New insights in mechanisms for development of ovarian hyperstimulation syndrome

Kasum, Miro

Coll. Antropol. **34** (2010) 3: 1139–1143
Review

New Insights in Mechanisms for Development of Ovarian Hyperstimulation Syndrome

Miro Kasum

Department of Obstetrics and Gynecology, School of Medicine, Zagreb University, Zagreb, Croatia

A B S T R A C T

The ovarian hyperstimulation syndrome (OHSS) is typically an iatrogenic complication of induction ovulation occurring during the luteal phase or early pregnancy. However, the spontaneous form of OHSS is extremely rare and always reported during pregnancy. Several cases have been observed during multiple pregnancies and other cases were associated with hypothyroidisem. Moreover, a few mutations of the follicle-stimulation hormone receptor (FSHr) were recently described in spontaneous OHSS and normal levels of human chorionic gonadotrophin (HCG). In these cases, a molecular basis for the pathogenesis of the spontaneous OHSS was identified. These mutations displayed promiscuous sensitivity and activation by both HCG and thyroid stimulating hormone (TSH). The disease always occurs in the presence of either exogenous or endogenous HCG which is thought to play a crucial role in the develpoment of OHSS. The hallmark of OHSS is an increase in capillary permeability resulting in a fluid shift from the intravascular compartment into the third space. It is assumed that HCG induces the release of certain ovarian vasoactive substances or mediators that have potent and direct systemic effects on the vascular system. It was demonstrated that the endothelium, along with the ovary is a primary target for HCG. Of all the different vasoactive components, vascular endothelial growth factor (VEGF) is the principal mediator and the most responsible for increased capillary permeability. It is produced and secreted in the ovary or in the endothelium, and acts through the VEGF receptor-2 or high affinity receptors (KDR and flt 1), respectively. In addition to VEGF, HCG may trigger activation of the renin-angiotensin system and kinin-kallikrein system together with releasing of interleukins (6,18), endothelial-cell adhesion molecules, von Willebrand factor, angiogenin and endothelin-1, that also increase vascular permeability.

Key words: *OHSS, pathogenesis, mediators, VEGF, FSH receptor*

Introduction

Ovarian hyperstimulation syndrome (OHSS) is almost in all cases an iatrogenic, and potentially life-threatening complication of ovarian stimulation. It is typically associated with the use of exogenous gonadotrophins and aggressive controlled ovarian hyperstimulation or occasionally with clomiphene citrate, occurring during the luteal phase or early pregnancy. However, some forms of OHSS always reported during pregnancy may be associated extremely rarely with a spontaneous ovulatory cycle, usually in the case of multiple gestations, hydatid mole, hypothyreoidism, polycystic ovary syndrome (PCOS), and follicle-stimulating hormone receptor (FSHr) mutations[1,2]. Spontaneous forms of OHSS are generally reported to develop between 8 and 14 weeks amenorrhoea, differing from iatrogenic OHSS usually starting between 3 and 5 weeks amenorrhoea.

In the initial form of OHSS, the increase in size of the ovaries is accompanied by abdominal discomfort. In a more advanced form, the ovaries become cystic and this will often result in abdominal distension and pain, nausea, vomiting and sometimes diarrhoea. Severe forms are characterized by a massive ovarian enlargement with the formation of multiple ovarian cysts associated with extravascular fluid shifts resulting in the development of ascites. This extravascular protein-rich exudate accumulates in the peritoneum, in the pleura, and even in the pericardiac space and is associated with intravascular

Received for publication March 1, 2009

volume depletion and haemoconcentration, hypoalbuminaemia, liver dysfunction, hypovolaemia, oliguria, electrolyte imbalance and thromboembolic phenomena. The manifestations of OHSS are believed to result from an increased capillary permeability of mesothelial surfaces under the action of one or several vasoactive factors, which leads to a loss of protein-rich fluid from the intravascular compartment into the third space[3]. Risk factors for developing OHSS include age <35 years, low body mass index, higher absolute or rapidly rising serum estradiol levels, PCOS, higher doses of exogenous gonadotrophins, and previous episodes of OHSS[4].

Since the 1960s, OHSS has been repeatedly reclassified and in some case, up to six grades of severity have been distinguished. A real effort to achieve a consensus on the modern classification of OHSS by a panel of experts should be made, in a manner similar to the consensus that had been reached by the professional societies on the definition of polycystic ovarian syndrome (Thesaloniki ESHRE/ASRM-Sponsored Consensus Workshop Group 2008)[5]. The overall incidence of OHSS is estimated at 0.6–14%, with 1–10% of cases being classified as mild to moderate and 0.2–5% as severe. The World Health Organisation (WHO) has calculated the world-wide incidence of severe OHSS as 0.2–1% of all cycles occurring in assisted reproduction. The mortality rate is estimated as one in 45,000 to one in 50,000[6]. Although the prevalence of the severe form of OHSS is small (0.2–5%) nevertheless, as this is an iatrogenic complication of a non-vital treatment with a potential fatally outcome, the syndrome remains a serious problem for specialists dealing with infertility.

The pathogenesis of OHSS is a complex process and still unclear. It is assumed that certain ovarian biosynthetic components produced in excess during induction of ovulation initiate the cascade of events that result in the syndrome. Human chorionic gonadotrophin (HCG) either exogenous or endogenous (e.g. pregnancy derived) is the factor which triggers OHSS and seems to be the pivotal stimulus of the syndrome in a susceptible woman, because elimination of HCG will prevent the full-blown picture of the syndrome[1,2]. Early OHSS is an acute consequence of the exogenous HCG administration before oocyte retrieval and is usually related to an excessive ovarian response to gonadotrophin stimulation. It is noteworthy that the kinetics of the symptoms are closely related to the lifespan of the corpus luteum. During iatrogenic OHSS, in the absence of pregnancy, the symptoms and complications will resolve spontaneously with the onset of the menses. Late OHSS is induced by endogenous HCG from the initiated pregnancy and is observed only in the patients who become pregnant, especially in those with more than one gestational sac, and is more likely to be severe. However, late OHSS is reported as being able to complicate a non-conception cycle also following additional administration of HCG during the luteal phase. OHSS with onset >10 days after oocyte retrieval is classified as »late« OHSS and the earlier onset as »early« OHSS. Although late onset OHSS is strongly associated with pregnancy, a surprisingly high initial pregnancy rate was observed even in early OHSS (50% *per* embryo transfer) and a higher risk of preclinical miscarriage rate (31.8%)[7].

The pathophysiology of spontaneous OHSS has not yet been eluciated. In certain circumstances – for example, in multiple pregnancy, hydatid mole or PCOS – 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 because only several cases have been observed. This could be taken as an indicator that HCG is a major – but not the only – triggering mechanism in OHSS[8]. Moreover, after exclusion the cases with 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 may allow understanding of this enigmatic disorder[9]. Other cases of spontaneous OHSS were associated with hypothyreoidism and it was suggested that the high levels of thyroid-stimulating hormone (TSH) could stimulate the ovaries[10]. On the other hand, there have been several reports of familial or habitual spontaneous cases of severe OHSS. In these cases, a molecular basis for the pathophysiology of the spontaneus OHSS was identified for the first time because molecular–genetic evidence of a defect in the FSHr was found[2]. The recent identification of mutations in the FSHr gene in several patients shows that mutations may have a role in certain forms of OHSS. The FSHr mutation appears to cause a reduction in ligand specifity, which allows 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 (LH) receptors on granulosa cells which may also be stimuated by HCG, inducing massive follicular luteinization together with the secretion of vasoactive mediators responsible for the development of the syndrome. The interaction between HCG and FSHr could be an essential prerequisite in the development of spontaneous OHSS and could explain why symptoms in spontaneous cases of OHSS appear later than in iatrogenic. Moreover, high levels of thyroid-stimulating hormone (TSH) might be also capable of stimulating a mutated FSHr in the same way as HCG with hypothyroidism[10,11]. In addition to five different activating FSHr gene polymorphisms which were recently described, Asp567Asn, Asp567Gly, Thr449Ile, Thr449Ala, Ile445Thr, a new mutation, Ile445Thr, was found in a patient with spontaneous OHSS of the first trimester of pregnancy with a normal

HCG level. When tested functionally, this mutant displayed promiscuous activation by both HCG and TSH together with detactable constitutive activitiy. In constrast, no mutations were found in the FSHr 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 concetrations of HCG or TSH[12]. 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 polymorphisms in the hormone receptor genes or glycoprotein hormone genes. However, 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[13].

Recent investigations have focused on various vasoactive substances and mediators, because it is clear that profound alterations in the vascular compartment are the major initial changes that lead to the full appearence and maintenance of OHSS. Thus, either exogenous or endogenous HCG may induce the release of mediator that has potent and direct systemic effects on the vascular system and that may be responsible for the pathophysiology and clinical consequences. Among the many candidates that may mediate the action of HCG on the vascular tree, there are few that are highly involved in the pathogenesis of the syndrome: vascular endothelial growth factor (VEGF), other cytokines (interleukins 1, 2, 6, 8, 10, 18 and tumor necrosis factor-alfa), estradiol, prostaglandins, ovarian-renin angiotensin system, insulin-like growth factor 1, epidermal growth factor, transforming growth factors, von Willebrand factor, endothelial adhesion molecules, angiogenin, endothelin-1, ovarian kinin-kalikrein system and histamines[1,14].

Of all the different candidates, VEGF, also known as vascular permeability factor, has been proposed as the main cytokine involved in the pathophysiology of OHSS. Current findings suggest that this heparin-binding dimeric polypeptid, with a moleular weight of 40–46 kDa, is the principal mediator and the most responsible for increased capillary permeability leading to extravasation of protein-rich fluid and subsequently OHSS. It has been shown that VEGF increase dramatically after HCG stimulation suggesting a role for HCG hormone regulation of VEGF production and secretion in luteinized granulosa cells[15]. Using an in-vivo murine model to induce OHSS it was clearly demonstrated that VEGF is produced, expressed and secreted in the ovary and that it acts through the VEGF receptor-2 to increase vascular permeability in response to HCG. The reversal of the increased vascular permeability using a synthetic VEGF receptor-2 inhibitor (SU5416) provides new insights into the prevention of OHSS[16]. Another potential source and target for vasoactive substances is the endothelium because high-affinity VEGF receptors (KDR and flt1) are located almost exclusively in the vascular endothelia. It was demonstrated that the endothelium, along with the ovary, is a primary target for HCG. As a result, VEGF and its KDR receptors are stimulated, resulting in an accute release of VEGF and increased capillary permeability in response to HCG. Blocking VEGF action with specific antibodies prevents the changes induced by HCG such as modifications in the actin fibers indicative of increased capillary permeability observed by confocal microscopy[17]. Permeability assays demonstrated that vascular endothelial cadherin, an interendothelial adhesion molecule, may play a role in the development and progression of severe capillary permeability in severe OHSS. HCG and VEGF produce a significant increase in vascular endothelial cadherine release, which is involved in the loosening of endothelial intercellular junctions[18,19]. A novel paradigm suggests that HCG can increase endothelial permeability by up-regulating VEGF in co-cultures of luteinized granulosa cells, by altering expression of the endothelial cell-specific adhesion protein claudin-5[20]. It is a clinical observation that not all women with a high response develop OHSS and absolute values of serum VEGF seem useless in predicting which woman will develope OHSS[21]. This individual variability was related to significantly higher level of alfa2-macroglobulin, that binds VEGF to a greater degree than occurs in patients who develop OHSS. Patients who had a raised alfa2-macroglobulin value in the stimulation phase developed OHSS less frequently. Interestingly, a major serum protein, alfa2-macroglobulin, plays an important role as an antagonist to VEGF and influencing the severity of OHSS, suggesting that it may act by removing and inactivating free VEGF[22].

In addition to VEGF as the principal mediator by which HCG might increase capillary permeability in OHSS, other cytokines – particullary interleukins 1, 2, 6, 8, 10, 18 and tumor necrosis factor-alfa – appear to be involved in the aggravation of OHSS. Significantly higher levels have been observed particularly in ascites and serum from OHSS patients. A statistically significant correlation between serum interleukins (6, 18) and capillary hyperpermeability was recorded, suggesting a possible role in the pathophysiology of severe OHSS[23,24]. Because estrogen levels are greatly elevated in OHSS patients, it was postulated that the increase in its production causes the increase in capillary permeability. If the values are over 3000–3500 pg/mL at the time of HCG injection, the risk of developing OHSS is high. However, its reliability has been questioned especially since OHSS also occurs in patients who conceive spontaneously and whose pre-ovulatory estradiol levels are far less than those encountered after pharmacological ovarian stimulation. Therefore, most research groups consider that estradiol is not an active mediator of OHSS, but rather that high serum values make it a marker hormone for patients who are at risk[25]. Patients with PCOS who have a tendency towards OHSS usually have insulin resistence and increased insulin levels. Although insulin can stimulate the release of VEGF in the corpus luteum, serum insulin levels do not

appear raised in OHSS patients[26]. In patients with OHSS, there is a marked increase in the serum levels of plasma renin, norepinephrine, vasopressin, and atrial natriuretic peptide. In early-onset OHSS, HCG may trigger activation of the renin-angiotensin system in addition to the release of VEGF and other mediators. Gonadotrophins, as well as HCG, increase production of the renin from prorenin in luteinized thecal cells and its activity in the follicle and in peritoneal fluid. Activation of the renin-angiotensin system is apparently a causative pathological mechanism in the development of OHSS[27]. There also appears that activation of the kinin-kallikrein system enhances capillary permeability and vasodilatation in OHSS patients[28]. Three of the best examined endothelial-cell adhesion molecules (E-selectin, vascular cell adhesion molecule-1 and intercellular adhesion molecule-1), were shown to be elevated in ascitic fluid and serum of patients with severe OHSS. The exaggerated leukcyte recruitment and transendothelial migration described in OHSS may cause leukocyte-mediated tissue damage and capillary hyperpermeability, linking these molecules in the pathogenesis of the syndrome[29]. In severe cases of OHSS prior to clinical manifestations, von Willebrand factor, a large adhesive glycoprotein, is also released in excess amounts by endothelial lesions. This could be helpful in planning early, prophylactic treatment of the syndrome[30]. The polypeptide angiogenin was shown to be increased 40-fold in serum and 10-fold in ascitic fluid in women with OHSS compared with women undergoing ovulation induction who did not suffer from OHSS. Thus, angiogenin may play a role in the process of increased vascular permeability in patients wih OHSS[31]. The endothelial derived peptide known as endothelin-1 is a potent vasoconstrictor that also increases vascular permeability with other vasoactive factors[32]. The role of prostaglandins and histamine is secondary to other factors and there is no evidence for their primary role in the pathogenesis of OHSS[1,2].

In conclusion, several recent findings of FSHr mutations which allow activation of the mutated receptor by HCG in patients with spontaneous OHSS and normal levels of HCG, provide the molecular basis for the pathogenesis of the syndrome. Either exogenous or endogenous HCG is thought to play a crucial role in the development of OHSS. It is assumed that HCG induces the release of certain ovarian byosythetic components or mediators that are thought to be responsible for the increased capillary permeability. Of all the different vasoactive substances, VEGF has been proposed as the main cytokine in the pathophysiology of OHSS, in addition to interleukins, ovarian renin-angiotesin system, kinin-kallikrein system, von Willebrand factor, endothelial-cell adhesion molecules, angiogenin and endothelin-1.

REFERENCES

1. GARCIA-VELASCO JA, PELLICER A, Curr Opin Obstet Gynecol, 15 (2003) 251. — 2. BINDER H, DITTRICH R, EINHAUS F, KRIEG J, MUELER A, STRAUS R, BECKMANN MW, CAPISTI S, Int J Fertil, 52 (2007) 11. — 3. DELVIGNE A, ROZENBERG S, Hum Reprod, 8 (2002) 559. — 4. ARAMWIT P, PRUKSANANONDA K, KASETTRATAT N, JAMMEECHAI K, Am J Health Syst Pharm, 65 (2008) 1148. — 5. GOLAN A, WEISSMAN A, Reprod BioMed Online, 19 (2009) 28. — 6. KOL S, Hum Reprod, 18 (2003) 1557. — 7. PAPANIKOLAOU EG, TOURNAYE H, VERPOEST W, CAMUS M, VERNAEVE V, VAN STEIRTEGHEM A, DEVROEY P, Hum Reprod, 20 (2005) 636. — 8. LUDWIG M, GEMBRUCH U, BAUER O, DIEDRICH K, Hum Reprod, 13 (1998) 2082. — 9. MICHAELSON-COHEN R, ALTARESCU G, BELLER U, REENS R, HALEVY-SHALEM T, ELDAR-GEVA T, Fertil Steril, 90 (2008) 1869. — 10. BORNA S, NASERY A, Fertil Steril, 88 (2007) 705. — 11. DELBAERE A, SMITS G, OLANTUNBOSUN O, PIERSON R, VASSART G, COSTAGLIOLA S, Hum Reprod, 19 (2004) 486. — 12. DE LEENER A, MONTANELLI L, VAN DURME J, CHAE H, SMITS G, VASSART G, COSTAGLIOLLA S, J Clin Endocrinol Metab, 91 (2006) 555. — 13. D ALVA CB, SERAFINI P, KOHEK MB, LATRONICO AC, MENDONCA B, Fertil Steril, 83 (2005) 1695. — 14. PELLICER A, ALBERT C, MERCADER A, BONILLA-MUSOLES F, REMOHI J, SIMON C, Fertil Steril, 71 (1999) 482. — 15. WANG T, HORNG S, CHANG C, WU H, TSAI Y, WANG H, SOONG Y, J Clin Endocrinol Metab, 87 (2002) 3300. — 16. GOMEZ R, SIMON C, REMOHI J, PELLICER A, Endocrinology, 143 (2002) 4339. — 17. ALBERT C, GARRIDO N, MERCADER A, RAO CV, REMOHI J, SIMON C, PELLICER A, Mol Hum Reprod, 8 (2002) 409. — 18. VILLASANTE A, PACHECO A, RUIZ A, PELLICER A, GARCIA-VELASCO A, J Clin Endocrinol Metab, 92 (2006) 314. — 19. SOARES SR, GOMEZ R, GARCIA-VELASCO A, PELLIUCER A, Hum Reprod Update, 14 (2007) 321. — 20. RODEWALD M, HERR D, DUNCAN WC, FRASER HM, HACK G, KONRAD R, GAGSTEIGER F, KREINBERG R, WULFF C, Hum Reprod, 24 (2009) 1191. — 21. MATHUR R, HAYMAN G, BANSAI A, JENKINS J, Fertil Steril, 78 (2002) 1154. — 22. MCELINNEY B, ARDILL J, CALDWELL C, MCCLURE N, Hum Reprod, 17 (2002) 1548. — 23. RIZK B, ABOULGHAR M, SMITZ J, RON-EL R, Hum Reprod Update, 3 (1997) 255. — 24. BARAK V, ELCHALAL U, EDELSTEIN M, KALICKMAN I, LEWIN A, ABRAMOV Y, Fertil Steril, 82 (2004) 415. — 25. ABOULGHAR, Hum Reprod, 18 (2003) 1140. — 26. DELVIGNE A, KOSTYLA K, DE LEENER A, LEJEUNE B, CANTINIAUX B, BERGMANN P, ROSENBERG S, Hum Reprod, 17 (2002) 1994. — 27. ANDO H, FURUGORI K, SHIBATA D, HARATA T, MURATA Y, MIZUTANI S, Hum Reprod, 18 (2003) 1219. — 28. UJIOKA T, MATSUURA K, TANAKA N, OKAMURA H, Hum Reprod, 13 (1998) 3009. — 29. GARCIA-VELASCO JA, ARICI A, Clin N Am, 13 (2002) 127. — 30. OGAWA S, MINAKAMI H, ARAKI S, OHNO T, MOTOYAMA M, SHIBAHARA H, SATO I, J Assist Repod Genet, 18 (2001) 114. — 31. ABOUGHAR MA, MANSOUR RT, SEROUR GI, ELHELW BA, SHAARAWY M, Hum Reprod, 13 (1998) 2068. — 32. DAVIS JS, RUEDA BR, SPANEL-BOROWSKI K, Reprod Biol Endocrinol, 1 (2003) 89.

M. Kasum

University Department of Obstetrics and Gynecology, Petrova 13, 10 000 Zagreb, Croatia
e-mail: mkasum@gmail.com

NOVI UVIDI U MEHANIZMIMA NASTANKA OVARIJSKOG HIPERSTIMULACIJSKOG SINDROMA

S A Ž E T A K

Ovarijski hiperstimulacijski sindrom (OHS) je tipična jatrogena komplikacija indukcije ovulacije koja se javlja u luteinskoj fazi ciklusa ili u ranoj trudnoći. No, spontani oblik OHS je iznimno rijedak i javlja se uvijek u trudnoći. Nekoliko ih je slučajeva opaženo za vrijeme višestrukih trudnoća, dok su drugi slučajevi bili povezani s hipotireozom. Pored toga, nedavno je kod spontanog OHS s normalnim razinama humanog korionskog gonadotropina (HCG) opisano nekoliko mutacija folikularno stimulirajućeg hormona (FSH). U tim slučajevima prepoznata je molekularna osnova u nastanku spontanog OHS. Takve mutacije odražavaju miješanu osjetljivost i aktivnost prema HCG i prema tireoidnom stimulirajućem hormonu (TSH). OHS se javlja uvijek nazočnosti egzogenog ili endogenog HCG za kojeg se smatra da igra glavnu ulogu u razvijanju bolesti. Pojačana kapilarna propusnost je obilježje OHS koje rezultira pomakom tekućine iz intravaskularnog prostora u odjeljak trećeg prostora. Smatra se da HCG inducira otpuštanje vazoaktivnih tvari ili medijatora, koje imaju snažne i izravne učinke na krvožilni sustav. Pokazano je da su endometrij kao i jajnik primarna ciljna mjesta na koja djeluje HCG. Od svih raznovrsnih vazoaktivnih tvari, vaskularni endotelni faktor rasta (VEFR) je glavni medijator i najodgovorniji za pojačanu kapilarnu propusnost. On nastaje i luči se u jajniku i endotelu, a djeluje preko svojih receptora tipa-2 odnosno KDR i flt 1. Osim poticanja VEGF, HCG može aktivirati sustave renin-angiotenzina i kinin-kalikreina sustav, a isto tako otpušta interleukine (6,18), adhezivne molekule endotela, Willebrandov faktor, angiogenin i endotelin-1, koji isto povisuju vaskularnu propusnost.