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CASE REPORT

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Spontaneous ovarian hyperstimulation syndrome: A case report

Monica Wambui[1]*, Idyoro J. Ojukwu[2], Rosa C. Ndiema[3]

[1] Private practitioner, KMA Centre; Department of Obstetrics and Gynecology, Avenue Hospital, Nairobi, Kenya.

[2] Department of Obstetrics and Gynecology, Mater Misericordiae Hospital, Nairobi, Kenya

[3] Department of Obstetrics and Gynecology, Kenyatta National Hospital, Nairobi, Kenya

***Correspondence:** drwambuim@gmail.com

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Abstract

Background: Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication caused by excessive response to controlled ovarian stimulation. It is characterized by ovarian enlargement and the formation of multiple cysts. When OHSS occurs in spontaneous pregnancies it is known as spontaneous OHSS (sOHSS).

Case presentation: A 31-year-old para 2+0 gravida 3 presented with gross abdominal distention at 11 weeks of gestation. Abdominopelvic ultrasound revealed a single viable fetus at 12 weeks and 4 days with large multicystic adnexal masses, which were suggestive of mucinous cystadenoma. Follow-up magnetic resonance imaging revealed ovarian hyperstimulation syndrome. Initial CA-125 levels were >600 U/ml. Her symptoms were mild and resolved with conservative management. She eventually delivered preterm at 33 weeks.

Conclusion: Pregnancy with sOHSS is a rare condition and may not be obvious. It may mimic other ovarian tumors, leading to premature termination of a normal pregnancy and unnecessary surgical intervention.

Keywords: ovarian enlargement, ovarian hyperstimulation syndrome (OHSS), spontaneous ovarian hyperstimulation syndrome (sOHSS)

Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication caused by excessive response to controlled ovarian stimulation during assisted reproductive treatment (ART) (1–3). When OHSS occurs in spontaneous pregnancies it is known as spontaneous OHSS (sOHSS). It is characterized by ovarian enlargement and the formation of multiple cysts (4). It can complicate up to 20-30% of ART cycles (1, 5). However, it is rare in spontaneous pregnancies. When present in spontaneous pregnancies it is usually associated with polycystic ovarian syndrome, molar pregnancies, hypothyroidism, multiple gestation, gonadotrophin-secreting pituitary adenomas, and follicle-stimulating hormone receptor (FSHR) gene mutations (3). Other risk factors for the development of OHSS and sOHSS include age <35 years, previous history of OHSS, low basal metabolic index (BMI), use of high doses of gonadotropins, high basal level of antimüllerian hormone (AMH), rapid increase in serum estradiol levels, high number of follicles, high level of vascular endothelial growth factor (VEGF), and high inhibin B levels (1,3–5). It has also been documented in nonpregnant women (4, 5). It may present as a severe condition with complications, such as ascites, abdominal compartment syndrome, renal dysfunction, acute respiratory distress syndrome, thromboembolic disease, and

hemodynamic instability (1, 3), requiring hospitalization or may be associated with mild abdominal discomfort. Diagnosis may not be obvious in spontaneous pregnancies because the condition may mimic other ovarian tumors (6). This is a case of sOHSS in a patient who eventually underwent preterm delivery.

Case presentation

A 31-year-old para 2+0 gravida 3 with 2 previous cesarean delivery scars presented at the Avenue Hospital antenatal clinic for her first visit at 7 weeks and 6 days. The first cesarean delivery was due to breech presentation at term, and the second was due to preterm labor with placenta previa at 32 weeks. She had a history of elevated blood pressure noted two months prior to conception but had not been administered any treatment. There was a positive maternal history of hypertension. She was on the combined oral contraceptive pill, which she stopped two months before conception. At the time of presentation, she had mild emesis and heartburn. Her weight was 70 kg, blood pressure was 138/80 mmHg, and pulse rate was 59 beats per minute (BPM). Her antenatal screening results were unremarkable (**Table 1**).

Obstetric ultrasound at 8 weeks of pregnancy revealed a single viable fetus. The ovaries were enlarged; the right ovary was 16 cc, and the left ovary was 20 cc, and they appeared polycystic (**Figure 1**). The patient was started on folic acid and antiemetics. She then presented two weeks later with severe abdominal pain for one week, bloating, heartburn, and vomiting. Her weight was 71.5kg, blood pressure was 130/90mmhg and pulse rate was 85 BPM. On abdominal examination, she was noted to have generalized distension and tenderness, mainly at the epigastrium. The patient was managed with esomeprazole 40mg once daily (OD), methyldopa 250mg three times a day (TDS), phloroglucinol 80mg twice daily (BD), and an antiflatulent.

At 11 weeks and 6 days, she reported improvement in symptoms, although she still had abdominal distention. Her weight had increased to 73kg, blood pressure was 120/80 mmHg, and pulse rate was 80 BPM. On abdominal examination, she had gross distension, and it was difficult to palpate the uterus. She also had palpable masses on the right and left lumbar regions, with tenderness on the left lumbar region. Abdominopelvic ultrasound revealed a single viable fetus at 12 weeks and 4 days with large multicystic masses superior to the uterus; on the left (195×107×90) mm, and on the right (191×77×80) mm, there was no ascites. Ultrasound findings suggested of mucinous cystadenoma of the ovaries. She was sent for ovarian tumor marker screening. Her cancer antigen 125 (CA-125) levels were markedly elevated at >600 U/ml; however, other markers were within the normal reference ranges (**Table 2**). A follow-up abdominopelvic magnetic resonance imaging showed a single intrauterine fetus, both ovaries were grossly enlarged and extended into the abdominal cavity, bearing multiple large cysts with a spoke wheel appearance and an average cyst diameter of 4.8 cm separated by thin septae; the left ovarian width was 13 cm, right ovarian width was 11 cm; free fluid was noted in the Pouch of Douglas and paracolic gutters. No pelvic wall lymph nodes were observed. The urinary bladder, cervix, and vagina appeared grossly normal. An impression of ovarian hyperstimulation syndrome in early pregnancy was made (**Figure 2**). The thyroid function test was unremarkable (**Table 3**). She continued with the previous medication as an outpatient, and prenatal supplements (iron and calcium) were added.

Table 1. Antenatal screening results

Parameter	Value (Reference range)
Hemoglobin	14.2g/dl (11.5-14g/dl)
Hematocrit	42.6% (33-44%)
Platelets	$277\times10^3/mm^3$ ($150\text{-}400\times10^3/mm^3$)
HIV	Negative
Syphilis	Negative
Hepatitis B surface antigen	Negative
Urinalysis	Normal

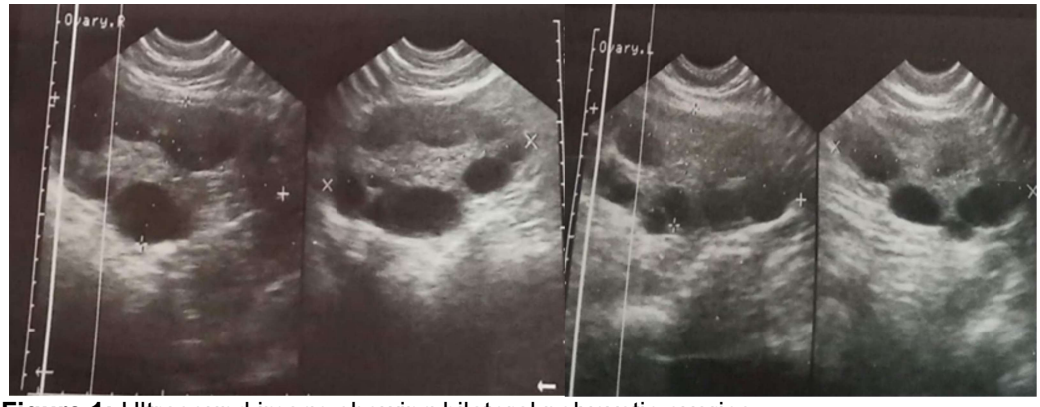

Figure 1: Ultrasound image showing bilateral polycystic ovaries.

Table 2. Ovarian tumor marker results

Parameter	Value (Reference range)
Cancer antigen (CA-125)	>600 U/ml (0-35 U/ml)
CA 19-9	5.67 U/ml (0-37 U/ml)
Carcinoembryonic antigen (CEA)	0.79 ng/ml (0-2.9 ng/ml)
Alpha-fetoprotein (AFP)	22.40 ng/ml (0-40 ng/ml)

She was subsequently reviewed at 12 weeks and 6 days and reported reduced appetite, occasional vomiting, and weight loss. Her weight had decreased to 70kg, blood pressure was 120/70mmHg, and pulse rate was 84 BPM. On abdominal examination, she had a mass equivalent to 28 weeks. Distention was reduced compared with the previous assessment. The patient still had palpable ovaries in the right and left lumbar regions. She was advised to continue prenatal supplements, methyldopa, and antiemetics; an appetite stimulant was also administered. At 14 weeks and 6 days, she reported improvement in symptoms, improved appetite, and subsided vomiting. Her weight was 70kg, and the other vital signs were unremarkable. The fundal height was 26 weeks, and the fetal heart rate (FHR) was 147 BPM. Repeat CA-125 levels were 147.3 U/ml. Obstetric ultrasound showed a single viable fetus at 15 weeks; placenta was anterior and not low lying; and bilateral cystic ovarian masses: on the right measured (108×68×90) mm, the largest cyst was 48 mm, and on the left (108×56×96) mm, the largest cyst was 42 mm. The plan was to continue with methyldopa and prenatal supplements.

At 18 weeks and 6 days, she was doing well, her appetite was normal, she experienced occasional bloating, and she reported experiencing quickening. Her weight was 73kg, and her other vital signs were within the reference ranges. The abdomen was soft and non-tender, and the fundal height was 22 weeks with an FHR of 146 BPM. The bilateral ovarian masses were still palpable in the lumbar region. Obstetric ultrasound showed a single viable intrauterine fetus at 18 weeks and 5 days, the placenta was normal, and gross fetal anomalies were not detected. The maternal ovaries were reducing in size but still enlarged; the right ovary measured 63×73×42 mm and the left 61×76×37 mm. Her CA-125 levels was markedly reduced to 38.24 U/ml. The plan was to continue with the previous medication. At 22 weeks and 6 days, the patient was doing well, and fetal movements were noted. Fundal height was 26 weeks, and FHR was 144 bpm. Her CA-125 levels normalized at 27.18 U/ml (**Figure 3**). Obstetric ultrasound showed a single viable fetus at 22 weeks and 6 days. The placenta was normal, but the cervix was noted to be approximately 2.2 cm dilated with funneling. The ovaries were still enlarged 69×40×41 mm and 70×40×41 mm. The plan was to add 400mg of micronized progesterone at night and continue with the other medications. She was also advised to take pelvic rest, including abstinence from penetrative sexual intercourse.

Table 3. Thyroid function test results

Parameter	Value (Reference range)
Free triiodothyronine (FT3)	4.88 pmol/L (3-7 pmol/L)
Free thyroxine (FT4)	18.56 pmol/L (9-23 pmol/L)
Thyroid-stimulating hormone (TSH)	2.13 µIU/ml (0.4-5.6 µIU/ml)

On review at 26 weeks and 6 days, the patient was doing well although she reported fatigue and heartburn. Her weight was 74kg, and she had unremarkable vital signs. The fundal height was 26 weeks, and the FHR was 151 BPM. Oral glucose tolerance test result was normal. The ovarian masses were still palpable. She was continued on the previous medications, and an antacid was added. At 30 weeks and 6 days, she was doing well. Her weight had increased to 76kg. The fundal height was 30 weeks, and the FHR was 146 BPM. She was sent for an obstetric ultrasound to follow up on the status of the cervix and ovarian masses, but she could not do it. The plan was to continue with medication and review in three weeks. The patient had preterm labor at 33 weeks and delivered vaginally while being prepared for an emergency cesarean delivery. The outcome was a live female infant weighing 2000g with a good Apgar score but was admitted to the neonatal intensive care unit due to prematurity. On review three weeks postpartum, she was doing well, but her blood pressure was signficantly elevated at 144/108 mmHg. The breasts were active, and the uterus was well-involuted, with a fundal height at 16 weeks. Lochia was minimal and the was perineum clean and well healed. Pelvic ultrasound showed a normal uterus with a normal endometrium; the ovaries were still enlarged; the right ovary was 17cc with an 18-mm follicle, and the left one was 46cc with a 35-mm cyst. She was given 500mg of methyldopa TDS and 20mg of nifedipine once daily. On review 6 weeks postpartum, the patient was stable; her blood pressure was 110/80mmHg and the pulse was 100 BPM. On abdominal examination, there was gaseous abdominal distention, no areas of tenderness, and the uterus

was completely involuted; there were no palpable masses. She was

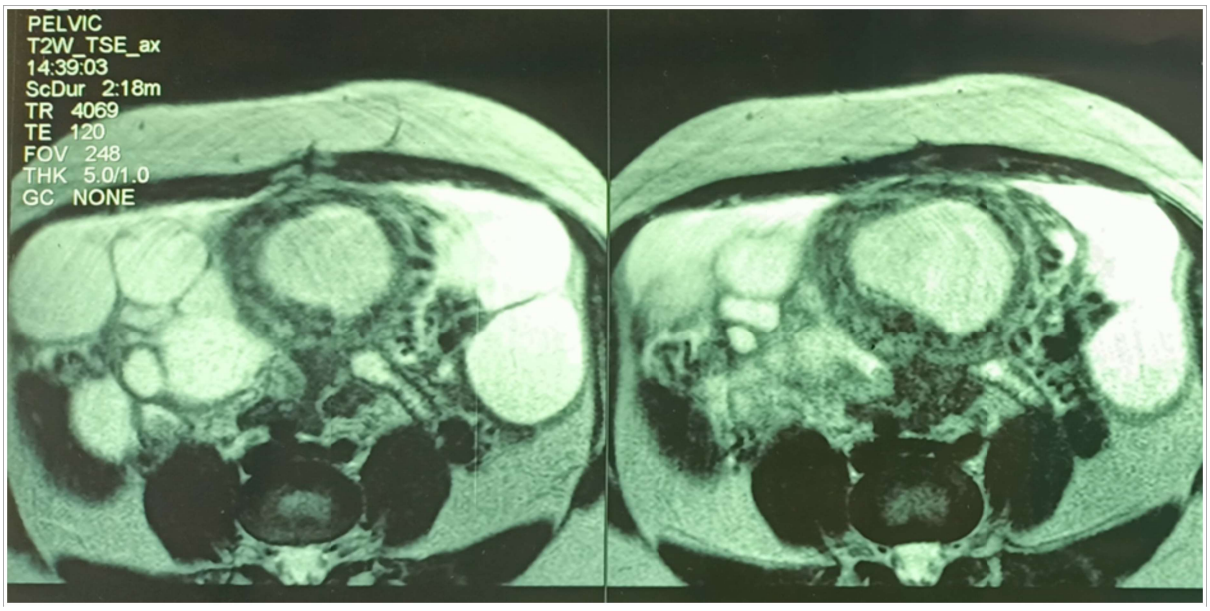

Figure 2: Abdominopelvic magnetic resonance imaging showing grossly enlarged ovaries (arrows) bearing large multiple cysts extending into the abdominal cavity.

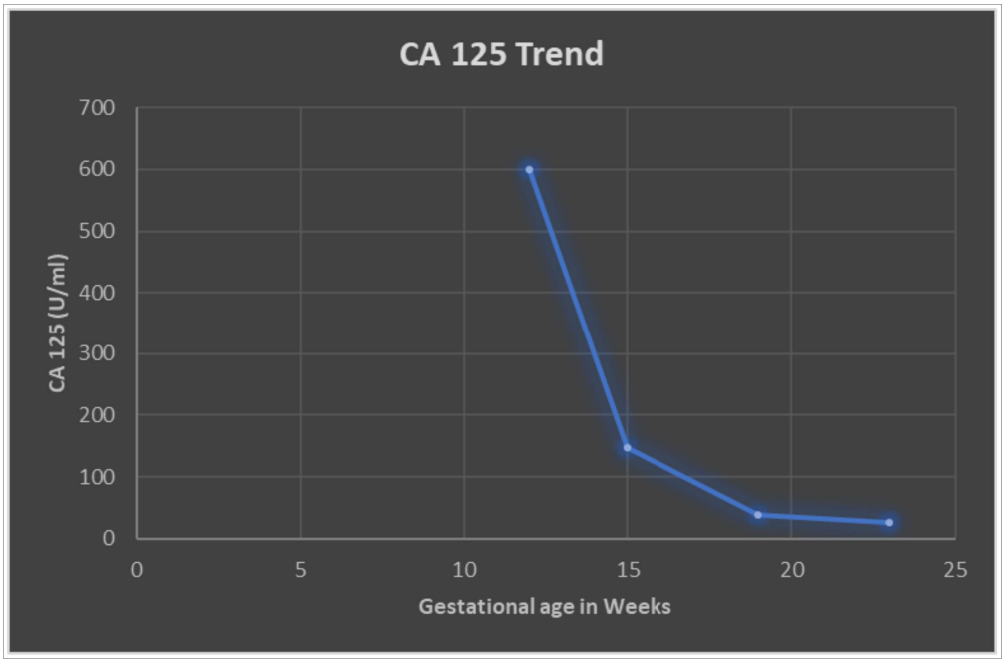

Figure 3: Graph showing cancer antigen 125 (CA-125) trend.

She was advised to continue treatment with antihypertensives.

Discussion

Spontaneous OHSS is a rare condition associated with several risk factors. In our case, the identifiable risk factors were age and polycystic ovaries. Conception was spontaneous, and investigations for other risk factors were negative. Iatrogenic OHSS occurs early in pregnancy between three and five weeks; but sOHSS occurs later between 8 and 14 weeks (3, 5). In our case, the symptoms became evident at 11 weeks of gestation. The pathophysiology of OHSS is related to arteriolar vasodilation and increased capillary permeability resulting in intravascular volume shifting to the extravascular space (1–3). Ovarian stimulation causes marked ovarian enlargement associated with overproduction of proinflammatory and vasoactive cytokines, leading to increased capillary permeability. The use of human chorionic gonadotrophin (hCG) as an ovulatory trigger in ART, associated with the

development of OHSS; as hCG directly increases VEGF production (2). VEGF causes angiogenesis and increased vascular permeability (1-2, 5), and the severity of OHSS has been directly linked to VEGF levels. Elevated levels of proinflammatory immune cytokines (interleukin (IL-1β), IL-6, IL-8, and tumor necrosis factor α) are characteristic of OHSS and are responsible for the increased capillary permeability (1).

The pathogenesis of spontaneous OHSS is not fully understood, but it may be due to the abnormal sensitivity of hCG to mutant FSHR (3, 5), increased FSH levels, or excessive secretion of glycoprotein hormones with the same subunit; such as thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and hCG (4, 5). High TSH levels are observed in primary hypothyroidism and rarely in TSH-secreting adenomas. Patients with sOHSS related to high TSH levels can be treated with thyroid hormone replacement therapy (4) which gives a good prognosis. The intraovarian renin-angiotensin system (RAS) also plays a role in the pathogenesis of OHSS (2, 5). The ovarian RAS is involved in regulating vascular permeability, angiogenesis, endothelial proliferation, and prostaglandin release. Human chorionic gonadotrophin strongly activates the RAS, as evidenced by the high renin activity in the follicular fluid of women with OHSS. Overstimulation of this cascade together with increased VEGF levels leads to OHSS. Mutations of the FSHR gene that increase the sensitivity of the receptors are probably also involved (4). The cysts normally regress 3-6 months after development.

Clinical manifestations of OHSS are related to increased vascular permeability and the resultant loss of protein-rich fluid to the extravascular space (2, 5). Symptoms include abdominal distention and discomfort caused by ovarian and uterine enlargement and ascites (4). The severity of symptoms is related to the degree of organ enlargement and associated organ dysfunction. The ovaries may have multiple enlarged cysts that may rupture, leading to hemoperitoneum or peritonitis (1). In the presence of massive ascites, intra-abdominal pressure may increase, leading to end-organ dysfunction (1). This may involve the renal, respiratory, hepatic, gastrointestinal, and cardiovascular systems (5); and may result in end-organ failure (1). Impaired intra-abdominal venous drainage may cause renal, intestinal, and hepatic edema. This condition may lead to hepatic injury, paralytic ileus, and intestinal edema, which presents with severe vomiting and diarrhea (1). It also impairs organ perfusion and causes tissue hypoxia, leading to deranged liver enzymes and electrolytes when the liver and kidneys are involved, respectively (1). Other metabolic abnormalities may also occur. Hemoconcentration causes hypercoagulability and may lead to thrombotic events (2, 5). Patients are also at a high risk of infection due to decreased levels of immunoglobin A (IgA) and IgG. Critical patients may present with hypovolemic, cardiogenic, or septic shock. This may be caused by gastrointestinal or third space loss (4), pericardial effusion, cardiac tamponade, massive pulmonary embolism, or infection (1).

Complications associated with OHSS include ovarian torsion, ascites, abdominal compartment syndrome, renal dysfunction, acute respiratory distress syndrome, thromboembolic disease, and hemodynamic instability (1, 3-5). Critical patients require admission and emergency treatment (1). Some studies have shown an increased risk of preterm birth in patients with severe OHSS (7, 8). This may be due to the elevated proinflammatory cytokine levels (7). The first-line investigation should include pelvic ultrasound (1, 3, 6). It is cost-effective and noninvasive; and shows the status of the fetus, ovaries, and presence of ascites. Ovarian malignant tumors should be ruled out. In our case, the first ultrasound was suggestive of mucinous cystadenoma, which necessitated screening for tumor markers. The ovaries in OHSS and sOHSS appear bilaterally polycystic with a thin capsule wall (3). Malignant ovarian tumors are characterized by a unilateral solid cyst with a thick capsule wall (3, 6). The incidence of ovarian malignancy in pregnancy is approximately 1-6% (6). CA-125 levels normally increase in pregnancy (6); In the first, second, and third trimesters levels may go up to 52, 31, and 56 U/ml, respectively (9). Despite this, the levels may help distinguish between benign and malignant lesions and can also be used for patient monitoring. In our case, the CA-125 levels were markedly elevated initially and subsequently decreased as the symptoms abated. Laboratory studies should also include hCG to rule out molar pregnancy and TSH to screen for hypothyroidism. In critically ill patients, investigations should include screening for end-organ dysfunction (1). This should include a complete blood count, liver function test, electrolytes, urea and creatinine, and blood gas analysis for those presenting with shock. The management of OHSS and sOHSS is mainly supportive (1, 5). Mild and moderate forms are managed as outpatients, but inpatient management is necessary for severe cases. Conservative treatment is the primary management option, with surgery being reserved for cases complicated by ovarian rupture, ovarian torsion, intra-abdominal hemorrhage, or ectopic pregnancy (3–5).

Conclusion

Iatrogenic OHSS is a self-limiting disease that is predictable during ovulation induction. Preventive measures should be implemented to reduce the risk of moderate to severe disease. Spontaneous OHSS cannot be predicted; early and accurate diagnosis is key to appropriate supportive management. Pregnancy with sOHSS is a rare condition, that is not easily diagnosed in the early phase. Obstetricians should consider it as a potential diagnosis in patients presenting with ovarian masses in pregnancy to avoid premature termination of a normal pregnancy and unnecessary surgery, which may compromise the future fertility of the patients.

Informed consent

Informed consent for publication was obtained from the patient.

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Declarations

Conflicts of interest

None

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