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Brazilian Journal of Case Reports

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Case Report

Exceptional Case of Spontaneous Ovarian Hyperstimulation Syndrome in Complete Molar Pregnancy: A Case Study

Juliana Barbosa Guimarães [1], Adriana Bruno [2, 3], Márcia Maria Pedreira da Silveira [3], Andrea Railla Nogueira Rodrigues [1], Milena Bastos Brito [2]

[1] Department of Gynecology, Obstetrics and Human Reproduction, Federal University of Bahia, BA, Brazil.
[2] Professor at the Department of Gynecology, Obstetrics and Human Reproduction at the Faculty of Medicine of Bahia - Federal University of Bahia (FMB- UFBA), Salvador, Bahia, Brazil.
[3] Bahia Trophoblastic Disease Center (Climério de Oliveira Maternity of Bahia Federal University), Salvador, Bahia, Brazil.

* Correspondence: andrearailla@gmail.com.

Abstract: Spontaneous ovarian hyperstimulation syndrome (OHS) is an uncommon condition. We report the case of a 38-year-old woman admitted to the emergency department with vaginal bleeding, pelvic pain, and an extraordinarily high human chorionic gonadotropin (hCG) level of 1,000,000 mIU/mL. Uterine aspiration confirmed a complete hydatidiform mole. Ten days post-discharge, she returned, exhibiting severe abdominal pain, vomiting, an hCG level of 46,769 mIU/mL, and ultrasound evidence of theca lutein cysts (right ovary: 1329 cm^3; left ovary: 500 cm^3) along with ascites. Suspected of having OHS, she was hospitalized for clinical management. Treatment included intravenous hydration, analgesia, thromboprophylaxis, and daily laboratory tests, leading to symptomatic improvement despite rising hCG levels. After a 35-day hospital stay, she commenced chemotherapy at a specialized cancer hospital. This case emphasizes the importance of healthcare professionals being alert and aware of the possibility of this diagnostic suspicion in such cases, particularly highlighting the need for hospitalization in moderate to severe instances.

Keywords: Chorionic gonadotropin; Gestational Trophoblastic disease; Hydatidiform Mole; Ovarian cysts; Ovarian hyperstimulation syndrome.

Citation: Rodrigues ARN, Guimarães JB, Brno A, Brito MB, Silveira MMP. Exceptional Case of Spontaneous Ovarian Hyperstimulation Syndrome in Complete Molar Pregnancy: A Case Study. Brazilian Journal of Case Reports. 2024 Oct-Dec;04(4):43-49.

Received: 14 February 2024
Accepted: 21 March 2024
Published: 24 March 2024

1. Introduction

Ovarian hyperstimulation syndrome (OHSS) results from excessive ovarian stimulation due to elevated gonadotropin levels [1]. It is usually a complication due to ovulation induction treatments. However, it can also occur spontaneously, although this is rare [2]. The pathophysiology of this syndrome, characterized by increased vascular permeability, is not fully understood but is associated with elevated human chorionic gonadotropin (hCG) levels [1, 2]. Gestational trophoblastic disease (GTD) is an uncommon disease [3]. There are few reports in literature about OHSS in spontaneous pregnancy, especially in molar pregnancy [4], which makes the management of cases with this association challenging. We report below a rare case of spontaneous Ovarian hyperstimulation syndrome after complete hydatidiform mole (CHM).

2. Case Report

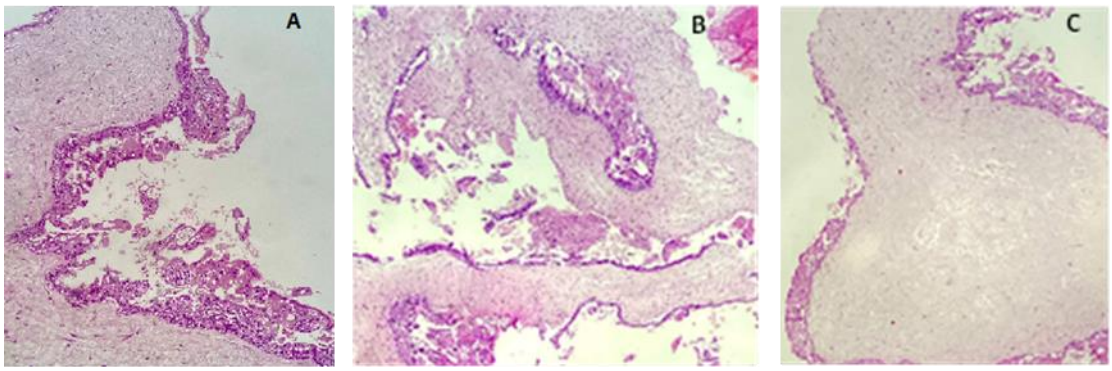
Our patient, a 38-year-old woman on her second pregnancy with a history of a cesarean birth seven years prior, was admitted to the emergency room of the Climério de

Oliveira Maternity of Bahia Federal University, the reference center for gestational trophoblastic diseases in the state of Bahia, Brazil. She reported moderate pelvic pain and mild vaginal bleeding. On examination, her vital signs were stable. Her uterus fundus was noted to be 6 cm above the pubic symphysis, and mild vaginal bleeding was observed during a vaginal examination.

Upon admission, the patient's hCG level was extremely high at 1.000.000 mIU/mL. Pelvic ultrasound findings were remarkable: the uterus was significantly enlarged, measuring 1974 cm^3, with a heterogeneous endometrium featuring anechoic areas, measuring 97 mm with a well-defined edge. Additionally, both ovaries were enlarged, with the right and left ovaries containing anechoic cystic images of varying sizes, their volumes estimated at 252 cm^3 and 182.2 cm^3, respectively. Manual vacuum aspiration was carried out successfully without any complications.

By the second day in the hospital, due to the persistence of molar tissue in the uterine cavity as confirmed by ultrasonography, a second uterine aspiration was necessary. The patient remained clinically and hemodynamically stable throughout her hospital stay. She was discharged in good condition five days after the second evacuation. Her hCG level had decreased to 85.227 mIU/mL at discharge. She was advised to use oral contraceptives and to follow up at the GTD Reference Center. Anatomopathological examination confirmed the diagnosis of a CHM, as shown in Figures 1A, 1B, and 1C.

Figure 1. A to C. Microscopic appearance of the anatomopathological study result: Complete Hydatidiform Mole.



Ten days after being discharged from the hospital, the patient sought medical attention again, this time with severe abdominal pain, nausea, vomiting, and increased vaginal bleeding. During the physical examination, she showed signs of abdominal distention and tenderness upon palpation, along with a palpable mass that extended from the pelvis to the umbilical scar. Ultrasonography indicated significant changes: there were bilateral theca lutein cysts. The volumes of the right and left ovaries were notably enlarged, measuring 1329 cm^3 and 500 cm^3 respectively (Figures 2 and 3). Additionally, ascites was present. The patient's hCG level was recorded at 48,769 mIU/mL.

Other laboratory results were within normal limits, including hematocrit (36.5%), hemoglobin (11.7 g/dL), leukocyte count (8950 cells/mm^3), sodium (135 mEq/L), potassium (4.8 mEq/L), albumin (3.8 g/dL), urea (13 mg/dL), creatinine (0.7 mg/dL), total bilirubin (0.2 mg/dL), and liver enzymes (AST 20 U/L and ALT 17 U/L). A chest radiograph revealed no abnormalities. The combination of clinical symptoms, significant ovarian enlargement, and ascites led to the diagnosis of spontaneous ovarian hyperstimulation syndrome, classified as moderate [5]. The patient was admitted for treatment, which included intravenous hydration and deep vein thrombosis prophylaxis with enoxaparin. Pain management was addressed with both simple analgesics and opioids, specifically tramadol hydrochloride. Antiemetics such as ondansetron and metoclopramide were administered to control nausea and vomiting. A strict fluid balance was maintained, and her condition

was closely monitored with daily laboratory tests, including blood count, electrolytes, renal function, and liver enzymes.

Figure 2. Pelvic ultrasound - right ovary with multiple cysts. Volume: 1329 cm³.

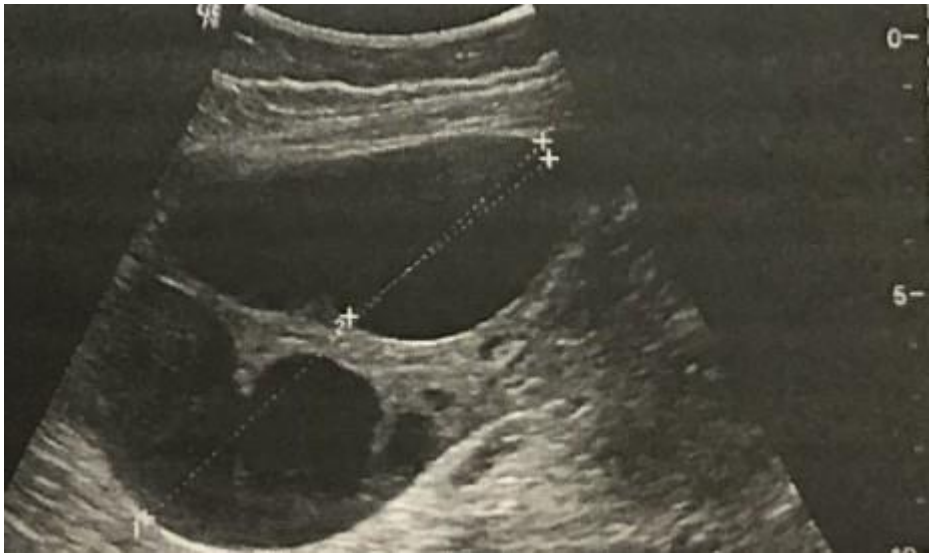
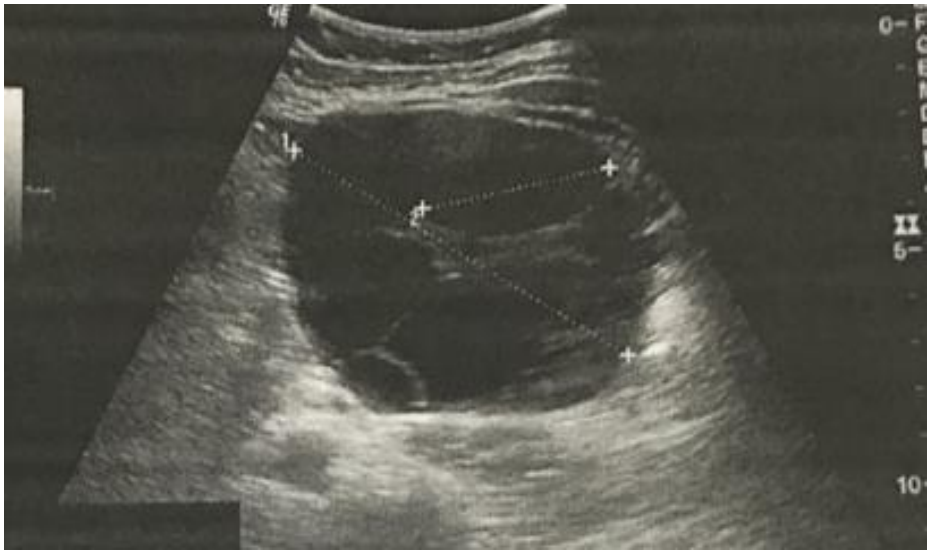


Figure 3. Pelvic ultrasound - left ovary with multiple cysts. Volume of 500 cm³.



During hospitalization, the patient experienced intermittent episodes of worsening abdominal pain, despite the use of analgesics. During posttreatment surveillance with weekly hCG measurements, there was a rise in hCG levels (48,769 → 72,695 → 87,239 mIU/mL) which enabled the early detection of postmolar gestational trophoblastic neoplasia (GTN) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO) [3]. She was discharged from the hospital in good condition, after 35 days, to follow-up with the oncology service for chemotherapy treatment. Additionally, she was oriented about the importance of maintaining contraceptive measures.

According to the FIGO staging and the World Health Organization scoring system based on prognostic factors [3], the patient was classified with low-risk GTN stage I score 4 (GTN I:4). Monochemotherapy for low-risk GTN was administered with methotrexate (MTX) and folinic acid in an 8-day regimen (50 mg MTX intramuscularly on days 1, 3, 5, 7 with 15 mg folinic acid orally 24 hours after MTX on days 2, 4, 6, 8). The patient underwent 12 cycles of chemotherapy (including 3 cycles of consolidation), and the hCG levels

normalized after 6 months of therapy. There were no reports of adverse effects. Pelvic ultrasound at the end of chemotherapy showed a uterine volume of 120 cm^3, an endometrium measuring 5 mm, a right ovary with a volume of 137.6 cm^3 with cysts, and a left ovary with a volume of 6.8 cm^3. The patient continued with monthly follow-ups at the GTD Reference Center, advised on the importance of using contraceptive methods for at least 1 year after achieving hCG negativity following the completion of chemotherapy.

3. Discussion

This case report highlights the diagnosis of spontaneous ovarian hyperstimulation syndrome in the context of a molar pregnancy, following uterine evacuation necessitating hospitalization for clinical management. After a 35-day hospital stay, the patient was discharged to undergo 12 chemotherapy sessions for post-molar gestational trophoblastic neoplasia. Ovarian hyperstimulation syndrome can be divided into two groups: iatrogenic or spontaneous [1]. The first group primarily occurs after the use of gonadotropins in assisted fertilization treatments, especially when associated with other risk factors: age under 30, high ovarian reserve, polycystic ovary syndrome, and previous history of ovarian hyperstimulation [1]. The spontaneous form, in turn, is rare and often reported during pregnancy [4].

Although the pathophysiological mechanism of OHSS is not fully understood, literature describes that high levels of hCG lead to the release of vasoactive substances by the ovaries, such as interleukins and tumor necrosis factor. As a result, vasodilation occurs, promoting mesothelial hyperpermeability with fluid leakage into the extravascular space. This process results in significant clinical consequences, including hemoconcentration, hypovolemia, worsened renal function, and hypercoagulability [2, 5]. Recent studies link a mutation in the FSH receptor gene, which increases its basal activity and sensitivity to hCG, with the development of OHSS [6]. However, not all spontaneous cases may be related to this mutation. Clinical situations resulting in elevated levels of hCG can also activate a similar process of recruitment, growth, and follicular luteinization. Glycoprotein hormones, such as hCG, LH, FSH, and TSH, are composed of a common alpha subunit and a hormone-specific beta subunit. The beta subunits of hCG and LH, which are very similar to each other, bind to the same receptor, while TSH and FSH bind to their respective receptors. The mutations in the FSH receptor mentioned reduce its specificity for its natural ligand, allowing hCG to also activate this mutated receptor [7, 8].

Elevated hCG levels in CHM are linked to a higher incidence of clinical symptoms, including hyperemesis, hyperthyroidism, preeclampsia, and theca lutein cysts. Consequently, these patients face a heightened risk of experiencing ovarian enlargement, with theca lutein cysts developing in about 20% of cases. Nevertheless, instances of spontaneous OHSS in the setting of GTD are infrequently documented in medical literature [4]. Research indicates that spontaneous ovarian hyperstimulation syndrome typically manifests later, between 8 and 14 weeks of amenorrhea, in contrast to iatrogenic cases, which tends to develop earlier, within 3 to 5 weeks [2]. Cases of OHSS associated with molar pregnancy can emerge after uterine evacuation, as illustrated in this case, in which it is worsened 10 days after evacuation. The condition's progression in such patients can rapidly deteriorate post-evacuation, with symptoms intensifying on average after 7.5 days, alerting the importance of maintaining surveillance in the postoperative period [4, 7]. A noted case involving a suspected CHM and OHSS presented with clinical worsening after four days of uterine evacuation with pericardial effusion, requiring drainage and intensive care unit admission; After a 10-day hospital stay, the patient was referred to oncology due to biopsy and cytology results indicating choriocarcinoma [8].

For a woman presenting with GTD and exhibiting signs and symptoms suggestive indicative of OHSS, clinicians should be aware and consider this diagnostic hypothesis. Initial assessment should include an anamnesis and physical examination, followed by a pelvic ultrasound and other complementary tests to evaluate the severity of the condition [1]. The Royal College Obstetrics and Gynecology classifies OHSS based on its severity. It

is considered mild when there is an increase in ovarian volume associated with abdominal pain and distension; moderate, if nausea, vomiting, and ascites are present, with ascites being identifiable through ultrasound [5]. Severe cases are characterized by clinical evidence of ascites, pleural effusion, oliguria, hemoconcentration, and altered electrolytes [1, 5]. In the case described, the patient was diagnosed with a moderate form of the disease upon hospital admission, exhibiting symptoms such as abdominal pain and distension, nausea, vomiting, and ascites, as confirmed by ultrasonography.

Most cases of OHSS are self-limited and resolves spontaneously, with the initiation of conservative management, aimed at treating signs and symptoms [5]. Mild to moderate cases can be managed with outpatient follow-up, ensuring constant monitoring. However, hospitalization should be considered if the patient is unable to manage pain adequately, cannot consume adequate fluids due to nausea/vomiting, or faces limitations for outpatient follow-up, as was the case in this report. In severe and critical forms, which can lead to potentially fatal complications, hospital treatment with a multidisciplinary approach is necessary, with the most serious cases requiring intensive care unit monitoring [5, 9].

The treatment of OHSS consists of clinical support, which includes intravenous hydration to increase intravascular fluid volume, thereby restoring organ perfusion. This is complemented by the prescription of antiemetics and analgesics. Non-steroidal anti-inflammatory drugs should be avoided due to the risk of renal function deterioration. Thromboprophylaxis is recommended for severe and critical cases, as well as for all hospitalized patients [5]. Cabar described an instance of OHSS in a spontaneous single pregnancy at 12 weeks of gestation, requiring hospital intervention. The treatment strategy encompassed clinical and ultrasound evaluations, venous hydration, and thromboprophylaxis, culminating in a spontaneous recovery within 6 days [7]. Such clinical strategies are essential in the treatment, prognosis, and reduction of morbidity and mortality among patients, and should therefore be implemented early in the diagnosis and grading of ovarian hyperstimulation syndrome.

The indication for treating ascites with paracentesis is reserved for cases where abdominal pain and distension do not respond to analgesic treatment, or in instances of respiratory distress and/or oliguria that remain unresponsive to hydration measures. The use of diuretics is generally contraindicated due to the risk they pose in exacerbating hypovolemia and hemoconcentration. Nevertheless, diuretics may become necessary in scenarios where oliguria persists despite adequate fluid replacement and ascites drainage. It is essential to conduct daily monitoring through laboratory tests, including blood count, leukocyte count, and assessments of renal function [5].

In cases of CHM, several risk factors can predispose to the progression to gestational trophoblastic neoplasia. These include the presence of theca lutein cysts greater than 6 cm in diameter, a pre-evacuation uterine size exceeding the expected size for gestational dates, hCG levels exceeding 100.000 mIU/mL, or a history of cesarean section [9, 10]. The reported case exemplifies this progression, as it featured all the aforementioned risk factors, ultimately leading to the development of postmolar GTN.

The patient progressed to a low-risk category of GTN, which is defined as stages I, II, or III with a score below 7, indicating a lower risk of chemoresistance. For such cases, the initial treatment typically involves a single chemotherapeutic agent, either MTX or actinomycin D, due to the lower likelihood of resistance. As observed in this case, the patient responded favorably to treatment with methotrexate. It is important to highlight those conditions such as ascites, ovarian cystosis, and pleural effusion can lead to the accumulation of MTX in these areas, potentially slowing the clearance of the drug and elevating the risk of toxicity [11]. Despite the presence of ascites and significantly enlarged ovaries in this case, the patient began chemotherapy following recovery from OHSS without experiencing adverse effects. This underscores the necessity of resolving any fluid accumulations before initiating cancer treatment with methotrexate to mitigate the risk of drug toxicity.

The importance of a multidisciplinary approach in more complex and severe cases cannot be overstated. Early recognition of OHSS is critical, especially in women with GTD. Health professionals must be vigilant in identifying the signs and symptoms of the syndrome and initiate prompt treatment based on the severity classification. Such proactive measures are essential to mitigate the morbidity and mortality associated with this condition [12]. This study presents inherent limitations due to its descriptive nature, which prevents the testing of hypotheses regarding the relationships between ovarian hyperstimulation syndrome and molar pregnancy. However, it makes significant contributions by providing insights that support previous case reports on the interconnection of these rare conditions, thereby enriching the scientific literature and highlighting the vital need for appropriate diagnosis and intervention.

Future research should be encouraged to build a stronger and more comprehensive evidence base concerning the relationship between these entities. Considering the rarity of these events, multicentric studies examining the dimensions of the ovaries as well as other risk factors and their potential link to ovarian hyperstimulation syndrome, including its mild forms which might be underdiagnosed, are vital for deepening the understanding of this occurrence.

4. Conclusions

This case report highlights the complexity of molar pregnancies, particularly how they can be complicated by spontaneous Ovarian Hyperstimulation Syndrome. It underscores the critical importance of vigilant follow-up in patients with suspected Gestational Trophoblastic Disease post-uterine evacuation. Clinicians must consider the possibility of OHSS in women presenting with abdominal pain accompanied by ovarian cystosis and trophoblastic disease. While most cysts regress spontaneously, requiring no surgical intervention, it is crucial to remain alert to exceptions, such as adnexal torsion, which necessitate surgical management. This case serves as a reminder of the nuanced approach needed in the diagnosis and management of GTD and its complications.

Funding: None.

Research Ethics Committee Approval: This case report study was approved by the Research Ethics Committee of the Climério de Oliveira Maternity/ Federal University of Bahia (CAAE: 51333021.2.0000.5543). The patient signed an informed consent form.

Acknowledgments: We thank Climério de Oliveira Maternity for encouraging this research and for contributing to provide excellent care for patients with gestational trophoblastic disease in the state of Bahia.

Conflicts of Interest: None.

Supplementary Materials: None.

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