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An OHSS-Free Clinic by segmentation of IVF treatment

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ABSTRACT: Published data indicate a significant increase in ovarian hyperstimulation syndrome globally. The occurrence of approximately three maternal deaths per 100 000 stimulated women has been reported, and extrapolation of these figures to a global situation would give an impressive number. The syndrome can be erased by applying ovarian stimulation using the combination of GnRH antagonist with GnRH agonist to trigger ovulation. In this case, the strategy is to freeze all of the oocytes or embryos for later use.

Key words: ovarian stimulation / OHSS / vitrification / GnRH antagonist / GnRH agonist

Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of ovarian stimulation. Regarding moderate cases, the disorder has an incidence of ~5% (Delvigne, 2009). The incidence of the cases requiring hospitalization is up to 2% (Papanikolaou *et al.*, 2005).

Given its relatively low incidence among the patient population undergoing ovarian stimulation, one could speculate that the impact of the syndrome may not be so important. Nonetheless, a more detailed analysis of the current literature demonstrates that the situation is actually very different.

Firstly, while the reported incidence of OHSS requiring hospitalization is ~2%, several reports indicate an increase in the incidence of severe forms of the syndrome and in the proportion of patients hospitalized (Abramov *et al.*, 1999; Cunha-Filho *et al.*, 2003). In addition, published data support a statistically significant increase in pregnancy-related complications among IVF pregnancies in women who suffered from OHSS compared with IVF controls (Abramov *et al.*, 1998; Courbiere *et al.*, 2011). However, the most devastating consequence of OHSS is that it may be a serious threat to the patients' life. One could hypothesize that a lethal outcome may be sporadic (Semba *et al.*, 2000; Fineschi *et al.*, 2006). However, results from reports regarding maternal mortality rates due to OHSS in the Netherlands and the UK demonstrate an incidence of ~3 deaths per 100 000 IVF cycles performed (Confidential Enquiry into Maternal and Child Health, 2007; Braat *et al.*, 2010).

Those figures are worrisome if one considers that the reported annual number of IVF/ICSI cycles among 32 European countries was more than 450 000 in 2006 and that the number of cycles in the USA almost reached 150 000 in 2008 (Centre for Disease Control and Prevention, 2008; de Mouzon *et al.*, 2010). Therefore with such numbers of cycles and the rapid expansion of assisted reproduction treatments (ARTs), the total number of maternal deaths related to OHSS worldwide may be far greater than initially expected. Furthermore, the fact that linkage of IVF and maternal deaths is not allowed by the Human Fertilization and Embryology Act, and that women may not even disclose ART to maternity services suggest that the incidence may even be underestimated (Bewley *et al.*, 2011).

Taking into account the reports regarding mortality rates related to OHSS and the rapid increase in the number of IVF/ICSI cycles over the years, one would consider that the loss of a substantial number of women yearly worldwide is almost unacceptable. It seems that the introduction of OHSS-Free Clinics cannot be postponed (Devroey and Adriaensen, 2011).

The use of the GnRH antagonist protocol

Improving the patients' welfare starts by optimization of the ovarian stimulation protocol, in order to minimize the patients' burden, the risks and the psychological stress (Devroey *et al.*, 2009).

Besides the inhibition of the premature LH surge, GnRH antagonists are associated with less side-effects in comparison with the GnRH agonists (Lambalk *et al.*, 2006). Their patient-friendly profile is attributed to their different mode of pharmacological action on the pituitary (Reissmann *et al.*, 2000). The antagonistic analogue has an immediate action and thus can be administered only when there is a need for suppressing the LH surge, resulting in a much shorter duration of stimulation and absence of side-effects caused by profound hypoestrogenaemia (Borm and Mannaerts, 2000; Fluker *et al.*, 2001). There appears to be no clinically significant difference in terms of live birth rates between GnRH antagonists and agonists:

two meta-analyses comparing the two classes of GnRH analogue have calculated almost identical odds ratios (0.82 and 0.86) for the probability of live birth, although the difference compared with GnRH agonists was statistically significant in one analysis (Al-Inany et al., 2006) and not in another (Kolibianakis et al., 2006). The difference is unlikely to be of clinical significance (Devroey et al., 2009). A very recent meta-analysis by Al-Inany could not demonstrate any evidence of a difference in live birth rates between the use of GnRH antagonists compared with long GnRH agonist protocols (Al-Inany et al., 2011).

Importantly, the majority of trials clearly support that GnRH antagonists result in a significantly lower incidence of OHSS compared with GnRH agonists (Tarlatzis and Kolibianakis, 2007).

Ovulation triggering

Even though GnRH antagonist therapy is associated with a significant reduction in the occurrence of severe OHSS, the syndrome cannot be excluded when ovulation has been triggered with hCG. Although hCG has been the gold standard for ovulation triggering for decades, due to its long half-life with levels remaining elevated even after 6 days of administration, it is responsible for an increased incidence of OHSS (Gonen et al., 1990). Several trials have been performed to test the effect of triggering ovulation with different doses of urinary hCG (Abdalla et al., 1987; Wikland et al., 1995; Kolibianakis et al., 2007). Triggering with 5000 or 10 000 IU appears to be effective as far as oocyte recovery is concerned. However, both dosing schedules may lead to severe OHSS (Kolibianakis et al., 2007). Also it appears that the hCG serum concentration on the day of hCG administration is a determining factor of OHSS incidence (Shapiro et al., 2005).

The utilization of GnRH agonist for triggering ovulation in antagonist cycles has been a breakthrough in the elimination of OHSS (Itskovitz et al., 1991; Shalev et al., 1994). It was clearly demonstrated that triggering final oocyte maturation with GnRH agonist is an effective alternative to hCG for inducing follicular maturation with the potential benefit of preventing OHSS (Segal and Casper, 1992). Following this trial, a significant amount of information has been published regarding agonist triggering in IVF cycles with data from randomized trials clearly indicating that the incidence of OHSS in GnRH antagonist cycles is ~0% when triggered with a GnRH agonist. This model has been tested in oocyte donors (Melo et al., 2009).

However, even from the first published reports regarding agonist triggering, the possibility of a luteal phase defect in cycles triggered with a GnRH agonist has been mentioned (Segal and Casper, 1992). In the first randomized controlled trials comparing GnRH agonist triggering and hCG administration, the pregnancy rates were significantly decreased in the agonist triggered condition (Humaidan et al., 2005; Kolibianakis et al., 2006). GnRH agonist triggering has a combined negative effect on the function of the corpus luteum and on the function of the endometrium (Humaidan et al., 2005, 2009). Although more research is needed, GnRH agonist triggering, followed by rescue of the luteal phase has gained a lot of interest. The use of intensive luteal phase support in the form of intramuscular progesterone combined with estradiol (E_2) patches has been proved to overcome the luteal phase defect in two recent randomized controlled trials (Engmann et al., 2008; Diluigi et al., 2010). The approach of using 1500 units of hCG at oocyte retrieval has also been shown to correct the luteal phase and pregnancy rates have been normalized in the GnRH antagonist and GnRH agonist combination cycles (Humaidan et al., 2006, 2010). Eventually, luteal phase supplementation with low-dose hCG has to be fine tuned in additional randomized trials, possibly with a dual administrations of hCG. Further research into the protocols for luteal phase supplementation after GnRH agonist triggering may result in the identification of the most optimal protocol, eliminating any potential difference in pregnancy rates. This would allow agonist triggering and fresh embryo replacement to become a standard of care for infertile patients.

Cryopreservation of oocytes and embryos

An alternative approach to luteal phase rescues in GnRH antagonist and GnRH agonist combination stimulation cycles is a freeze-all strategy.

Oocyte cryopreservation

Oocyte cryopreservation may be the best current option for patients with increased risk for OHSS. The excellent oocyte survival rates after oocyte vitrification justifies the use of oocyte cryopreservation as a routine approach (Kuwayama et al., 2005; Cobo et al., 2008; Nagy et al., 2009). A large randomized trial has shown that in oocyte donation programmes, vitrified oocytes after warming result in pregnancy rates comparable to those of fresh oocytes, and therefore it is a valuable modality (Cobo et al., 2010). These results are further enhanced by the conclusions of a recent non-inferiority randomized trial, which clearly supports that fertilization, embryo development and ongoing pregnancy rates after ICSI are comparable when using fresh or vitrified oocytes (Rienzi et al., 2010). Moreover, in a recent publication, pregnancy rates as high as 80% after oocyte vitrification have been reported (Kim et al., 2010).

Vitrification of oocytes in patients at risk of OHSS has been tested in an observational trial in which ovulation triggering was performed with a GnRH agonist. The results have clearly demonstrated that oocyte vitrification not only decreased the risk for OHSS but also resulted in significantly higher pregnancy rates compared with coasting in patients at risk of OHSS (Herrero et al., 2011).

Some may undeniably argue that oocyte cryopreservation is superfluous, given the rapid progress made in embryo cryopreservation and the increases in the pregnancy rates related to frozen embryo transfers. However, oocyte freezing is also an option for couples who do not desire embryo cryopreservation. A trial regarding the expectations and perceptions of frozen embryo holders revealed that many couples are concerned about frozen embryo disposition for ethical reasons (Nachtigall et al., 2010). Since ethical concerns regarding embryo cryopreservation have been raised, in the end, oocyte freezing may be a more attractive and realistic alternative for certain groups of society (Heng, 2007).

Embryo cryopreservation

Established for several years, cryopreservation of all embryos after GnRH agonist triggering is a safe alternative for patients at risk for OHSS. A prospective cohort trial has shown that treating patients at risk of severe OHSS with an antagonist protocol, where ovulation

has been triggered with an agonist and freezing all embryos can result in a cumulative birth rate of 37.3% (Griesinger *et al*., 2007). It also has to be taken into account that in this study, a substantial number of embryos are not yet thawed. Several randomized controlled trials have highlighted similar pregnancy rates whether using elective cryopreservation of all embryos or fresh embryo transfer (Ferraretti *et al*., 1999; Aflatoonian *et al*., 2010; Surrey *et al*., 2010).

Observational results from the most recent CDC report in 2008 suggest that no difference in live birth rates is present between fresh and frozen/thawed cycles in sufficiently sized clinics in the USA (Centre for Disease Control and Prevention, 2008).

The live birth rates after replacement of frozen-thawed embryos has been augmented substantially by the widespread use of vitrification for embryo cryopreservation. Embryo vitrification is related to significantly higher embryo survival and subsequent development rates (Balaban *et al*., 2008). It also appears that vitrification results in significantly higher ongoing pregnancy rates compared with slow and ultra-rapid freezing (AbdelHafez *et al*., 2010). Given the fact that vitrification results in increased pregnancy rates, it is likely that this progress made in embryo freezing systems over the last decade can bridge the gap in live birth rates between fresh and frozen/thawed cycles. In addition, it has been reported that the use of vitrification is an efficient method for patients at risk for OHSS (Selman *et al*., 2009).

Of course, after freezing, the implantation potential of an embryo transfer is also related to the protocol used for endometrial preparation. Despite the fact that several randomized trials have examined the effects of different methods of endometrial preparation for frozen embryo replacement, evidence is still lacking (Glujovsky *et al*., 2010). Natural cycles, with or without hCG administration, have been used (Fatemi *et al*., 2010), and endometrial preparation with exogenous E_2 and progesterone, with or without the addition of GnRH agonist, has also been applied (Surrey *et al*., 2010).

Conclusion

The balance between the desire for pregnancy and the patients' safety is a top priority. The concept of an OHSS-Free Clinic has become a reality. This approach should include pituitary down-regulation using a GnRH antagonist, ovulation triggering with a GnRH agonist and vitrification of oocytes or embryos. Then the marked consequences of the occurrence of OHSS could not influence the patients' physical health, their psychological health and their willingness to undergo further fertility treatments (Verberg *et al*., 2008). The impact of the syndrome for each individual with OHSS is substantial.

The strategy to obtain an OHSS-Free Clinic is closely related to the segmentation concept. It consists of optimization of the ovarian stimulation, including GnRH agonist triggering in a GnRH antagonist cycle (segment A). Segment B then consists of optimum cryopreservation methods for oocyte or embryo vitrification. Segment C includes embryo replacement in a receptive, non-stimulated endometrium in a natural cycle or with artificial endometrial preparation.

Authors' roles

All the authors contributed substantially to the paper. P.D. initiated the concept of segmentation. N.P.P. performed the literature search and the input on oocyte/embryo freezing. C.B. developed the use of GnRH antagonists. All the authors approved the final form of the manuscript prior to submission.

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