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Review

Spontaneous Ovarian Hyperstimulation Syndrome

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A B S T R A C T

Spontaneous forms of the ovarian hyperstimulation syndrome (sOHSS) are nearly always reported between 8 and 14 weeks of pregnancy and also with follicle-stimulating hormone (FSH) producing pituitary adenoma. The syndrome has been previously reported in rare instances of increased production of human chorionic gonadotrophin (hCG) such as multiple pregnancies, hydatiforme mole, polycystic ovary disease and elevated concentrations of thyroid-stimulating hormone (TSH) in hypothyreoidism. High levels of these hormones are able to stimulate by natural promiscuous activation the wild-type FSHr, resulting in sporadic presentations of the syndrome. Since 2003, only six different activating FSHr gene mutations have been reported in cases of familial or habitual sOHSS. In addition to five mutations which have been found in the transmembrane helices (Asp567Asn, Asp567Gly, Thr449Ile, Thr449Ala, Ile545Thr), the first germline mutation (c.383C > A, p. Ser 128 Tyr) in the extracelullar domain was identified. All five mutants were abnormally activated by TSH and normal levels of hCG while displaying constitutive activity. In contrast to these mutations, the p.Ser128Tyr mutant displayed an increase in sensitivity only toward hCG. Accordingly, the mutated FSHrs, may be hyperstimulated by the pregnancy-derived hCG or TSH, inducing the occurrence of the syndrome. In the differential diagnosis, malignancy, pregnancy luteoma and hyperreactio luteinalis would have to be excluded. In almost all of the cases the disease regresses spontaneously and could be managed expectantly or conservatively, but with termination of pregnancy or surgery in cases of complications.

Key words*: spontaneous ovarian hyperstimulation syndrome; pathogenesis; follicle-stimulation hormone mutations*

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a rare and potentially life-threatening complication during controlled ovarian stimulation. It can be associated with severe morbidity and may even be fatal. Fortunately, the prevalence of the severe form of OHSS is small, ranging from 0.5–5%, or 0.2–1% as calculated by the World Health Organization (WHO), of all stimulation cycles in assisted reproduction. It is typically an iatrogenic complication of ovulation induction associated with the use of exogenous gonadotrophins and human chorionic gonadotrophin (hCG), compounded by embryonic hCG in case of conception, occurring during the luteal phase or early pregnancy. In its most severe forms, OHSS involves massive ovarian enlargement with multiple cysts, vascular hyperpermeability, fluid shifts resulting in extravascular fluid accumulation, hypovolemia, hemoconcentration, renal failure, thromboembolic phenomena, and, even death[1].

However, some extremely rare forms of sOHSS were reported during pregnancy and may be associated with a spontaneous ovulatory cycle. sOHSS have also been associated with follicle-stimulation hormone (FSH) – producing pituitary adenoma and it is thus not restricted to pregnancies. The syndrome has been previously reported in rare instances, most often in situations where there is a supraphysiologic production of hCG, such as multiple gestations or hydatiforme mole, polycystic ovary disease and in cases of hypothyreoidism in pregnancy with the high levels of thyroid-stimulating hormone (TSH)[2]. On the other hand, there have been repeated reports of familial or habitual spontaneous cases of severe OHSS[3–5]. Recently, several mutations of the FSH-receptor (FSHr) were described in patients presenting with sOHSS of the first trimester of pregnancy with normal levels of hCG[4–6]. The absence or presence of FSHr mutations have allowed

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the creation of a pathophysiological classification of sOHSS into three types. Type I corresponds to the mutated FSHr cases, type II corresponds to the sOHSS secondary to high levels of hCG and the third one is related to hypothyreoidism[6].

Pathophysiology

In the pathophysiology of OHSS, hCG, either exogenous (to induce ovulation or as a luteal phase support) or endogenous (pregnancy derived), is the factor which triggers OHSS. Vascular endothelial growth factor (VEGF) and VEGF-2 receptors are produced in human granulosa-lutein cells and VEGF acts

through its receptors as the main mediator because of its prominent role in the pathologic vascular hyperpermeability in response to hCG. In addition to, hCG and VEGF individually produce a significant increase in VE-cadherin release, which is a soluble cell adhesion molecule involved in the loosening of endothelial intercellular junctions and may play a key role in the pathophysiology and progression of vascular hyperpermeability[7].

The pathophysiology of sOHSS has not been eluciated yet. In certain circumstances – for example, in multiple pregnancy or hydatid mole – it is theoretically possible that there could be a greater likelihood of OHSS, since hCG values may be raised above the normal level. However, even within these entities the prevalence of OHSS is very low and only several cases have been observed[8,9]. This could be taken as an indicator that hCG is a major, but not the only, triggering mechanism in OHSS. Moreover, after excluding the cases with FSHr mutations, gestational trophoblastic disease, multiple pregnancies and iatrogenic OHSS, none of the patients with elevated hCG experienced OHSS. It was suggested that elevated hCG cannot be responsible for OHSS as a single factor and a combination of mechanisms is responsible for this enigmatic disorder[10]. Other cases of sOHSS were associated with hypothyreoidism and it was suggested that the high levels of TSH could stimulate the ovaries[11,12]. In addition to, sOHSS in a woman with PCOS and in a singleton pregnancy with otherwise normal history have been described[13,14]. It has been shown in the cases of sOHSS with no mutations in the FSHr gene, that high levels of hCG or TSH were able to stimulate TSH and FSH receptors in conditions that mimic high ligand concentrations. High concentrations of hCG, as found in molar or multiple pregnancies, and increased levels of TSH in hypothyreoidism, could therefore also stimulate the wild-type FSH receptors expressed in developing follicles. This natural promiscuous activation of FSH receptors by high levels of hCG and TSH is the likely explanation for these sporadic sOHSS presentations[6,15].

Since 2003, in several mutations of the FSHr of familial or habitual sOHSS, a molecular basis for the pathophysiology of the sOHSS was identified and for the first time –genetic evidence of a defect in the FSHr was found. In addition to five different activating FSHr gene mutations which have been found only in the transmembrane helices (Asp567Asn, Asp567Gly, Thr449Ile, Thr449Ala, Ile545Thr), the first germline mutation (c.383C > A, p. Ser 128 Tyr) in the extracelullar domain of the FSHr responsible for sOHSS was identified. All five FSHr mutants were abnormally sensitive and activated by TSH and normal levels of hCG while displaying constitutive activity. Contrary to these mutations, the p.Ser128Tyr mutant displayed increase in affinity and sensitivity toward hCG and did not show any constitutive activity, nor promiscuous activity by TSH. The FSHr mutation appears to cause a reduction in ligand specifity, which allowes activation of the mutated receptor by hCG. When tested in vitro, the functional response of the mutant receptor displayed an enhanced basal activity and an increased sensitivity to hCG. The abnormal functionality of mutant FSH receptors in vitro provides a straightfoward explanation for their implication in the OHSS development in-vivo. The mutated FSHr expressed in the developing follicles, abnormally sensitive to hCG, may be hyperstimulated by the pregnancy-derived hCG. Accordingly, the follicles may start growing, enlarge and finally acquire luteinizing hormone receptors on granulosa cells which may also be stimulated by hCG, inducing massive follicular luteinization together with the secretion of vasoactive mediators responsible for the development of the syndrome. Moreover, TSH might also be capable of stimulating a mutated FSHr in the same way as hCG with hypothyreoidism[4–6,16–18]

In contrast, no mutations were found in the FSHr from patients with high hCG or TSH levels, indicating that for those patients, spontaneous OHSS results from the natural promiscuous stimulation of a wild-type FSHr by very high concentrations of hCG or TSH. However, in all patients in whom no mutation was found in the FSHr gene, the possibility that a somatic mutation with manifestations in the ovaries, but absent from leukocytes, which could be responsible for the syndrome, cannot be excluded. Such a mutation should occur very early in the development to account for the bilateral involvement of the ovaries, but in the absence of clinical indication for ovarian biopsies, this hypothesis could not be tested as suggested by Leener et al.[6].

This molecular basis for the pathophysiology of spontaneous OHSS opens up new perspectives for a better understanding of the way in which iatrogenic OHSS develops. While a mutation in the FSHr gene should be sought in patients with habitual or familial OHSS, it would be interesting in iatrogenic cases of severe hyperstimulation to search for mutations in the hormone receptor genes or glycoprotein hormone genes. It was found that the FSHr genotype did not play a significant role because of the absence of FSHr activating mutations in women with iatrogenic OHSS[19]. However, allelic variants of FSH receptors have been associated with the response to FSH in stimulation procedures, as well as with the severity of OHSS when present[20]. Although a significant enrichment in the allele N680 was observed as the severity of OHSS increased, identification of mutation of the FSHr, Ser680Asn, in the FSHr gene cannot enable which

patients will develop OHSS, but could predict the severity of symptoms among iatrogenic OHSS patients[21].

Clinical Figure

Symptoms in cases of sOHSS appear later than those in iatrogenic cases. Spontaneous forms of OHSS usually develop between 8 and 14 weeks of pregnancy, differing from iatrogenic OHSS generally starting between 3 and 5 weeks amenorrhoea. In spontaneous cases, massive enlargement of multiple follicles would be induced through the hyperstimulation of the FSHr by endogenous hCG, whereas in iatrogenic cases it would be induced endogenous by FSH before ovulation. Both the constitutive activity of the mutant receptor and its increased sensitivity to hCG would be implicated in the generation of sOHSS. Alternatively, the promiscuous activation of the FSHr by hCG might be sufficient to induce the condition, as suggested by the spontaneous occurrence of the syndrome in patients with trophoblastic disease. As hCG usually peaks between 8 and 10 weeks of pregnancy and declines thereafter, the initiation of follicular growth by pregnancy-derived hCG could start between 6 and 10 weeks amenorrhoea. The occurrence of the symptoms is closely related to the lifespan of the corpus luteum, and the development the syndrome is expected to occur in parallel to the massive follicular luteinization, thus between 8 and 14 weeks amenorrhoea culminating at the end of the first trimester of pregnancy[2,18].

Differential Diagnosis

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. Virilization is common in these patients and in their female infants. This condition is frequently unilateral and asymptomatic and the majority of cases are diagnosed unexpectedly by ultrasonograpy or during the course of cesarean section[22]. In contrast, hyperreactio luteinalis usually presents with bilateral ovarian enlargement, which is caused by multiple theca lutein cysts. It is generally asymptomatic and frequently occurs in patients with gestational trophoblastic disease, multiple pregnancies and fetal hydrops in the third trimester of pregnancy[23]. In very rare cases of idiopathic sOHSS secondary to supraphysiologic secretion of FSH, the presence of FSH-producing neuroendocrine tumour and pituitary adenoma should be considered[24,25]. To avoid unnecessary laparotomy, the importance of careful diagnosis with MR scans to differentiate spontaneous OHSS from ovarian cystic neoplasm should be emphasized[26].

Diagnosis

In cases of normal Doppler ultrasonography and benign ascitic cytology the possibility of malignancy could be ruled out, and the diagnosis of sOHSS should be considered[27]. The severity of the syndrome is related to the degree of ovarian follicular response and estrogens produced by the developing follicles, which may reach high levels. Therefore, an estradiol level could serve as a key marker of the degree of sOHSS[28].

Treatment

Clinicians must bear the differential diagnosis of sOHSS in mind if a patient presents with gross ascites and other symptoms of ovarian cancer, which also may be sign of OHSS. By taking all possible differential diagnoses into account, unnecessary laparotomy could be avoided [2.] Since the syndrome is usually self-limiting, many authors recommend the continuation of pregnancy. In the almost all cases the disease regresses spontaneously with the time or delivery. Although hospitalization is required in most cases the patient could be managed expectantly without complications[27]. Conservative management with thyroid hormone replacement seems to be the best therapeutic approach for sOHSS women with uncontrolled hypothyroidism[11]. Monitoring of hemodynamic status, intravenous crystalloid and albumin infusion, prophylaxis of thrombosis and paracentesis are the main principles of management[28]. Termination of pregnancy can be considered when conservative management fails, but surgery should be reserved only for cases of ovarian rupture, torsion and intraperitoneal hemorrhage[2,27].

Conclusion

Although sOHSS is a very rare complication of early pregnancy between 8 and 14 wweks of amenorrhea, it does not preclude a successful pregnancy outcome. The importance of differential diagnosis is advisable in order to prevent an unnecessary radical approach and to enable close observation with appropriate expectative and conservative management of the syndrome.

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SPONTANI OVARIJSKI HIPERSTIMULACIJSKI SINDROM

S A Ž E T A K

Spontani (s) oblici ovarijskog hiperstimulacijskog sindroma (OHSS) se javljaju skoro uvijek u trudnoći između 8. i 14. tjedna, no isto tako i kod adenoma adenohipofize nastalim nastalim s folikularno stimulirajućim hormonom (FSH). Ranije se sindrom javljao u rijetkim slučajevima povećanog stvaranja humanog korionskog gonadotropina (hCG) kao što su višestruke trudnoće, grozdasta mola, policističnih jajnika i povišenih koncentracija tiroidnog stimulirajućeg hormona (TSH) u hipotireozi. Povišene razine ovih hormona bi prirodnom miješanom aktivacijom poticale izvorni tip receptora (r) FSH, što bi rezultiralo sporadičnom slikom sindroma. Od 2003. g. objavljeno je samo 6 različitih aktivirajućih mutacija FSHr u slučajevima familijarnog ili habitualnog sOHSS. Pored 5 mutacija receptora koje su nađene u membrani heliksa (Asp567Asn, Asp567Gly, Thr449Ile, Thr449Ala, Ile545Thr), identificirana je i prva mutacija na izvanstaničnoj domeni (c.383C > A, p. Ser 128 Tyr). Svih 5 mutacija nepravilno se aktiviraju s TSH i normalnim razinama hCG, uz zadržavanje konstitucijske aktivnosti. Nasuprot ovim mutacijama, p.Ser128Tyr mutacija odražava povećanu osjetljivost samo prema hCG. Tako promijenjeni FSHr mogu biti stimulirani od strane hCG izvedenog iz iz trudnoće ili TSH, dovode do pojave sindroma. U diferencijalnoj dijagnozi treba isključiti zloćudnu bolest, luteom trudnoće te lutealnu hipereakciju. U gotovo svim slučajevima bolest nestaje spontano, a liječi se ekspektativno ili konzervativno, dok u slučaju komplikacija kirurški ili prekidom trudnoće.