Prediction of ovarian hyperstimulation syndrome

Challenging the estradiol mythos

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Ovarian hyperstimulation syndrome (OHSS) is a serious and potentially life-threatening complication of ovulation induction. The syndrome almost always presents either after hCG administration in susceptible patients or during early pregnancy. Despite many years of clinical experience, the pathophysiology is poorly understood and there is no reliable test to predict patients who will subsequently develop severe OHSS. Nevertheless, excessive estradiol (E2) levels are commonly used as a predictor for the development of severe OHSS. The aim of this debate is to challenge this E2 mythos by demonstrating the reported versatility in the chosen E2 level in which patients develop OHSS; present pathophysiological evidence which paradoxically supports a preventive rather than a detrimental effect of E2 against OHSS, followed by a possible explanation which may sort out the aforementioned chaos. Additional studies are required to elucidate the pathophysiology of OHSS which may ultimately lead to new strategies in the prediction, prevention and treatment of severe OHSS.

Key words: estradiol/inflammatory response/OHSS/prediction/pathophysiology

Introduction

Navot et al. (1992) have reviewed the epidemiological, hormonal, and ultrasonographic characteristics of patients prone to develop ovarian hyperstimulation syndrome (OHSS). These included young age (<35 years), lean habitus, and hormonal or morphological signs of polycystic ovary syndrome (PCOS) with an excessively high estradiol (E2) response (>4000–6000 pg/ml, in IVF cycles) on the day of hCG administration and with multiple (more than 35) small and intermediate follicles that will yield more than 30 oocytes on retrieval. These characteristics were further supported by Asch et al. (1991) who demonstrated that the combination of E2 levels >6000 pg/ml on the day of hCG administration and more than 30 retrieved oocytes is associated with an 80% chance of developing severe OHSS. In addition, several other studies suggested withholding hCG in non-IVF cycles when peak serum E2 levels were >2000 pg/ml (Haas and Seibel, 1994), and in IVF cycles when peak serum E2 exceeded 6000 pg/ml (Navot et al., 1996). If these threshold levels are reliable, however, how can we explain the occurrence of severe OHSS in patients who conceived spontaneously (Zalel et al., 1995), in those with low serum E2 levels on the day of hCG administration (Levy et al., 1996) or the well known practice that high estrogen levels do not always lead to hyperstimulation (Blankstein et al., 1987)?

These versatile observations actually suggest that the previously accepted risk factors, especially high serum E2 levels, are unreliable for the prediction of severe OHSS.

What other observations support this notion?

In our investigation of the role of albumin in the prevention of severe OHSS, we found that different studies defined high-risk patients by different E2 threshold levels, ranging from 1906 to 6000 pg/ml. Most used a level of ~3000 pg/ml (Orvieto and Ben Rafael, 1998a). Therefore if we rely on the aforementioned study of Asch et al. (1991), which also found an almost negligible risk of OHSS in IVF cycles with serum E2 <3500 pg/ml and/or less than 20 oocytes obtained at follicular aspiration, then most of the patients in the studies on the preventive role of albumin would not be expected to develop severe OHSS. Moreover, the reported cases of severe OHSS in the control groups with E2 levels around 3000 pg/ml further support the non-reliability of the previously stated level of E2 for the prediction of severe OHSS. Furthermore, even when all the aforementioned predictive variables were combined, the prevalence of severe OHSS in the ostensibly high risk
Evidence paradoxically supports a preventative effect of E$_2$ against OHSS

Ovarian hyperstimulation syndrome was noted to be similar to vascular leak syndrome (VLS) (Orvieto et al., 1995; Orvieto and Ben-Rafael, 1998b), which may be attributable to the massive increase in systemic inflammatory cytokines observed during the course of severe OHSS (Orvieto and Ben-Rafael, 1998b) or to neutrophil activation (Carey et al., 1997). In earlier studies, our group found that neutrophil and endothelial activation, as reflected by the observed increase in L-selectin and E-selectin levels respectively, was significantly attenuated during controlled ovarian stimulation (COS) until the peak in serum E$_2$, and stimulated thereafter by hCG administration (Orvieto et al., 2000, 2001), a trend that is exactly opposite to that shown for serum E$_2$ levels (Figure 1). This observed attenuation in neutrophil and endothelial activations and the observed inhibition of cytokine-mediated endothelial activation by E$_2$ supplementation which was demonstrated even in the transcriptional level (Caulin-Glaser et al., 1996), suggest that E$_2$ may actually attribute to attenuation rather than activation of the systemic inflammatory response observed during the course of severe OHSS. This suggestion is in accordance with Farhi et al. (2000) who found that the addition of E$_2$ to the progesterin luteal support regimen in patients at risk of developing OHSS may have a beneficial effect on pregnancy and implantation rates with negligible incidence of severe OHSS (J.Farhi, personal communication).

How can we sort out the chaos?

A possible explanation for the ostensibly contradictory findings may be extrapolated from our prospective experimental study (Orvieto et al., 1998), which suggested that the occurrence of different, unrelated ovarian response mechanisms to COS could account for both (i) the ovarian enlargement and excessive steroidogenesis and (ii) the release of the intermediate factor, causing an increase in capillary permeability (Figure 2). This is in keeping with the known clinical practice that OHSS usually develops in patients having marked multiple follicular development, which is linked to increased E$_2$ production and serum levels (our first mechanism), while the hCG promotes the ovarian secretion of vasoactive substance(s) (our second mechanism) causing OHSS. Furthermore, this assumption resolves the unreliable role of E$_2$ level in the prediction of severe OHSS and is in accordance with the observations that OHSS almost always develops after hCG or in early pregnancy, and may even occur in patients who conceived spontaneously (Zalel et al., 1995), and in those with low (Levy et al., 1996) or high (Blankstein et al., 1987) serum E$_2$ levels on the day of hCG administration.

Additional studies are required to elucidate the pathophysiology of OHSS which may ultimately lead to new strategies in the prediction, prevention and treatment of severe OHSS.

References

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Figure 1. L-selectin and E-selectin levels in relation to estradiol level during COS for IVF. Day-s = day in which adequate suppression was achieved; Day-hCG = day of or day prior to hCG administration; Day-OPU = day of oocyte retrieval. (Adapted with modification from Orvieto et al., 2000, 2001.)

Figure 2. Ovarian response mechanisms to gonadotrophin.


