnancy.[14] Risk factors include gestational trophoblastic disease, multiple pregnancies, chronic kidney diseases and hypothyroidism. Most patients are asymptomatic and it is incidentally discovered during routine ultrasound examination or during CS.[14] Some patients reported abdominal pain due to ovarian torsion or haemorrhage.[1,13] However, the patient did not have any risk factors for HL; there was no feature of torsion or haemorrhage during any of her admissions. As the ovarian cysts were considered benign by their ultrasound appearance, and as no cyst accidents occurred, she was conservatively followed-up.

Hyperandrogenism is a normal physiological change in pregnancy due to an increase testosterone production by hCG stimulation, adrenal influence and reduced renal clearance of testosterone.[8] Maternal virilisation is rare, as protective mechanisms such as increased serum sex hormone binding globulin in pregnancy and placental aromatase conversion of androgen to oestrogen reduce excess androgen exposure in the mother and the fetus.[13,15] Maternal virilisation is reported in 20–30% of cases of HL due to severe hyperandrogenism.[1] Virilisation is rarely seen in OHSS.[6] The current patient was noted to have features of virilisation by 35 weeks of pregnancy. Even though the sonological morphology of ovarian cyst looked benign, the patient was planned for postnatal MRI to exclude the rare possibility of an androgen secreting tumour.

Cavoretto *et al.* authored an extensive review compiling 96 cases of HL reported from 1955 to 2013.[5] They reported preeclampsia in 24% and fetal growth restriction in 12% of cases. Mean gestation at delivery was 35 weeks. Oophorectomy was reported in 40% in this group. Pregnancies complicated by HL is reported to have higher incidence of pre-eclampsia, growth restriction and preterm delivery.[16] This is attributed to the elevated beta hCG levels seen in HL.[14,16] The current patient's baby was delivered by lower segment CS at 36 weeks due to breech presentation with intrauterine growth restriction and abnormal dopplers. Exposure to high androgen levels after 12 weeks of pregnancy may not produce virilisation in female fetuses as seen in the current case. Placental aromatisation of androgens as well as increased fetal exposure to oestrogen may offer protection to the fetus from maternal androgens.[14,17] Failure of lactation was not observed which is reported in women with high androgen levels.[17]

The current patient had postnatal imaging which excluded androgen secreting tumour. She was followed-up in the gynae-endocrine clinic which revealed spontaneous regression of ovaries as well as resolution of hyperandrogenism.

Conclusion

This unique case showed was diagnosed with OHSS and HL. Both diagnoses shared similar ultrasonographic appearance. A conservative approach was used to manage both conditions, reserving surgical intervention for cyst accidents. Pregnancy can be continued to term unless maternal or fetal complications occur. In cases of maternal virilisation, ovarian androgen secreting tumours as well as other pathologies should be excluded. Awareness of the pathology, ultrasound features, judicious imaging, close fetomaternal monitoring can lead to a successful pregnancy outcome and avoid oophorectomy.

AUTHORS' CONTRIBUTION

JS and TR managed the case. Endocrinology follow-up was carried out by MSS and NRH. JK and MSSH analysed the radiological data. ISHG drafted the manuscript. All authors critically reviewed the manuscript and approved the final version.

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