Regulation of endothelial permeability in the primate corpora lutea: implications for ovarian hyperstimulation syndrome

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Abstract

In a developing human corpus luteum, a closely regulated cellular communication system exists between the luteal steroidogenic cells and endothelial cells. This system guarantees the vascularization process during luteal formation. The process is combined with rapid release of large amounts of progesterone into the bloodstream. The regulation of endothelial proliferation and permeability by LH and human chorionic gonadotropin (hCG) is integral to this process. On the cellular level, endothelial permeability is regulated by intercellular junctions, such as adherens junctions (AJ) and tight junctions (TJ), which act as zipper-like structures between interacting endothelial cells. Several cell junctional proteins are localized to the corpus luteum, including Occludin, Nectin 2, Claudin 1, and Claudin 5, as well as, vascular endothelial (VE)-Cadherin. It has been assumed that regulation of AJ- and TJ-proteins is of particular importance for permeability, and accordingly, for the functionality of the corpus luteum in early pregnancy, because treatment with hCG induces downregulation of junctional proteins in the luteal vessels. The effect of hCG on the adhesive molecules is mediated by VE growth factor (VEGF). On a functional level, the hCG-dependent and VEGF-mediated decrease in junctional proteins causes a decrease in the density of cell–cell closure and, accordingly, an increase in endothelial permeability. In doing so, the different junctional proteins are not only directly influenced by VEGF but also interact among themselves and influence each other reciprocally. Disturbances in this strictly, regulated interactions may explain the development of pathologies with increased vascular permeability, such as the ovarian hyperstimulation syndrome.

Introduction

The corpus luteum is a transitory active endocrine gland undergoing cyclic growth and degeneration. It plays a central role in the maintenance of pregnancy. The preovulatory luteinizing hormone (LH) surge causes ovulation and rapidly initiates the transformation of ovulated follicle into corpus luteum. Thus resulting in progesterone synthesis, which is essential for implantation and maintenance of gestation (Stocco et al. 2007). In primates, if pregnancy does not occur, regression of the corpus luteum occurs 14 days after ovulation. However, in case of pregnancy, the survival of the corpus luteum is dependent on the effect of human chorionic gonadotropin (hCG) synthesized in the placenta (Matsubara et al. 2000, Baird et al. 2003, Duncan et al. 2005, Del Canto et al. 2007, Dickinson et al. 2008, 2009). In the absence of pregnancy, maintenance of the mid-luteal corpus luteum can be achieved by administration of iatrogenic exogenous hCG (Illingworth & Heap 1971). In addition to fibroblasts, pericytes, and immune cells, the corpus luteum consists of endothelial cells, granulosa lutein cells, and theca lutein cells (in non-primates, the latter are often also called small or large steroidogenic luteal cells). Granulosa lutein cells are capable of triggering angiogenesis, by causing sprouting from proximal blood vessels to obtain nutrients, oxygen, and hormone precursors: all of which are necessary to produce large amounts of progesterone (Fraser & Lunn 2001). Along with the necessary angiogenesis for progesterone synthesis, the permeability of luteal vessels must be tightly regulated. This regulation ensures the entry of nutrients, oxygen, and hormone precursors into the tissue, as well as, the release of progesterone from the tissue into the vessels. The responsible factors for controlling vascular permeability are thereby endothelial cells and cell–cell junctions. Permeability is mediated by strictly regulating the opening and closing of the cell–cell junctions (Bazzoni & Dejana 2004, Dejana 2004, Walz et al. 2005). Therefore, any disturbance in junctional organization might result in an inadequate endothelial function, leading to pathological conditions, due to
vessel wall structural modification. Typical clinically important examples caused by increased vascular permeability are edema and ovarian hyperstimulation syndrome (OHSS), which includes abdominal bloating and feeling of fullness, nausea, diarrhea, and slight weight gain, and which is associated with assisted reproduction (Delvigne & Rozenberg 2003). During assisted reproduction procedures, hCG administration is used to induce ovulation and luteinization of the ruptured follicles thus enhancing the risk of OHSS (Fatemi et al. 2007). This syndrome is characterized by increased capillary permeability leading to leakage of fluid from the vascular compartment (Delvigne & Rozenberg 2002). Therefore, further understanding of the molecular regulation of the corpus luteum might help in the treatment of OHSS not only symptomatically but also influencing the causal connection. This review aims to summarize the cellular regulation of endothelial permeability in primate corpora lutea and its implication on OHSS.

**Basics of cell–cell communication and molecular regulation of endothelial permeability**

Endothelial cells function as doormen, regulating the transfer of molecules into the vasculature and the underlying tissue. In addition, diverse junctions also have a key regulatory function such as gap junctions, adherens junctions (AJ), and tight junctions (TJ). Gap junctions are intercellular connections between cells, connecting the cytoplasm of two cells directly, thus allowing various molecules and ions to pass freely between cells (Lampe & Lau 2004). Regarding the regulation of paracellular permeability, at least two different types of intercellular junctions are involved: the AJ and TJ. These junctions are localized in the lateral cell membrane between neighboring endothelial cells (Fig. 1), sealing the space between the cells. The AJ and TJ are formed by different families of transmembrane proteins that promote homophilic cell–cell interactions and transfer of intracellular signals (Dejana et al. 2009a). Many reports support the concept that intercellular junctions are dynamically remodeled not only in embryogenic cells, but also in resting cells (Dejana et al. 2009b). Adhesive membrane proteins of AJ and TJ form adhesive complexes, which act as zipper-like structures between interacting cells (Nelson & Veshnock 1987, Yap et al. 1997, Chitaev & Troyanovsky 1998, Cavey et al. 2008). These proteins are localized hierarchically from the apical to the basal pole of the lateral membrane. In the most apical position, the Claudin TJ protein family is localized followed by Occludin and the Nectin family (Morita et al. 1999). Unlike the TJ, the AJs are localized more basal than apical, mainly consisting of the cadherin family (Fig. 1). The endothelial cells express tissue-specific transmembrane adhesion proteins: the AJ vascular endothelial (VE)-Cadherin, the TJ Claudin 5, and the TJ Nectin 2 (Nitta et al. 2003, Dejana 2004, Herr et al. 2013). VE-Cadherin and Claudin 5 are key components of adherens and tight endothelial junctions respectively. It has been suggested that VE-Cadherin controls Claudin 5 expression by preventing the nuclear accumulation of FOXO1 and β-catenin, which repress the Claudin 5 promoter. This indicates that a crosstalk mechanism operates between these junctional structures (Gavard & Gutkind 2008; Fig. 1). Knockdown of Claudin 5 in mice is associated with normal embryological development, yet due to a defective blood–brain barrier function, the Claudin 5-deficient mice die shortly after birth (Nitta et al. 2003). In comparison, VE-Cadherin deficient mice experience severe lethal defects during developmental angiogenesis (Carmeliet et al. 1999). This suggests a role for VE-Cadherin going far beyond promoting only structural functions between endothelial cells. In addition to VE-Cadherin and Claudin 5 interactions, the Nectin-system has recently been described as a novel modulator of AJ and TJ. Nectin consists of at least four members (Nectin 1–4). However, the focus of this paper is on Nectin 2, because it is the only member of the Nectin system that could be localized to the endothelium of the granulosa lutein compartment of the primate corpus luteum (D Herr, I Bekes and C Wulff, unpublished observation).

**Distribution of cell junctional proteins in the human corpus luteum**

The distribution of TJ and AJ in the primate CL is summarized in Table 1. Different cell junctional
proteins are localized in the mid-luteal human corpus luteum, including the TJ proteins Occludin, Claudin 1, Claudin 5, and Nectin 2, as well as the AJ protein VE-Cadherin (Groten et al. 2006, Herr et al. 2013). The distribution of these cell–cell contacts varies in different cellular compartments within the corpus luteum. In humans, Occludin is continuously localized in the plasma membrane of endothelial cells of mid-luteal granulosa lutein and theca capillaries as well as in the granulosa lutein cells itself. However, Occludin could not be detected in the theca lutein cells (Groten et al. 2006). The presence of Occludin in epithelial and endothelial cells has also been discovered in other species tissues, such as rat lung, human liver, mouse brain, and others (Langbein et al. 2002, Leach et al. 2002, Butt et al. 2012, Errede et al. 2012, You et al. 2012).

On the other hand, Claudin 1 is exclusively localized in the plasma membrane of granulosa lutein cells. Unlike the Occludin, which has a continuous belt-like formation, Claudin 1 during early-, mid-, and late-luteal phases of the human corpus is discontinuous (Groten et al. 2006). This distribution is similar to that seen in the human ovarian surface epithelium (Zhu et al. 2004). However, Claudin 1 is unexpressed in the luteal endothelial compartment. This is different compared with endothelial cells of the brain and of rat salivary glands (Fujibe et al. 2004, Peppi & Ghabriel 2004). In contrast to Claudin 1, Claudin 5 is exclusively localized in the endothelial compartment of the human corpus luteum (Groten et al. 2006). Claudin 5 is mainly expressed in capillaries and in large vessels of the theca endothelium (Groten et al. 2006). However, VE-Cadherin occurs in both, capillary endothelium of the granulose lutein and theca compartment of the corpus luteum (Groten et al. 2006). There is no exact explanation for the varied regulated expression of those molecules, yet it is clear that in diverse cellular compartments a certain combination of various adhesion and junctional proteins are responsible for cell–cell communication and adhesion (Groten et al. 2006; Table 1).

### Functional influence of hCG on cell junctional proteins in the human corpus luteum

The cyclic growth and differentiation of the corpus luteum are regulated by gonadotropins (Fraser et al. 1999, Fraser & Lunn 2000, Wulff et al. 2001a, Fraser & Duncan 2005). Within normal cycle, influenced by LH, the lifespan of the primate corpus luteum is generally restricted to 14 days. However, in case of pregnancy, due to hCG, it survives several months, which is called ‘luteal rescue’. For the human corpus luteum, it has been demonstrated that luteal rescue is associated with the expansion of luteal vessels (Wulff et al. 2001a), which probably includes the re-arrangement of cell–cell contacts such as junctional proteins. Therefore, it is of high interest to focus on hCG-dependent regulation of TJ and AJ in human corpus luteum.

In the rescued human corpus luteum of simulated early pregnancy (women who had received hCG exogenously), Claudin 1 and Occludin are significantly down-regulated in the granulosa lutein compartment (Groten et al. 2006). Furthermore, luteal rescue by hCG induced a decrease in Occludin, Claudin 5, and VE-Cadherin in the endothelial cell compartment of human corpora lutea (Groten et al. 2006). This observation is in line with studies in rats in which hCG deceased the expression of Claudin 5 mRNA (Kitajima et al. 2006), which was associated with increased vascular permeability (Albert et al. 2002, Kitajima et al. 2006).

It has been assumed that regulation of AJ and TJ proteins is highly important for supporting the corpus luteum function in the maintenance of early pregnancy. Downregulation of cell junctions may be required to increase intercellular space, ensuring invasion and expansion of new vessels within the granulosa lutein cell compartment, and it may also be required for increasing endothelial permeability in the vascular compartment (Rodewald et al. 2007) to be able to release and uptake molecules such as progesterone or VEGF (Wulff et al. 2000). This increase may facilitate the distribution of hormones needed for the maintenance of early pregnancy.

### Influence of VEGF on cell junctional proteins in the primate ovary

It has been shown that hCG decreases the amount of cell–cell adhesion molecules with its above-described effects on luteal angiogenesis and permeability. In addition, as inhibition of VEGF has major hindering effects on ovarian angiogenesis, development, and function (Wulff et al. 2001b, 2002, Taylor et al. 2007), there are data supporting the hypothesis that VEGF controls cell junctional proteins in the mid-luteal phase of the primary corpus luteum of the marmoset (Rodewald et al. 2007). The TJ protein Occludin is localized to the plasma membrane of granulosa cells

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Table 1 Distribution of junctional proteins in the primate corpus luteum based on immunolocalization of TJ and AJ proteins in the CL from the mid-luteal stage (Groten et al. 2006, Herr et al. 2013).

<table>
<thead>
<tr>
<th>Protein</th>
<th>Endothelium (granulosa compartment)</th>
<th>Endothelium (theca compartment)</th>
<th>Granulosa lutein cells</th>
<th>Theca lutein cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occludin</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Claudin 1</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Claudin 5</td>
<td>Present</td>
<td>Present (large vessels)</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>VE-Cadherin</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Nectin 2</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
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</table>
(Rodewald et al. 2007). In primates (marmoset), during follicular development, the amount of Occludin decreases continuously and disappears completely at the ovulatory stage (Rodewald et al. 2007). The loss of Occludin may be involved in antrum formation, because antrum formation involves alteration in granulosa cell–cell adhesion and sealing. This observation is supported by immunoblot studies in rat and mouse granulosa cells of antral follicle, showing decreased amount of adhesion molecules (Sundfeldt et al. 2000, Kawagishi et al. 2005).

However, inhibition of VEGF in marmoset in vivo, by treating with VEGF-antagonist VEGF-trap leads to a significant increase in Occludin (Rodewald et al. 2007). Thereby, focus of the staining is the cytoplasm. Nevertheless, the percentage of the protein which is localized in the cytoplasm is non-functional (Alexander & Elrod 2002). Accordingly, inhibition of normal vascular development severely affects cell–cell adhesion and communication in the granulosa compartment through the disruption of Occludin-delineated TJ (Schmitt et al. 2004).

The TJ protein Claudin 5 in the marmoset follicle is exclusively localized to vessels of the theca cell compartment, and the amount of protein increases during follicular development (Rodewald et al. 2007). During mid-luteal corpus luteum, Claudin 5 is also present in the vasculature and an increase in Claudin 5 results from inhibition of VEGF by a VEGF trap. Evidently, Claudin 5 plays a role in contact-inhibition of endothelial cells, thus decreasing the endothelial cell proliferation and the vessels being stabilized (Rodewald et al. 2007). As soon as endothelial cells are in contact with the neighboring cells, the adhesion molecules link together and the cells become less affected by the pro-angiogenic effect of VEGF (Rodewald et al. 2007). Cell-adhesion is crucial for angiogenesis regulation (Nakhuda et al. 2005). It has been shown, that inhibition of VE-Cadherin is followed by suppression of angiogenesis and degeneration of the vascular compartment in the mid-luteal phase corpus luteum (Nakhuda et al. 2005). VEGF acts as a key molecule for the regulation of angiogenesis in the ovary (Wulff et al. 2000, 2001a,b,c, 2002). In addition, a close interrelation has been shown between VEGF and adhesion signaling pathways. Endothelial AJ are a downstream target of VEGFR2 signalling suggesting to be involved in the modulation of endothelial permeability (Esser et al. 1998). Therefore, it is reasonable that inhibition of VEGF in vivo affects the Claudin 5 protein localization and expression in the ovary (Rodewald et al. 2007).

Cell junctional proteins and permeability

Recently, using endothelial cells (HUVEC) in an in vitro model, it has been suggested that hCG may have a direct effect on endothelial permeability and VE-Cadherin expression (Villasante et al. 2007). However, the meaning and signaling of an assumed endothelial cell LH/hCG receptor are unclear. It is most likely that the receptor has a hormone transcytosis function, meaning that the gonadotropin can be delivered through the endothelium to the target cell (Misrahi et al. 1996). In order to investigate the cellular regulation of endothelial cells in the corpus luteum, an in vitro human cell co-culture representation was developed as a model for studying the effects of stimulatory agents on endothelial and granulosa lutein cells, as well as the molecular interactions between those cells (Rodewald et al. 2009). It has been previously published that during simulated maternal recognition of pregnancy, there is a decrease in luteal endothelial Claudin 5 protein in the presence of hCG (Groten et al. 2006). Moreover, a paracrine effect of hCG on endothelial Claudin 5, as well as on endothelial permeability, was observed in the presence of granulosa lutein cells (Rodewald et al. 2009). The major effect of hCG on endothelial permeability and Claudin 5 expression remains indirect, occurring only in the presence of granulosa lutein cells. Therefore, an hCG-dependent factor secreted by granulosa lutein cells was likely to be responsible, and this factor effecting endothelial cells is VEGF. Indeed, hCG stimulation of granulosa lutein cells increased VEGF protein production, as has been shown in previous papers (Neulen et al. 1998, Fraser et al. 2005, Rodewald et al. 2009). In addition, hCG has been demonstrated to trigger VEGF expression in human luteal steroidogenic cells in vivo (Wulff et al. 2001c). Increased levels of VEGF are capable of acting directly on neighboring endothelial cell (Rodewald et al. 2009). The regulatory function of VEGF on endothelial cell permeability has previously been shown in cell culture experiments (Albert et al. 2002, Villasante et al. 2007). In vivo, VEGF caused increased fenestration and defect in liquid tightness of vessels, as well as angiogenesis of rodent muscle cells (Zacchigna et al. 2007). VEGF is therefore a strong candidate for the paracrine effects on endothelial cell permeability. It is likely that this is mediated through the regulation of adhesion proteins (Wright et al. 2002, Lampugnani et al. 2006). In addition, it has been shown that inhibition of the VE-Cadherin system using antibodies in vivo can inhibit angiogenesis, an vascular permeability in rat ovary (Nakhuda et al. 2005). Indeed, VEGF increases Claudin 5 release in endothelial cells, which is associated with increased permeability (Rodewald et al. 2009). This finding indicates a direct link between hCG, VEGF, Claudin 5, and increased endothelial permeability.

It should be noted that the effects of VEGF synthesized in ovary not only affect ovarian vessels but may also influence the permeability of the vasculature of other organs. Such effects are observed in peritoneal vessels, resulting in ascites or edema, which have implications in disorders such as ovarian cancer (Herr et al. 2012).
Interactions of cell junctional proteins in endothelial cells

On a structural level, functional interactions of junctional proteins acting as regulators of vascular permeability are present in several systems such as the blood–brain–barrier and the peritoneum (Akutagawa et al. 2002, Willis et al. 2013). Despite the fact that the corpus luteum is among the most highly vascularized tissues, and vascular permeability is likely to play a critical role in its function, these mechanisms are relatively unexplored in the corpus luteum. Junctional proteins are dynamic structures undergoing uninterrupted rearrangement during embryonic development.

Obviously, there is a flow-like movement in a basal-apical direction. Such movement also occurs in resting cells, such as normal epithelial sheets, but solely at the junctions formed by moving cells (Kametani & Takeichi 2007). These highly dynamic intercellular junctions interact in order to control vascular permeability in response to outside signals (Furuse & Tsukita 2006, Van Itallie & Anderson 2006). Consecutively, co-existence of those proteins has been described for different tissues in different species, especially concerning the expression of AJ and TJ in the vascular system of the human corpus luteum (Herr et al. 2013). The AJ protein VE-Cadherin and the TJ protein Nectin 2 and Claudin 5 are co-localized in the vasculature of the mid-luteal human corpus luteum (Herr et al. 2013). hCG treatment of granulosa lutein in co-culture with endothelial cells decreases the production of VE-Cadherin, Nectin 2, and Claudin 5 proteins in the endothelial cells (Herr et al. 2013). Thereby, this in vitro effect is mediated by VEGF. The reciprocal influence of VE-Cadherin, Nectin 2, and Claudin 5 as regulators of permeability in endothelial cells has been investigated in vitro as follows: the downregulation of VE-Cadherin or Claudin 5 induces a decrease in the respective alternate proteins, whereas knockdown of Nectin 2 does not influence VE-Cadherin and Claudin 5 (Herr et al. 2013). Those changes in the junctional proteins not only remain on a structural level but can also be translated in functional alterations. hCG-induced downregulation of junctional proteins results in an increased rate of endothelial permeability in vitro (Herr et al. 2013). In addition, switching off of VE-Cadherin, Nectin 2, and Claudin 5, performing an siRNA knockdown, causes a successive increase in endothelial permeability of each different protein (Herr et al. 2013), thus demonstrating its important role in the functionality of the human corpus luteum.

These results indicate that VE-Cadherin and Claudin 5 play a major role in the regulation of endothelial permeability via Nectin 2. In addition, Nectin 2 also influences vascular permeability directly. However, the opposite pathway of Nectin 2-dependent, VE-Cadherin, and Claudin 5 expression/production seems to be inexistent. As these three proteins are co-localized in the vessels of the human corpus luteum and down-regulated by hCG via VEGF actions, we hypothesize that hCG induces a chain reaction by downregulating VE-Cadherin and/or Claudin 5, which interact with other adhesion proteins such as Nectin 2 consecutively resulting in increasing luteal permeability (Herr et al. 2013; Fig. 2).

Clinical implications: the OHHS

The OHSS (Fig. 3) is a complication that is observed in women undergoing assisted reproduction procedures. Severe OHSS occurs in ~1.4% of all cycles (Klemetti et al. 2005). VEGF plays a key role in the pathogenesis of OHSS. During assisted reproduction, multiple-follicular growth is induced by follicle-stimulating hormone to obtain a sufficient number of fertilizable oocytes. Thus, ovulation is induced by hCG treatment, which is followed by luteinization of preovulatory follicles. Accordingly, multiple corpora lutea are formed, which synthesize VEGF. VEGF is then released into the blood stream in turn causing highly elevated levels of VEGF in OHSS patients (Pietrowski et al. 2012). Owing to two waves of VEGF, the OHSS occurs as an early-onset form in response to exogenously dispensed hCG, as well as late-onset form (Fig. 4).

In this case, hCG is secreted from the implantation pregnancy and may be associated with the conception cycles, especially multiple pregnancies, and is more likely to be severe (Papanikolaou et al. 2005).
Furthermore, VEGF is released locally into the abdominal cavity (van de Lagemaat et al. 2011). Both may affect junctional proteins in peripheral vessels such as the peritoneal vasculature. In this case, VEGF may suppress junctional proteins in the endothelium. Recent data have shown that these junctional proteins interact with each other (Herr et al. 2013). This suggests that increase in vascular permeability is enhanced, leading to loss of fluid in the extracellular space and, as a result, causing all symptoms of OHSS, including ascites and edema. In addition, VEGF originating from the ovary has been assumed to be responsible for the development of pleural effusion (Wang et al. 2002).

From a therapeutical point of view in patients with OHSS, gonadotropin-releasing hormone agonists can modulate vascular permeability via influencing the expression of the TJ protein Claudin 5 (Kitajima et al. 2006). Furthermore, in patients at risk of OHSS, the effect of VEGF on junctional proteins can be also inhibited by dopamine agonists, thus decreasing vascular permeability (Gomez et al. 2011, Kumar et al. 2011, Soares 2012). Several lines of evidence have also implicated dopamine as an etiological factor in the OHSS. However, to date, evidence has failed to support this contention (Gelety & Chaudhuri 1992). Therefore, a therapeutical perspective concerning the treatment of the OHSS might be influencing increased permeability in those patients via targeting VEGF. One corpus luteum should be enough to preserve pregnancy. Local treatment such as transvaginal injection of several corpora lutea with VEGF-antagonists may be considered. Currently, we are far from providing a concrete therapeutical option, because the pro-angiogenic effects of VEGF are urgently needed in pregnant women to maintain pregnancy. Occasionally, in patients with severe complications, induced abortion is performed in order to protect the health of the pregnant mother. However, in those cases, anti-VEGF treatment might be a better therapeutical option, with the potential to preserve the health of the patient along with her pregnancy.

**Summary**

Among others, the primate corpus luteum is regulated by cellular communication between luteal steroidogenic cells and endothelial cells, resulting in angiogenesis associated with luteal formation. Essential for this process is the tight control of the endothelial permeability. The luteal endothelial cells thereby express several AJ and TJ, such as Occludin, Claudin 1, Claudin 5, Nectin 2, and VE-Cadherin. It has been shown *in vitro*, as well as *in vivo*, that hCG induces downregulation of those junctional proteins in the luteal vessels via VEGF. An increased level of VEGF results in raised endothelial permeability in the corpus luteum and in the peritoneal vessels outside the ovary. Accordingly, this helps to ensure the supply of nutrients in the corpus luteum and...
the release of progesterone. However, in the case of OHSS, it can cause an escape of fluids from the peritoneal vessels into the abdominal cavity, resulting in ascites or pleural effusion. As this complication is due to VEGF, this factor might be a target for therapeutic approaches in order to treat patients with severe OHSS. Finally, in addition to well-established treatment, such as dopamine or metformin, there may be alternative management methods for severe OHSS. Basic knowledge of pathophysiology can help to treat OHSS but prevention is better than cure with mild stimulation regimes.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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