

# SPONTANEOUS OVARIAN HYPERSTIMULATION SYNDROME IN A NORMAL SINGLETON PREGNANCY

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## SUMMARY

**Objective:** It is known that most cases of ovarian hyperstimulation syndrome (OHSS) are associated with the therapies for ovulation induction. However, OHSS may rarely be associated with a spontaneous ovulatory cycle, usually in the case of multiple gestations, hypothyroidism or polycystic ovary syndrome.

**Case Report:** A case of OHSS in a woman who became pregnant naturally and who had no underlying disease is presented here. The patient was managed expectantly with no complications.

**Conclusion:** Although spontaneous ovarian hyperstimulation is a rare entity, it is important to differentiate it from other causes of ovarian enlargement. Occasionally, life-threatening situations may occur, but it is usually a self-limiting process. [*Taiwanese J Obstet Gynecol* 2006;45(3):272-275]

**Key Words:** normal pregnancy, spontaneous ovarian hyperstimulation syndrome

## Introduction

Ovarian hyperstimulation syndrome (OHSS) is considered to be an iatrogenic complication of ovulation induction therapy for *in vitro* fertilization in approximately 10% of cases [1]. In its most severe form, OHSS involves massive ovarian enlargement, formation of multiple ovarian cysts, fluid shifts resulting in extravascular fluid accumulation and intravascular volume depletion, renal failure, hypovolemic shock, and, in some cases, death. This severe form is rare, with a reported incidence of 0.5-5% among patients undergoing ovulation induction therapy [2].

Although OHSS most commonly occurs as a result of exogenous administration of gonadotropins, spontaneous OHSS has been reported in rare instances during pregnancy, most often in situations where there is supraphysiologic production of chorionic gonadotropin, such as multiple gestations or molar pregnancies. Chorionic gonadotropin production typically peaks

around the 9<sup>th</sup> week of gestation and decreases thereafter. In parallel with this course, spontaneous OHSS is usually most severe during the first trimester of pregnancy [2].

The pathologic features of OHSS, whether spontaneous or iatrogenic, include the presence of multiple serous and hemorrhagic follicular cysts lined by luteinized cells, a condition called hyperreactio luteinalis [1,2].

We describe a case of spontaneous OHSS in a woman who became pregnant naturally and who had no underlying disease.

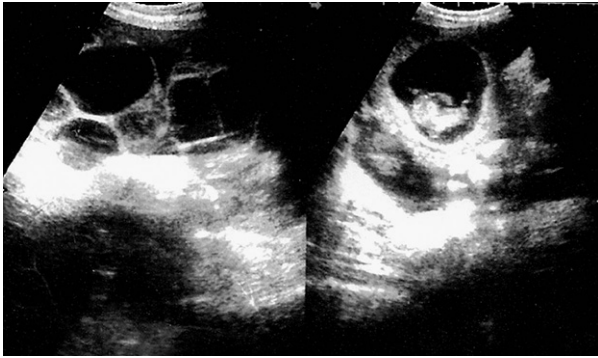
## Case Report

A 19-year-old primigravid patient was admitted to our clinic with the complaints of abdominal distension, pain and nausea; these complaints had been present for 4 days. She had regular menses before her pregnancy and had a gestation of 9 weeks 4 days based on her last menstruation. She had no history of ovulation induction or any medication within the last 6 months. She also had no history of acne or hirsutism. Family history was negative for both polycystic ovary syndrome and diabetes mellitus.

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**Figure.** Enlarged ovaries in the form of cystic masses are seen on the left and the fetus is seen on the right.

On admission, she had a blood pressure of 90/60 mmHg, while her pulse rate was 104 beats/minute. Bilateral pelvic masses extending to the upper abdomen were found on pelvic examination. The masses felt cystic, with lobulated surfaces, and they were freely mobile. She had a hemoglobin level of 12.3 g/dL and hematocrit was 35.3%. Both estradiol and  $\beta$ -hCG levels were elevated (6,200 pg/mL and 143,393 mIU/mL, respectively). The CA-125 level was 440 IU/mL. Other laboratory findings, including thyroid function tests and androgen levels, were within normal limits, except for serum albumin level, which was slightly lower than normal (3.2 g/dL). Ultrasonography showed a 10-week old live single intrauterine fetus and bilateral multilocular cystic masses measuring 15 cm in size on the left and 10 cm on the right (Figure). A mild degree of ascites was also noted. Chest X-ray and Doppler ultrasonographic studies were normal.

Since the patient had a high level of CA-125, bilateral multicystic ovaries and ascites, we decided to perform paracentesis to rule out malignancy. Pathologic examination showed benign cytology.

Due to the patient's history and laboratory findings, the diagnosis of spontaneous OHSS was considered. We decided to manage the patient expectantly since her vital signs and general condition were stable. Ultrasonography was performed, and complete blood count, serum electrolytes and albumin concentrations were measured every other day.

During the following 6 weeks, the patient required no intervention and laboratory findings remained within normal ranges; the ascites resolved and the bilateral ovarian masses decreased in size to 7 cm on the left and 5.5 cm on the right. At 20 weeks of gestation, the cysts could not be seen. The patient by then had been taken into our normal prenatal follow-up procedure and delivered a healthy female baby at 39 weeks of gestation.

## Discussion

The pathophysiologic mechanism underlying OHSS has yet to be elucidated. The severity of the syndrome is related to the degree of ovarian follicular response. Estrogens, produced by the developing follicles, may reach high levels and serve as markers of the degree of ovarian hyperstimulation [1,2].

According to some authors, OHSS will not develop until final follicular maturation and luteinization occurs in response to hCG or luteinizing hormone; this process results in the ovarian secretion of vasoactive substances that cause increased capillary permeability, triggering this syndrome. Possible mediators of increased vascular permeability include vascular endothelial growth factor, components of the renin-angiotensin system and cytokines [2,3]. Kemmann et al have postulated that increased levels of estradiol and androgen, beside the absence of synchrony between follicular gathering and ripening, might be the predisposing factors in patients undergoing ovulation induction treatments and also in nonstimulated cases [4].

On the other hand, some authors have suggested the presence of an underlying polycystic ovary syndrome in these cases, with the typical hormonal and ovulatory alterations associated with this dysfunction [5,6].

In our case, there was no history of polycystic ovary syndrome. Although estradiol was significantly elevated, androgen levels were within the normal range.  $\beta$ -hCG was significantly elevated in our case, but some authors reported low levels of  $\beta$ -hCG in such cases [3]. Consequently,  $\beta$ -hCG may not be a trigger in every case.

OHSS may also be associated with hypothyroidism, and there are some reports in the literature that support this relationship [7,8]. Elevated thyroid stimulating hormone levels may mediate ovarian hyperstimulation via nuclear thyroid receptors in the granulosa cells. Thyroid function tests were within normal limits in the present case.

OHSS has also been described in twin and molar pregnancies [9]. Our patient had a singleton pregnancy and, despite the high level of  $\beta$ -hCG, we did not suspect molar pregnancy.

Paracentesis showed benign cytology, and Doppler ultrasonography was normal in our case, thus excluding the diagnosis of ovarian malignancy. Although serum CA-125 was high in this patient, serum CA-125 measurements are not useful for differential diagnosis since they are usually elevated, as expected in patients with gross ovarian enlargement.

Pregnancy luteoma and hyperreactio luteinalis are two rare entities that should be included in the differential diagnosis of spontaneous OHSS. These conditions

are associated with large ovarian masses and were originally thought to reflect different ends of a pathologic spectrum resulting from hyperresponsiveness to hCG. It now appears that they are distinct clinical entities.

Pregnancy luteoma, which is a nodular hyperplasia of luteinized gonadal stromal or thecal cells, generally emerges during the last trimester of pregnancy and regresses spontaneously after delivery [10,11]. Most of the patients with pregnancy luteoma in their 30s and 40s are multiparous. Virilization is common in these patients and in their female infants. This condition is frequently unilateral and nonpalpable. Since it is generally asymptomatic, the majority of cases are diagnosed unexpectedly by ultrasonography or during the course of cesarean section or tubal ligation.

On the other hand, hyperreactio luteinalis usually presents with bilateral ovarian enlargement, which is caused by multiple theca lutein cysts. Some authors suggest that spontaneous OHSS and hyperreactio luteinalis are entities in a continuum [12]. Hyperreactio luteinalis frequently occurs in patients with gestational trophoblastic disease, multiple pregnancies and fetal hydrops. It is rare in singleton pregnancies. Although this condition is generally asymptomatic, it may present with acute abdominal symptoms when hemorrhage into the cysts, rupture or torsion occur. Virilization is rare in this condition and the cysts resolve following delivery. The majority of cases occur in the third trimester or immediately postpartum. Hyperreactio luteinalis presents with a more indolent course and is usually seen later than spontaneous OHSS, which presents more acutely and earlier in pregnancy [10,11,13]. Finally, the cardinal feature of OHSS, increased vascular permeability as manifested by edema and ascites, is not a usual finding in pregnancy luteoma and hyperreactio luteinalis. Based on these, and given the clinical features of the case, the diagnosis of spontaneous OHSS was established for our patient.

Time of onset and duration of the condition in this patient obviously differ from that of iatrogenic OHSS, which is usually seen earlier in the course of pregnancy. Spontaneous forms of OHSS generally develop between 8 and 14 weeks of amenorrhea, differing from iatrogenic OHSS, which usually starts between 3 and 5 weeks of amenorrhea. The recent identification of mutations in the follicle stimulating hormone (FSH) receptor gene, which display an increased sensitivity to hCG and are responsible for the development of spontaneous OHSS, helps us to understand this problem [14]. In iatrogenic OHSS, the follicular recruitment and enlargement occur during the administration of exogenous FSH. In the spontaneous form however, the follicular recruitment and growth occur later through the

promiscuous stimulation, by pregnancy-derived hCG, of a mutated FSH receptor that is abnormally sensitive to hCG or a wildtype FSH receptor in the presence of abnormally high levels of hCG. Thus, the symptomatology of spontaneous cases of OHSS usually develops at 8 weeks' amenorrhea and culminates at the end of the first trimester of pregnancy.

Since the syndrome is usually self-limiting, many authors recommend the continuation of pregnancy. In almost all cases, the disease regresses spontaneously with time or delivery. On the other hand, deaths due to hypovolemia, hemorrhage and thromboembolic phenomena have been reported [15]. Hospitalization is required in most cases. Monitoring of hemodynamic status, intravenous crystalloid and albumin infusion and prophylaxis of thrombosis are the main principles of management [6,14]. Termination of pregnancy can be considered when conservative management fails, but surgery should be reserved for cases of ovarian rupture, torsion and intraperitoneal hemorrhage.

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