Spontaneous ovarian hyperstimulation syndrome in a pregnant woman with hypothyroidism: a case report

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Objective: To study a rare case of spontaneous ovarian hyperstimulation syndrome in a naturally conceived pregnancy associated with overt hypothyroidism.
Design: Case report.
Setting: Endocrinology private practice.
Patient(s): A 32-year-old woman who was 13 weeks pregnant with bilaterally enlarged ovaries presumed to be secondary to hypothyroidism.
Intervention(s): Administration of levothyroxine and titration of the dose.
Main Outcome Measure(s): Regression of signs and symptoms of spontaneous ovarian hyperstimulation syndrome after 12 weeks of therapy.
Result(s): The patient was diagnosed with severe hypothyroidism, as confirmed by her elevated thyroid-stimulating hormone level. Ultrasound evaluation revealed ovarian enlargement secondary to multiple contiguous cysts with anechoic content. The patient was administered levothyroxine 175 μg/day. Results of hormonal studies demonstrated thyroid function normality at week 12 after treatment. Incomplete regression of ovarian cysts was also noticed within this period. At week 37, the patient developed preeclampsia, and cesarean delivery was recommended. An 8-month postpartum ultrasound evaluation revealed complete regression of the cysts.
Conclusion(s): Spontaneous ovarian hyperstimulation syndrome secondary to hypothyroidism may be the cause of ovarian enlargement, and levothyroxine replacement seems an appropriate primary therapeutic option. Proper endocrinological assessment of patients is recommended as it may avoid unfavorable outcomes. (Fertil Steril Rep® 2021;2:433–9. ©2021 by American Society for Reproductive Medicine.)
Key Words: Hypothyroidism, ovarian cysts, pregnancy, spontaneous ovarian hyperstimulation

Ovarian cysts are a common cause of elective gynecological surgery. However, some cysts are pathologically caused by nonneoplastic disorders and do not require surgery. Ovarian hyperstimulation syndrome (OHSS) secondary to treatment with exogenous gonadotropins, clomiphene citrate, and gonadotropin-releasing hormone has been described extensively in the literature. However, OHSS has been rarely reported in women with hypothyroidism during naturally conceived pregnancy (1–3). Primary hypothyroidism is an endocrine pathology highly prevalent globally, and the failure to recognize it as a possible etiology of ovarian cysts can lead to inadvertent oophorectomy. The literature shows, with low-quality evidence, that the cysts may regress spontaneously with the normalization of thyroid-stimulating hormone (TSH) and free thyroxine (T4) levels (4–6). This case report describes a rare clinical course of a pregnant woman with severe hypothyroidism who presented with OHSS, in whom oophorectomy was considered. In this case report and review of the literature, we outlined the pathophysiology and treatment of spontaneous ovarian hyperstimulation

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due to hypothyroidism in pregnancy to highlight the need for endocrinological evaluation of patients with multiple ovarian cysts (5).

MATERIALS AND METHODS

We conducted a literature search within the PubMed database using the keywords "case" AND "spontaneous ovarian hyperstimulation syndrome" AND "hypothyroidism" of papers published from 1989 to March 2021. We reviewed all case reports and case series published in Portuguese, French, and English. We focused particularly on cases of pregnant women with hypothyroidism. A total of 30 original articles were included in this narrative review. References of the identified publications were searched for similar research articles to be included in this article. No cases related to iatrogenic OHSS were considered in our review.

CASE REPORT

A 32-year-old primigravida with spontaneous pregnancy sought medical care due to hypothyroidism diagnosed during pregnancy at 13 weeks gestation. The patient presented with excessive drowsiness, constipation, xerosis, and weakness for the past 5 years and reported the continuous use of iron supplementation due to unspecified anemia since the age of 17 years. The patient's height was 1.45 m, and she weighed 40 kg. Physical examination revealed periorbital and lower limb edema and paleness of the mucous membranes. The first obstetric ultrasound evaluation revealed ovarian enlargement, secondary to multiple contiguous cysts with anechoic content, with thin walls, measuring 9.3 × 6.3 × 5.9 cm and 10.6 × 10.0 × 7.1 cm, as shown in Figure 1. Laboratory analyses revealed an increased level of TSH (100 mU/L) and reduced free T4 (0.25 ng/dl), anemia (hemoglobin 6.7 g/dl), and normal levels of leukocytes, platelets, urea, creatinine, and carcinoembryonic antigen. We observed, however, that CA-125 was elevated (56 U/ml). Levothyroxine treatment was initiated at 100 μg and was progressively increased to 175 μg. Iron supplementation was maintained. After discussion with the obstetrics team, conservative medical management was considered owing to a presumptive diagnosis of moderate spontaneous OHSS induced by severe hypothyroidism. At 18 weeks gestation, the patient underwent magnetic resonance imaging of the pelvis, which revealed expansive cystic lesions with multiple thin septa in both ovaries, without any solid component and with a small element of probable hemorrhagic content. Within 12 weeks, a remarkable decrease in the cysts was observed on ultrasonography, along with a decrease in TSH level. At week 37, the patient developed preeclampsia, and a cesarean section was performed, resulting in the birth of a healthy infant, weighing 2,200 g, with Apgar scores of 9 at 1 minute and 10 at 5 minutes. Pelvic ultrasound examination performed 8 months after child-birth was normal and showed complete regression of the ovarian cysts. Written informed consent was obtained from the patient before publication.

DISCUSSION

The patient's initial ultrasound assessment revealed an intrauterine singleton pregnancy and bilaterally enlarged ovaries, secondary to multiple contiguous thin-walled cysts with anechoic content. A wide range of diagnoses could be made given the presented picture. Since ovarian function is under the complex regulation of the hypothalamic-pituitary-ovarian axis (7), it can be affected by various disorders. Our differential diagnosis included dermoid cysts, Van Wyk and Grumbach syndrome, and spontaneous OHSS (6).

Dermoid Cysts

From an epidemiological perspective, approximately 70% of ovarian cysts diagnosed in women of childbearing age are dermoid cysts, which are caused by hormonal changes that occur during puberty and provoke the hyperstimulation of sebaceous glands present in the ovaries (8). However, the patient's ultrasound findings did not match the pathognomonic findings of a dermoid cyst.

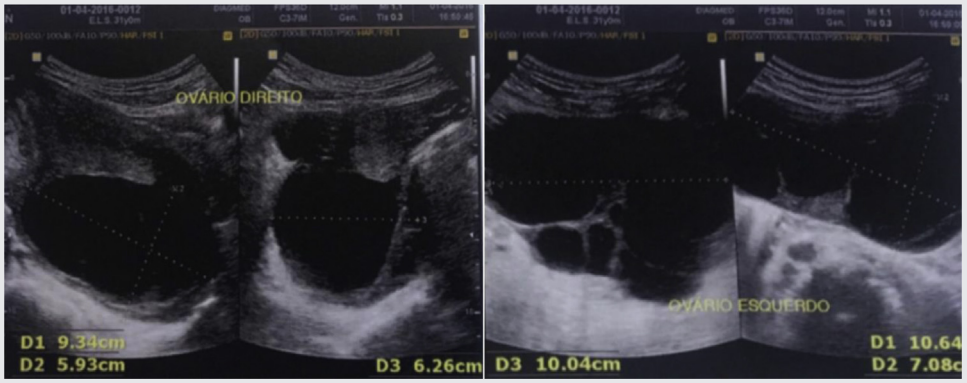
Van Wyk and Grumbach Syndrome and Follicle-Stimulating Hormone Receptor/TSH Cross-Reactivity

After rejecting the diagnosis of dermoid cysts, we presumed the diagnosis to be Van Wyk and Grumbach syndrome. This pathology is characterized by the early development of feminine secondary sexual characteristics due to high serum TSH levels, secondary to long-standing autoimmune thyroid disease or congenital hypothyroidism. The syndrome progresses with the hyperstimulation of ovarian follicle-stimulating hormone receptors (FSHr) by TSH, leading to the formation of ovarian cysts (3, 9–11). However, this diagnosis was also contested since our patient denied undergoing precocious puberty.

Although the patient's history did not match a classic Van Wyk and Grumbach case, part of the etiology of the syndrome may help in understanding the patient's pathology. The mechanism behind the cross-reactivity between TSH and FSHr is yet to be entirely elucidated. In this sense, most clinicians understand that high TSH levels, frequently observed in patients with hypothyroidism, can directly stimulate FSHr or induce a mutation that sensitizes them to this hormone (12–14).

FSHr, chorionic gonadotropin receptor, and thyrotropin receptor are likely to have evolved from a common ancestral gene, along with the β subunit of their corresponding hormones (FSH, chorionic gonadotropin, and thyrotropin, respectively), due to which a certain level of hormonal overlap can be expected in cases where they are found in high levels in the serum. Besides the similarity between the receptors and hormones in question, over 700 single-nucleotide polymorphisms and mutations of the FSHr gene may lead to increased sensitivity to other hormones. When a specific mutation occurs at the FSHr, the asparagine at the cytoplasmic end of the transmembrane helix VI is replaced by aspartate in codon 567, which makes the mutant receptor exceptionally sensitive to chorionic gonadotropin. Another possible mutation in the

FIGURE 1



Ultrasound showing bilaterally enlarged ovaries with multiple contiguous thin-walled cysts with anechoic content, measuring 9.3 × 6.3 × 5.9 cm (*right*) and 10.6 × 10.0 × 7.1 cm (*left*).

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FSHr is associated with the substitution of alanine by threonine in codon 449, increasing the receptor's sensitivity for both chorionic gonadotropin and TSH. (12, 15)

Ovarian Hyperstimulation Syndrome

Subsequently, the ultrasound findings, when correlated with the patient's laboratory and clinical history, led us to investigate our last presumed diagnosis, OHSS. Ovarian hyperstimulation syndrome is defined in the literature as the combination of ovarian enlargement due to the growth of cysts and vascular hyperpermeability, leading to the outflow of fluid toward the extravascular space, followed by hypovolemia and hemoconcentration (16). It results from the release of vasoactive peptides from granulosa cells. Although the main vasoactive peptide described in the literature is the vascular endothelial growth factor, other mediators such as angiotensin II, insulin-like growth factor 1, interleukins, tumor necrosis factor α, gonadotropins, and prostaglandins have also been associated with OHSS (2, 17, 18)

OHSS may manifest in two different ways: spontaneous OHSS and iatrogenic OHSS. Iatrogenic OHSS is mainly a consequence of ovulation induction procedures performed during in vitro fertilization cycles when exogenous gonadotropin stimulation combined with human chorionic gonadotropin (hCG) administration triggers the final oocyte maturation (19). It usually occurs between weeks 3 and 8 of gestation and is most associated with the classic systemic condition attributed to OHSS (18, 20). As the patient's pregnancy occurred spontaneously and there was no history of previous infertility treatment, her OHSS was confirmed to be spontaneous. Spontaneous OHSS tends to occur later than iatrogenic OHSS, usually demonstrating ovarian growth around weeks 8–14 of gestation (20, 21).

Spontaneous OHSS is an extremely rare condition and is almost always associated with the mutated FSHr gene, as previously mentioned, along with high levels of hCG (in hydatidiform mole and multiple gestations) and hypothyroidism. De Leener et al. (22) classify them as type I, type II, and type III, respectively.

Since the patient had a singleton pregnancy with normal levels of hCG, it is reasonable to dismiss spontaneous OHSS type II as the etiology. Type I and type III were the most probable diagnoses for the patient. To differentially diagnose the condition and confirm the diagnosis, it was necessary to perform genome sequencing of the FSHr gene (15, 21). However, the patient did not undergo genetic testing as the treatment and management would be the same, regardless of the type (I or III).

The symptoms of iatrogenic OHSS consist of abdominal pain, distension, nausea, vomiting, pleural effusion, hemoconcentration, ascites, and systemic edema (19, 23). It is noteworthy that the patient did not present any of the systemic conditions attributed to OHSS. Instead, our patient was anemic, which was similar to a case reported by Kanza et al. (24). This may be attributed to the differences in the etiopathogenesis of iatrogenic and spontaneous OHSS. Vasoactive substances released by hyperstimulated ovaries are primarily responsible for the increase in vascular permeability and are released more prominently in iatrogenic OHSS. Spontaneous OHSS, on the other hand, progresses with high levels of hCG, TSH, or with a mutated FSHr, and may or may not be associated with a systemic condition and extravascular outflow. Extravascular fluid retention may not occur, and usually, hemodilution may be observed (20, 24, 25). Our patient did not have distension and abdominal pain, which may be related to the chronicity of hypothyroidism. Since the patient suffered from this condition for a long time before receiving treatment, it is thought that the enlargement of the ovaries was gradual and, therefore, did not cause a painful reaction.

Other Theories Related to Hypothyroidism and Ovarian Cysts

The evaluation of hypothyroidism and ovarian cysts remains highly underestimated since there is no international

consensus on the exact association between both clinical conditions. Besides the previously mentioned theories (FSHr/TSH cross-reactivity and OHSS), there are several others that complement our patient's investigation. In brief, high TSH levels directly stimulate nuclear thyroid receptors found in granulosa cells (TRa and TRb), resulting in ovarian hyperstimulation (26, 27). Consistently high levels of thyrotropin-releasing hormone stimulate, along with TSH secretion, FSH secretion (3, 28); patients with ovarian hyperstimulation produce estriol via the 16-hydroxylation route, instead of the normal 2-hydroxylation pathway. Since estriol is less potent than estrogen in the gonadotropin release feedback pathway, an exaggerated FSH release is generated that hyperstimulates the ovaries (4). Furthermore, high levels of thyroid-releasing hormone may be responsible for the development of hyperprolactinemia, which could be responsible for making the ovaries more susceptible to the action of gonadotropins (9, 29).

Medical Management

Therapy for OHSS secondary to hypothyroidism is aimed at symptomatic relief (1). Although surgical excision of our patient's cysts was considered, given the possible complications already reported in the literature, such as infertility and increased risk of miscarriage (30, 31, 26), the medical team opted for conservative treatment instead. The proposed treatment and follow-up plan included replacing levothyroxine and monitoring cysts by imaging examinations, respectively. This drug is used as a treatment plan based on the causal relationship between hypothyroidism and spontaneous ovarian hyperstimulation, leading to the regression of ovarian cysts after initiation of thyroid hormone replacement therapy and TSH reduction, as seen in some cases. Hemotransfusion or paracentesis was not indicated during any part of the patient's pregnancy.

The patient was instructed to follow the prescription previously made, and at 25 weeks gestation, follow-up tests showed a significant reduction in her TSH level and an increase in free T4 level. In addition, ultrasonography revealed a decrease in the volume of cystic lesions. Postpartum follow-up, with pelvic ultrasounds, performed 8 months after the cesarean section, showed normal ovaries without cysts.

Narrative Review

Although some investigators correlate OHSS, hypothyroidism, and pregnancy, the level of evidence for these associations is still very low, mainly because only a few cases of spontaneous OHSS have been reported in the literature. Their details are included in Table 1. There are reported cases of spontaneous OHSS in polycystic ovary syndrome (24, 32), gonadotropin pituitary adenoma and pituitary enlargement (24, 33–35), hypothyroidism (4, 22, 24, 33, 34, 36–41), pregnancy (25, 32, 42–48), invasive mole or elevated human chorionic gonadotropin (49, 50) and hypothyroidism concomitant with pregnancy (1, 2, 20, 27, 51–52). This narrative review concentrates mostly on the different clinical courses and outcomes of the seven described cases in which spontaneous OHSS was related to pregnancy, concomitant with hypothyroidism.

As in our report, Sridev et al. (20) and Edwards-Silva et al. (53) reported patients who also presented with anemia, while only Dieterich et al. (52) reported a patient with the characteristic hemoconcentration found in the syndrome. Additionally, Edwards-Silva reported a high level of CA-125, which corresponds to the finding of our case. This increase has been reported in several benign conditions, including hypothyroidism and conditions that aggravate serous membranes (24). Furthermore, CA-125 is generally elevated in pregnant patients and patients with a gross ovarian enlargement (45). Finally, Delabaere et al. (51) and Dieterich reported a positive FSHr mutation (mutation D567N).

All case reports reveal adequate levothyroxine treatment, similar to our patient, with dosage varying from 50 to 200 mcg daily. In the cases described by Cardoso et al. (1), Nappi et al. (2), Borna et al. (27), Dieterich et al. (52), and Edwards-Silva et al.(53), the patients also underwent fluid replacement; only Dieterich et al., Edwards-Silva et al., and Delabaere et al. (51) reported that their patients received antithrombotic prophylaxis and analgesia. Surgical procedures were performed only for the patient reported by Dieterich et al., wherein the patient had to undergo paracentesis, and in the case described by Borna et al., wherein the patient underwent a laparotomy for a wedge biopsy of the cysts. Only the patient described by Edward-Silva et al. underwent a blood transfusion.

Cardoso et al. (1) and Borna et al. (27) reported a similar period of hormonal normalization as our patient, wherein TSH levels decreased after 12–15 weeks, while Nappi et al. (2) showed that hormone reduction occurred after 2 weeks of therapy. The case reports by Cardoso et al., Nappi et al., Borna et al., Delabaere et al. (51), and Dieterich et al. (52) show rapid regression in symptomatology after levothyroxine treatment for 2–8 weeks. However, in the case of Sridev et al. (20), the patient started showing improvement from week 14. This may be because the patient also had high levels of β-hCG. Cardoso et al. and Delabaere et al. described the same period to ovarian size normalization as our patient, i.e., 12 weeks, while Sridev et al. and Borna et al. reported no evidence of cysts only at 20 and 28 weeks, respectively.

In contrast to our patient, Cardoso et al.'s (1) patient went into preterm labor spontaneously, and Edward-Silva et al. (53) reported a preterm cesarean delivery. The remaining pregnancies were delivered at term, and all infants were born healthy. There were no complications described at birth, except for Edward-Silva's report, in which the patient had postoperative intraabdominal hematoma and anemia.

CONCLUSION

The etiopathogenesis behind the development of ovarian cysts, especially during the gestational period, is diverse. Our patient was diagnosed with ovarian hyperstimulation and ovarian cysts at the end of the first trimester of pregnancy, which underscores the importance of an early and appropriate multidisciplinary clinical investigation to avoid unfavorable patient outcomes. In many cases, conservative treatment with levothyroxine for spontaneous OHSS is

TABLE 1

Clinical assessment of adult spontaneous OHSS.

References	Age (y)	Pregnancy	Hypothyroidism	Abdominal pain / distension	Ascites	Pituitary enlargement	Hemoconcentration	Anemia	Oliguria	Mutation	LT4
This Case[a]	32	13 weeks	Yes	No	Yes	N/A	No	Yes	No	N/A	Yes
Chen et al. (36)	20	-	Yes	Yes	No	N/A	No	Yes	N/A	N/A	Yes
Sridev et al. (20)[a]	22	9 weeks	Yes	Yes	No	N/A	No	Yes	N/A	N/A	Yes
Ilanchezian et al. (22)	25	-	Yes	Yes	Yes	N/A	No	Yes	N/A	N/A	Yes
Kanza et al. (24)	19	-	Yes	Yes	Yes	Yes	No	Yes	N/A	N/A	Yes
Katulande et al. (33)	23	-	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	Yes
Chae et al. (42)	35	12 weeks	-	Yes	Yes	N/A	No	No	N/A	No	No
Kim et al. (34)	14	-	Yes	Yes	No	Yes	N/A	N/A	N/A	N/A	Yes
Oztekin et al. (43)	19	9 weeks	-	Yes	Yes	N/A	No	No	N/A	N/A	No
Cardoso et al. (1)[a]	25	11–12 weeks	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes
Nappi et al. (2)[a]	34	12 weeks	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	Yes
Rotmensch et al. (4)	21	-	Yes	Yes	Yes	N/A	No	Yes	N/A	N/A	Yes
Rajaram et al. (37)	19	-	Yes	Yes	No	N/A	No	Yes	N/A	N/A	Yes
Chai et al. (46)	23	-	-	Yes	Yes	N/A	N/A	N/A	N/A	N/A	No
Borna et al. (27)[a]	30	20 weeks	Yes	Yes	Yes	N/A	No	No	N/A	N/A	Yes
Navarro et al. (25)	30	11 weeks	-	Yes	No	N/A	No	Yes	N/A	No	No
Langroudi et al. (38)	15	-	Yes	Yes	Yes	N/A	No	No	N/A	N/A	Yes
Francisco et al. (44)	28	13 weeks	-	Yes	Yes	N/A	No	No	N/A	N/A	No
Di Carlo et al. (45)	26	7 weeks	-	Yes	Yes	N/A	Yes	No	N/A	Yes	No
Rachad et al. (49)	34	-	-	Yes	Yes	N/A	No	No	N/A	N/A	No
Delabaere et al. (51)[a]	23	8 weeks	Yes	Yes	No	No	No	No	N/A	No	Yes
Dieterich et al. (52)[a]	26	12 weeks (first) 6 weeks (second)	Yes	Yes	Yes	N/A	Yes	No	N/A	Yes	Yes
Lussiana et al. (48)	29	Abortion at 22 weeks	-	Yes	Yes	N/A	Yes	No	N/A	Yes	No
Uchida et al. (35)	40	-	-	No	No	No	N/A	N/A	No	Yes	No
Guvenal et al. (39)	28	-	Yes	Yes	No	N/A	No	No	N/A	N/A	Yes
Zalel et al. (32)	19	10 weeks	-	Yes	No	N/A	No	No	N/A	N/A	No
Erol et al. (40)	18	-	Yes	Yes	Yes	No	No	No	N/A	No	Yes
Rastin et al. (47)	28	8 weeks	-	Yes	Yes	N/A	Yes	No	N/A	N/A	No
Edward-Silva et al. (53)[a]	30	10 1/7 weeks	Yes	Yes	Yes	N/A	No	Yes	N/A	N/A	Yes
Taher et al. (41)	22	-	Yes	Yes	No	Yes	N/A	N/A	No	N/A	Yes
Michaelson-Cohen et al. (50)	36	10 weeks	-	Yes	Yes	N/A	Yes	No	N/A	No	No

Note: N/A = not applicable.

[a] Case report of spontaneous OHSS associated with pregnancy concomitant with hypothyroidism.

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sufficient to achieve a favorable clinical outcome and avoid possible surgical complications.

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