

TSH-induced post thyroidectomy spontaneous ovarian hyperstimulation syndrome: a rare case report of molecular mimicry

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Case Report

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Abstract

Background: Spontaneous ovarian hyperstimulation syndrome (sOHSS) is an exceptionally rare condition, particularly when associated with profound primary hypothyroidism (Type III sOHSS). Unlike the common iatrogenic form, it occurs without exogenous ovulation induction.

Case Presentation: We report a 26-year-old female with a history of total thyroidectomy for papillary carcinoma who presented to the emergency department with severe abdominal pain, diarrhea and tense ascites. Laboratory evaluation revealed a critical elevation of thyroid-stimulating hormone (TSH) and normal follicle-stimulating hormone (FSH) levels. Imaging confirmed bilateral multicystic ovarian enlargement and massive ascites. The clinical presentation was consistent with OHSS triggered by "specificity spillover," where extreme TSH levels cross-activate FSH receptors.

Conclusion: Prompt recognition of severe hypothyroidism as a cause of sOHSS is vital to avoid unnecessary surgical interventions. Management centered on levothyroxine replacement and supportive care resulted in the complete resolution of symptoms and radiologic findings, with a satisfactory clinical evolution.

Background

Ovarian hyperstimulation syndrome (OHSS) is a complex and potentially life-threatening systemic disorder resulting from an excessive ovarian response to stimulation (1). It is classically defined by the massive enlargement of the ovaries and a significant acute fluid shift from the intravascular compartment into third-space cavities, such as the peritoneum (ascites), pleura (pleural effusion), and pericardium (1). This shift is primarily driven by increased capillary permeability, leading to intravascular depletion, hemoconcentration, and a highly prothrombotic state (2). While OHSS is most recognized as an iatrogenic complication of assisted reproductive technology (ART) following the administration of exogenous human chorionic gonadotropin (hCG), spontaneous ovarian hyperstimulation syndrome (sOHSS) is an exceptionally rare clinical entity, occurring in only 0.2% to 1.2% of naturally conceived pregnancies or in association with profound endocrinopathies (2).

Spontaneous OHSS is classified into three distinct types based on its molecular etiology (3). Type I is caused by activating mutations of the follicle-stimulating hormone receptor (FSHR), type II results from abnormally high concentrations of endogenous hCG, typically seen in multiple gestations or gestational trophoblastic disease, and type III sOHSS is a rare category directly associated with severe, untreated primary hypothyroidism, manifesting in both pregnant and non-pregnant females (3). In pediatric and adolescent populations, this condition is known as Van Wyk-Grumbach Syndrome (VWGS), characterized by the clinical triad of severe hypothyroidism, isosexual pseudoprecocious puberty (including multicystic ovaries), and delayed bone age (3). In adult patients, particularly those with a history of total thyroidectomy, the absence of adequate hormone replacement can lead to the mature manifestation of this endocrinopathy (3).

The pathophysiological link between post-thyroidectomy hypothyroidism and sOHSS is rooted in the molecular structure of the glycoprotein hormone family (4). Thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and hCG share an identical α -subunit and possess β -subunits with more than 40% amino acid sequence homology (4).

In the absence of negative feedback following a thyroidectomy, the body hypersecretes thyrotropin-releasing hormone (TRH) and TSH (4). Serum TSH concentrations can reach extreme levels, often exceeding 100 to 500 mIU/mL. At these massive concentrations, TSH exhibits a phenomenon known as "specificity spillover," where it directly binds to and activates the wild-type FSH receptors on ovarian granulosa cells (4). This cross-reactivity stimulates follicular recruitment and cystic ovarian enlargement, perfectly mimicking FSH-mediated hyperstimulation (4). Furthermore, hypothyroidism alters peripheral estrogen metabolism, shifting it toward the production of weaker estriol, which reduces negative feedback at the pituitary level and further drives gonadotropin and TSH release (4). We present the case of a female patient with a history of thyroidectomy due to papillary carcinoma that developed OHSS due to an elevated TSH.

Case presentation

A 26-year-old female with a significant surgical history of total thyroidectomy and central neck dissection performed ten years ago due to papillary thyroid carcinoma, presented to the emergency department with a five-day history of progressive, colicky lower abdominal pain radiating to the lumbar region, associated with multiple episodes of diarrhea and emesis. She had been on long-term levothyroxine replacement therapy, though her recent adherence was suboptimal. Upon admission, physical examination showed significant tenderness in the right flank and the right iliac fossa; however, no signs of peritoneal irritation or rebound tenderness were documented. Complete blood count showed a normal leukocyte count in 7.650 cells/mcL, with no anemia or thrombocytopenia, and a normal urinalysis.

Due to persistence of abdominal pain, a contrast-enhanced CT-scan was performed, revealing bilateral complex adnexal cystic masses with thin internal septations (Fig. 1). The right-sided lesion measured 118 x 62 mm, while the mass on the left measured 69 x 84 mm. Notably, the vermiform appendix was found to be in direct contact with the right-sided lesion; however, no secondary inflammatory changes were observed in the appendiceal structure, and free fluid was also noted in the abdominal cavity (Fig. 1).

Comprehensive laboratory investigations revealed profound endocrine and metabolic disturbances. The thyroid profile demonstrated severe primary hypothyroidism, with a TSH level of 150 mIU/mL and a suppressed Free T4 (FT4) of 0.23 mIU/mL. The pregnancy test was negative. In the context of bilateral multicystic ovaries and ascites in a non-pregnant patient with a post-thyroidectomy history and no history of IVF, a diagnosis of Type III spontaneous ovarian hyperstimulation syndrome (sOHSS) was established. Additional investigations showed an elevated CA-125 marker in 49.50 U/mL, elevated

estradiol level in 589.91 pg/mL, elevated prolactin level in 87.17 ng/mL and normal FSH level in 7.14 mIU/mL.

The patient was admitted for inpatient management and intensive monitoring. The clinical management focused on three primary pillars: hormonal stabilization, with immediate re-initiation and titration of levothyroxine replacement therapy to address the underlying "specificity spillover" of TSH; fluid and electrolyte management, with initiation of intravenous fluid therapy with crystalloids to restore intravascular volume and correct dehydration caused by third-space fluid shifts and gastrointestinal losses; and symptomatic therapy, with administration of intravenous diuretics. Standard thromboprophylaxis with low molecular weight heparin (LMWH) was provided to mitigate the prothrombotic risk associated with hemoconcentration and bed rest. Throughout her hospitalization, the patient showed a favorable clinical evolution. There was progressive resolution of gastrointestinal symptoms and a significant reduction in abdominal pain.

The patient was discharged in stable condition following the complete resolution of her acute symptoms. She was scheduled for ambulatory follow-up to monitor the normalization of her hormonal profile (TSH and FT4) and to perform serial pelvic ultrasounds to document the expected regression of the ovarian cysts as she reached a euthyroid state.

Discussion

Spontaneous ovarian hyperstimulation syndrome (sOHSS) is an exceptionally rare clinical entity, particularly when it manifests outside of pregnancy (5). While iatrogenic OHSS is a well-known complication of assisted reproductive technology triggered by exogenous human chorionic gonadotropin (hCG), sOHSS is classified into three types based on molecular etiology (3). Type III sOHSS is specifically associated with profound, untreated primary hypothyroidism, and in adult patients, it represents the mature manifestation of the pediatric Van Wyk-Grumbach Syndrome (VWGS) (4). Precisely, our case is related to an uncontrolled postoperative hypothyroidism as the cause of the sOHSS.

The primary pathophysiological driver in Type III sOHSS is the phenomenon of "specificity spillover" (6). The glycoprotein hormone family—comprising thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and hCG—shares a common α -subunit and distinct β -subunits that exhibit over 40% amino acid sequence homology (6). Their respective G-protein coupled receptors also share significant structural similarity. In states of severe primary hypothyroidism, such as post-thyroidectomy without adequate replacement, the lack of negative feedback triggers a massive hypersecretion of thyrotropin-releasing hormone (TRH) and TSH (4).

When serum TSH levels reach extreme concentrations (often IU/mL), TSH cross-reacts with and directly activates wild-type FSH receptors on ovarian granulosa cells (4). This stimulates follicular recruitment and multicystic ovarian enlargement, perfectly mimicking FSH-mediated stimulation (6). In our case the patient exhibited a significant bilateral ovarian multicystic growth shown in the abdominal CT-scan that

was responsible for the clinical symptoms that the patient presented, which can mislead the diagnosis and be confused with other ovarian clinical entities such as cystadenomas.

Furthermore, hypothyroidism fundamentally alters estrogen metabolism (8). In euthyroid states, estradiol is primarily metabolized via the 2-hydroxylation pathway; however, severe hypothyroidism shifts this to the 16-hydroxylation pathway, producing estriol, a significantly less potent estrogen (8, 9). The resulting decrease in potent estradiol reduces negative feedback at the hypothalamic-pituitary level, further driving the compensatory release of TSH and gonadotropins (9). Additionally, elevated TRH levels stimulate pituitary lactotrophs, leading to hyperprolactinemia. Prolactin sensitizes the ovaries to gonadotropic stimulation and alters GnRH pulsatility to favor the transcription of FSH over LH, exacerbating the hyperstimulated state (9). Our patient had mild though significant hyperprolactinemia.

The management of OHSS, whether iatrogenic or spontaneous, is primarily supportive and symptom-centered, as the condition is typically self-limiting (10). For Type III sOHSS, the cornerstone of definitive treatment is the prompt initiation and titration of levothyroxine replacement therapy. Restoration of euthyroidism removes the "specificity spillover" stimulus, leading to the gradual regression of ovarian cysts and resolution of effusions, typically within weeks to months (10). Patients often exhibit a "reset" of the osmotic threshold, leading to hypo-osmolality and hyponatremia despite profound intravascular dehydration (11). Management focuses on restoring intravascular volume while preventing further third-space accumulation. Oral hydration guided by thirst is the most physiological approach. If intravenous fluids are required, crystalloids are used initially, though colloids (e.g., 20–25% human albumin) are preferred in severe cases to increase oncotic pressure and draw fluid back into the vascular compartment (12).

OHSS establishes a highly prothrombotic state due to hemoconcentration, increased capillary permeability, and venous stasis from enlarged ovaries (1). All hospitalized patients with moderate to severe OHSS should receive low molecular weight heparin (LMWH), such as enoxaparin 40 mg daily, to mitigate the risk of life-threatening thromboembolism (1). Ultrasound-guided paracentesis is indicated for patients with tense ascites, severe abdominal pain, or respiratory compromise. Drainage of ascitic fluid can improve renal perfusion by relieving intra-abdominal pressure (10).

A significant diagnostic challenge in sOHSS is the elevation of the tumor marker CA-125, which can rise to extreme levels due to mechanical stretching of the peritoneum, as occurred in our case. Combined with complex adnexal masses and ascites, this frequently leads to a misdiagnosis of ovarian malignancy (7). Furthermore, compensatory pituitary thyrotrophic hyperplasia can mimic pituitary macroadenoma on MRI (7). Clinical vigilance and routine thyroid function screening in patients presenting with bilateral multicystic ovaries are essential to prevent unnecessary surgical interventions, such as oophorectomy or transsphenoidal resection, which can be disastrous in these benign, reversible conditions (7). The patient presented in this case presented a significant regression of the ovarian multicystic masses during the follow-up.

Conclusion

This case highlights the critical importance of recognizing severe primary hypothyroidism as a reversible cause of spontaneous ovarian hyperstimulation syndrome. The "specificity spillover" of massively elevated TSH levels can perfectly mimic FSH-mediated hyperstimulation, leading to a complex clinical presentation of multicystic ovaries and massive ascites. Early endocrine diagnosis via thyroid function tests is vital to avoid unnecessary and invasive surgical procedures. Management centered on levothyroxine replacement and meticulous supportive care remains the gold standard, ensuring excellent clinical outcomes and the complete resolution of the syndrome.

Declarations

Conflicts of interest:

All authors declare no conflicts of interest.

Ethical Standards

Ethical compliance with the Helsinki Declaration, current legislation on research Res. 008430 – 1993 and Res. 2378 – 2008 (Colombia) and the International Committee of Medical Journal Editors (ICMJE) were ensured under our Ethics and Research Institutional Committee (IRB) approval, prior signing of informed consent by the patient.

The protocol for this article was previously approved by the Ethics Committee of our institution (Subred Integrada de Servicios de Salud Sur).

Consent to Publish

The patient subject of this report previously signed the written informed consent form in the presence of two witnesses, authorizing the anonymous use of all the information from her medical history and corresponding images in any publications with scientific or academic interest.

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Author Contribution

J.L.R.O.: Investigation, writing and editing, validation, supervision.M.F.L.W.: Writing and editing, data consolidation.D.L.M.P.: Supervision, investigation, revision of final manuscript.J.E.C.C.: Supervision, validation, revision of final manuscript.D.C.V.F.: Data consolidation and revision of final manuscript. J.C.V.S.: Figure preparation, writing of draft. V.M.H.: Figure preparation, writing of draft.

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Data Availability

All data supporting the findings of this study are available upon request to the corresponding author.

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Figures



Figure 1

Abdominal CT-scan showing bilateral complex adnexal cystic masses (red circle) in the (A) axial, (B) coronal, and (C) sagittal planes.