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Review Article

Avoiding Ovarian Hyperstimulation Syndrome – Current Primary and Secondary Preventive Strategies

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Abstract

Ovarian hyperstimulation syndrome (OHSS) is still a severe complication due to controlled ovarian stimulation for artificial reproductive technology. Even though multiple techniques to avoid OHSS have been discussed in the last decades, up to now no clear concepts for primary and secondary prevention exist. This review gives an overview over proposed strategies to avoid OHSS. In a retrospective analysis of 370 cycles of controlled ovarian stimulation for ART at our Department of Gynecology and Obstetrics we analyzed the risk of OHSS. An algorithm for choosing the starting dose of gonadotropins is presented, which is based on individual parameters as AMH, younger age, higher ovarian reserve for women with the diagnosis of polycystic ovarian syndrome.

Keywords: Ovarian hyperstimulation syndrome; Polycystic ovarian syndrome; Controlled ovarian stimulation

Introduction

The controlled ovarian stimulation (COS) is the main key to success for artificial reproductive techniques (ART). Follicular puncture and retrieval of more than one oocyte increase the chance of cultivating good quality-embryos and subsequent pregnancies. This relation is almost linear to the number of retrieved oocytes. But the possible benefits of controlled ovarian stimulation reach a maximum of about 15 oocytes and then the life birth rate is stable at a plateau [1]. Crossing this turning-point the risk of ovarian hyperstimulation (OHSS) increases dramatically.

Every ovarian endocrine stimulation bears the risk of OHSS depending on the individual ovarian reserve and sensitivity to stimulation. The ovarian hyperstimulation results in an unregulated increase of vascular permeability and fluid loss into the third space of the body. Protein loss and reduced oncotic pressure itself sustain the fluid imbalance [2]. The usual symptoms due to enlarged ovaries in early stage of OHSS are feelings of abdominal distension, bloating or pain. Dyspnea is the clinical red flag symptom for pleural effusion, often accompanied by low blood pressure, sickness, diarrhea and vomiting. The typical clinical sign of ascites and peritoneal irritation is the pain while walking and moving the legs. These conditions may lead to multiple organic failures with pericardial effusion, respiratory distress syndrome (RDS), arrhythmia, cardiac insufficiency, hepatic insufficiency, and/or oligo- or anuria. Even in early stages of OHSS and after clinical resolution of the acute syndrome the thromboembolic risk is increased [2].

A mild ovarian hyperstimulation is seen in about one third of controlled ovarian stimulations for IVF/ICSI. Severe OHSS with the necessity of hospitalization for infusions therapy, antithrombotic treatment and other possible interventions is rare but occurs in up to 5% [3].

A classification in three degrees was proposed by the WHO as early as 1973. According to this, mild ovarian hyperstimulation is defined as enlarged ovaries, the occurrence of small ovarian cysts and accompanying abdominal pain, without evidence of ascites. Rizk and Aboulghar further specified the moderate and severe manifestation of the syndrome [4]. This classification is shown in Table 1. A further discrimination of OHSS referring to underlying pathophysiology can be made by the time of occurrence. The late onset OHSS shows symptoms typically about 10 days after embryo transfer associated with rising endogenous hCG in early pregnancy. In contrast to this, in early onset OHSS a sensitive ovarian response to gonadotropins and additional exogenous hCG application lead to the development of OHSS. A prospective study of risk factors for OHSS with 624 women treated for IVF/ICSI showed that especially in multiple pregnancies the late onset mechanism is exaggerated. Besides the number of follicles and retrieved oocytes, high serum values of hCG either of exogenous or endogenous origin are the strongest causal factor of the development of OHSS [5].

Risk factors for OHSS

Risk factors which are known before starting gonadotropin stimulation allow primary preventive strategies to avoid OHSS. Low body mass index, younger age, higher ovarian reserve, higher doses of gonadotropins and known OHSS in previous stimulation cycles are associated with a higher risk of OHSS [6].

A frequent endocrine disorder of women, the polycystic ovarian syndrome, is a known risk factor for the development of OHSS and the time to recover after stimulation [7]. One of the diagnostic parameters of the PCOS is the polycystic ovarian sonomorphology, which comes along with clearly elevated ovarian reserve and high Anti-Mullerian Hormone (AMH) values in the serum. The basal AMH with a cut-off over 3.36 ng/ml shows 90.5% sensitivity and 81.3% specificity for OHSS in a study with 274 COS cycles [8]. The use of AMH as a predictive parameter was confirmed in further studies, e.g. a case-control study with 41 women with OHSS [9].

Preventive strategies for OHSS

There are different interventions to reduce the risk of OHSS through modifying the techniques of COS. The Table 2 shows the main

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Classification and clinical signs			
Moderate OHSS	- abdominal distension, pain, sickness, enlarged ovaries in ultrasound, sight ascites in the pouch - hematological parameters without pathology		
Severe OHSS	**Grade A**	**Grade B**	**Grade C**
	- dyspnea, vomiting, diarrhea, pain - Massive ascites, pleural effusion, - Normal hematological parameter	- enhanced symptomatic Grade A - Laboratory: increased hematocrit, creatinine, liver enzymes	- secondary complications like renal failure, thromboembolism, respiratory distress syndrome

Table 1: Classification of OHSS [4].

	Aim	Strategies
Primary preventive strategies	Reducing the general risk of OHSS in ART	Individual low dose COS
	Reducing the risk of OHSS in women with high ovarian reserve or OHSS in previous cycles	Adaption of gonadotropin dosage according to individual risk factors Use of antagonist protocol Ovulation trigger with GnRHa
	Reducing the risk of OHSS in women with PCOS	Adaption of gonadotropin dosage according to individual risk factors Pretreatment with oral contraceptives Concomitant Metformin use In vitro maturation
Secondary preventive strategies	Recognizing women with early signs of OHSS in ART	Intensive monitoring with repeated hormonal testing and ultrasound to monitor response to COS and detect OHSS early
	Reducing the risks of early manifestation of OHSS during COS	Triggering of ovulation with reduced hCG-dosage Ovulation trigger with GnRH in antagonist protocol Use of Cabergoline Coasting strategy with withholding of gonadotropins Complex rescue strategy with cabergoline, change to antagonist protocol, reduction of gonadotropins and hCG

Table 2: Strategies to prevent OHSS.

primary and secondary strategies which are discussed considering the risk-reduction on the one hand, but also disadvantages and possible risks of the strategies.

Primary preventive strategies

Although concrete guidelines or recommendations for the choice of the stimulation protocol do not exist, in most reviews for women with higher OHSS risk the antagonist protocol is recommended. Especially the possible use of GnRH-trigger of ovulation is the main argument for this protocol [10]. As predictive parameter for the use of the antagonist protocol an AMH level of 5.6 ng/ml is proposed. Nevertheless, the long agonist protocol has the same efficacy [11] and is still often recommended even in women with a higher risk of OHSS [12]. The antagonist protocol may lead to a reduction of the incidence of OHSS with a hazard ratio of 0.61; 95% CI 0.23 to 1.64 in a meta-analysis of almost 1000 women in 9 controlled randomized studies [13]. But further studies are needed.

Up to now there are no clear recommendations for dosage finding of gonadotropins for COS with high risk for OHSS. One preventive strategy of OHSS is the individual dosing of gonadotropins (individual COS) as proposed by Fiedler and Ezcurra [14]. We use an individual dosage algorithm especially for women with PCOS and high OHSS risk.

Secondary preventive strategies

In the Cochrane meta-analysis of Kwan et al. the question of the best diagnostic preventive procedure to monitor COS-cycles was addressed [15]. Although there could not be found clear statistical data for the combined intensive monitoring, the ovarian ultrasound and repeated hormonal testing seems to be especially useful in women at a higher risk for OHSS. After starting stimulation with gonadotropins the number of follicles with a size of 10-14 mm in repetitive ultrasound scan and the serum estradiol levels with a value of over 2.500 pg/ml are good parameters to predict the development of OHSS [6].

Possible strategies to reduce the individual risk of OHSS after having started the ovarian stimulation with gonadotropins are

- Triggering of ovulation with a reduced dose of hCG,
- Triggering of ovulation with GnRH-analoga (GnRH-a) in antagonist protocol,
- Cabergoline starting at the day of ovulation triggering,
- Coasting,
- Oocyte-retrieval and freeze all PN/embryos and
- Cancellation of the cycle.

In the agonist-protocol the trigger with hCG may be reduced to 5.000 IU or even 2.500 IU with the same efficiency [14]. During the GnRH antagonist protocol, GnRH-receptors in the hypophysis are not down regulated and refractory as in the long agonist-protocol but merely inhibited competitively [16]. The application of GnRH-a results in an endogenous flare-up of LH, which can be used for the induction of ovulation and final maturation of follicles. In contrast to the application of hCG with a half-life time of 36 h, the LH flare-up is only a short endocrine response compared to the long lasting effect of hCG. In a meta-analysis Youssef et al. studied the effectiveness and safety of GnRH-a compared to hCG as final oocyte maturation and ovulation induction in 13 randomized controlled studies with embryotransfer in the stimulation cycle [10]. The use of GnRH-a trigger led to an effective reduction of the incidence of OHSS (OR 0.15, 95% CI 0.05 to 0.47). Unfortunately, the GnRH-a trigger protocol showed a lower ongoing

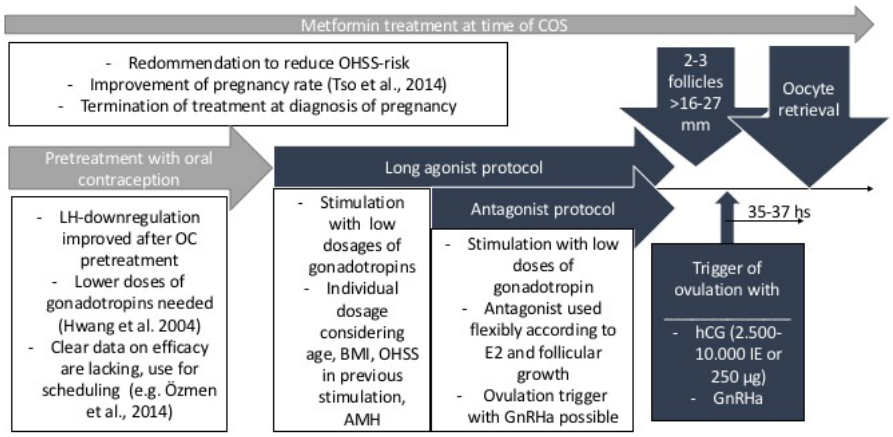

Figure 1: Strategies to reduce OHSS risk in women with PCOS in COH.

pregnancy rate than the hCG trigger (OR O.7, 95% CI 0.54 to 0.91), and higher early miscarriage rate (OR 1.74, 95% CI 1.1 to 2.75). The authors of this study conclude, that the GnRH-a trigger should only be used to avoid OHSS in cycles with fresh embryo transfer in selected cases and not as routine use.

Humaidan et al. showed that the discussed negative influence of the GnRH-a trigger on pregnancy rate may be counterbalanced by the supplemental use of hCG in low doses of 1.500 IU in the luteal phase [17]. Even with this technique, in women with high risk there are case reports of extreme responses with more than 26 oocytes collected, development of severe early onset OHSS, hospitalization and use of the freeze all–strategy [18].

Cabergoline as a dopamine antagonist can reduce vascular permeability mainly through reduction of VEGF. OHSS rates are reduced in women with high risk without impairment of the pregnancy rates [19]. Mainly 0.5 mg Cabergoline orally for 8 days starting at the day of ovulation induction or oocyte retrieval is used in the RCTs which were compared in this meta-analysis.

The coasting strategy implies that the gonadotropin-stimulation in high doses deteriorates the early onset OHSS. The withholding of gonadotropins through reduction or even cessation of gonadotropin application is proposed when the first ovarian follicles show a diameter of more than 16 mm. After estradiol levels are reduced under 3.000 pg/ml the hCG-triggering of ovulation should be performed. This procedure leads to atresia of the small antral follicles while bigger antral follicles persist. Mansour et al. showed that the strategy of cessation of gonadotropin-stimulation of less than 3 days effectively reduces the OHSS-risk but not the pregnancy rates [20]. In a retrospective study with 44 women Moon et al. showed that short coasting for 1-2 days is effective to prevent OHSS without impairing the pregnancy rates [21]. On average serum estradiol levels decreased after one day of coasting with complete withdrawal of gonadotropins for 25%, and on day two for 75%.

A current randomized controlled study with 118 women in each arm compares a complex rescue protocol to reduce the perceived high risk of OHSS with Cabergoline as the only preventive strategy [22]. Oral Cabergoline was combined with a change of protocol from agonist to antagonist protocol and reduction of gonadotropin dose, as well as reduction of hCG dose to 5.000 IE. A risk reduction for OHSS from 13.6% in the Cabergoline-only group to 5.1% in the antagonist rescue protocol was shown (p=0.025).

Cryopreservation of all retrieved oocytes is proposed as another strategy to reduce the incidence of late onset OHSS or aggravation of early onset OHSS. A delayed frozen-thawed embryo transfer in a later natural or hormonal replacement cycle seems to have higher implantation rates than in fresh cycle but without OHSS risk. Humaidan proposes the freeze all-strategy if 15 or more oocytes are retrieved to avoid OHSS [17].

A very pronounced early onset OHSS may result in cancellation of the cycle. This must be discussed with the couple in detail referring to the medical risk of the treatment and possible preventive strategies in later stimulation cycles [3].

Women with PCOS and risk for OHSS

Possible strategies to reduce OHSS risk in patients with PCOS are shown in Figure 1. A recent Cochrane review [23] showed a risk reduction of OHSS if the insulin-sensitizer metformin was used before and during controlled ovarian stimulation for IVF/ICSI especially in women with PCOS (OR 1.39, 95% CI 0.81 to 2.40), but this difference was not statistically significant. Although there was a significant difference in clinical pregnancy rate (OR 1.52; 95% CI 1.07 to 2.15), no difference was seen in life-birth rates in the metformin vs. placebo or no treatment group in the pooled analysis of 8 studies including 775 women with PCOS. It is even discussed that women with PCOS in spite of a normal BMI may benefit of Metformin in terms of the reduction of OHSS [24].

In vitro maturation (IVM) may be another primary preventive strategy for women with high OHSS risk, especially for women with PCOS or a history of OHSS in previous ART cycles. In contrast to the conventional IVF/ICSI-procedure, immature oocytes are used for artificial reproductive techniques with IVM. After a short FSH-priming, all antral follicles are punctured. All mature oocytes are used for IVF/ICSI at the day of oocyte retrieval [25] and immature oocytes after *in vitro* maturation in a specific IVM-medium at the following day [26].

The luteal phase is supported by exogenous progesterone and estradiol [27]. Although RCTs focusing on the use of IVM in women with PCOS are currently in process, still no clear data are existent to underline the risk adapted use of IVM [28]. Especially for women with a very high risk of ovarian hyperstimulation syndrome, IVM seems to be a risk-free alternative of ART [29]. In most areas of the world, a major problem is the low availability of IVM due to high expertise of the medical and laboratory staff, only few centers for reproductive medicine provide this special method of ART in Germany [27].

Even without any hCG administration, the use of GnRH-a trigger, low dose stimulation with 125, 150 or 187,5 IU rFSH and freeze all-approach, which has a comparable risk as IVM, there are several cases of severe OHSS. Those patients presented with an AFC of more than 18, 20, 25 follicles or a basal AMH value of 64,5 ng/ml [30-32]. In terms of primary preventive strategies, a difference should be made between patients at high risk in the normal range, e.g. basal AMH between 3,36 ng/ml and 15 ng/ml and patients with extreme values of more than 20 ng/ml AMH or AFC of more than 20 follicles. For those special cases, unstimulated IVM might be the only safe strategy. There is a need for large prospective studies for cut-off values, which distinguish those women from women who benefit from established strategies.

In a retrospective study in our reproductive unit of a university hospital in Germany we found a significant correlation of AMH levels and the risk of moderate OHSS (p=0,043). In this study 370 COS cycles for IVF/ICSI were analyzed. The women treated for IVF/ICSI had a mean age of 33.9 (25-45 years), mean BMI of 23.7 kg/m² (15.6-42.6), mean AMH-level of 3.5 ng/ml and a mean duration of infertility of 2.8 years [36]. As the preferred stimulation protocol the long agonist protocol with step-up individual dose-finding of gonadotropins was used (Table 3). About 30% of the women were stimulated in the antagonist protocol with individual COS.

At day 2 or 3 the embryo transfer with the maximal number of 3 embryos was performed. The clinical pregnancy rate per embryo transfer in this study was 34.4% of women without PCOS and 32.2% of women with PCOS, whereas the life-birth rate per embryo transfer was 28.9% (without PCOS) vs. 23.7% (with PCOS), although this difference was not statistically significant (p=0.543) (Figure 2).

In the subgroup analysis of women with PCOS and OHSS and subtle grouping into the Rotterdam-phenotypes, we found a significant differentiation of risks. PCOS (n=64 cycles) and non-PCOS cycles (n=301) did not differ in outcome parameters of fertilization rate (p=0.225), biochemical pregnancy rate (42.4 vs. 42.2%, p=0.547), clinical pregnancy rate (32.2 vs. 32.4%, p=0.434) and life-birth rate (23.7 vs. 28.9%, p=0.114). 39 women in our study presented at least 2 manifest diagnostic criteria of PCOS. Of those women, the smallest group showed hyperandrogenemia

Method of ART	Principles of treatment	Benefits	Risks, disadvantages
Standard IVF/ICSI	Controlled ovarian stimulation	Higher number of mature oocytes, higher number of embryos, possible selection Higher pregnancy rates per cycle (32.7% for IVF, 30.8% ICSI) [33]	OHSS, expensive medical treatment
In vitro maturation (IVM)	Short priming with gonadotropins	Low risk for OHSS, low cost for gonadotropins No increased risks of oocyte retrieval	Specialized ART-techniques only available in few centers in the world Theoretically genetical risk for imprinting defects, but not shown in current studies [29] High variation of pregnancy rates of 15.3% [27], up to 45.8% [35] Conflicting data for early miscarriage rates [35]

Table 3: Comparison of standard-IVF/ICSI and IVM.

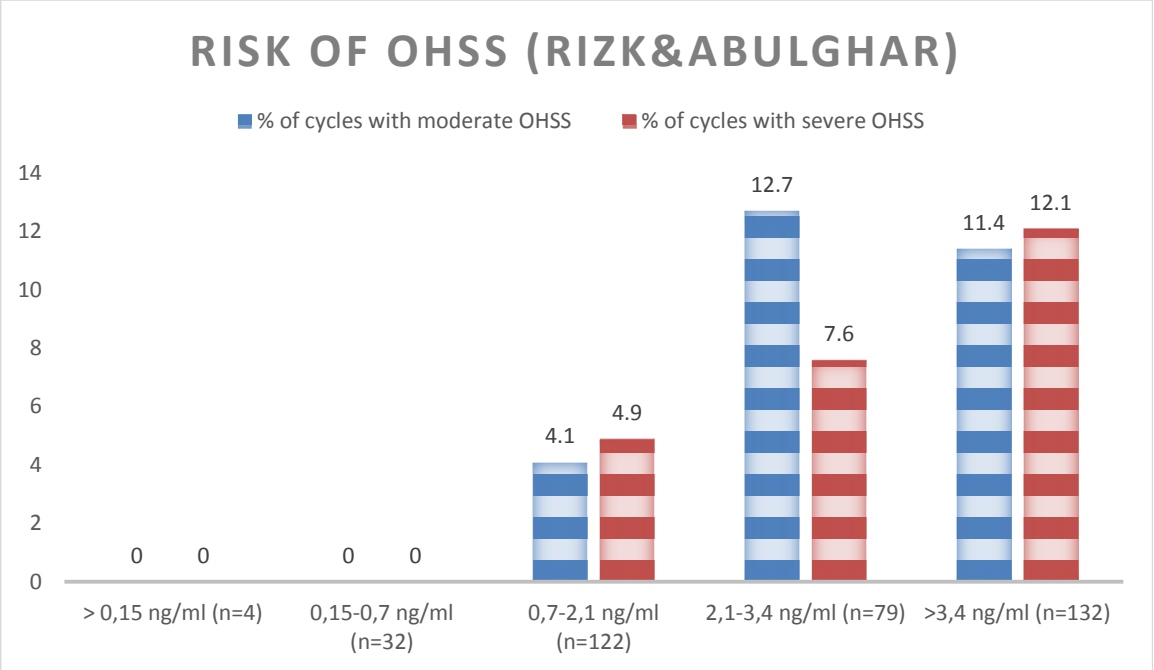

Figure 2: Risk of OHSS in correlation to AMH (retrospective analysis of 370 cycles of COS).

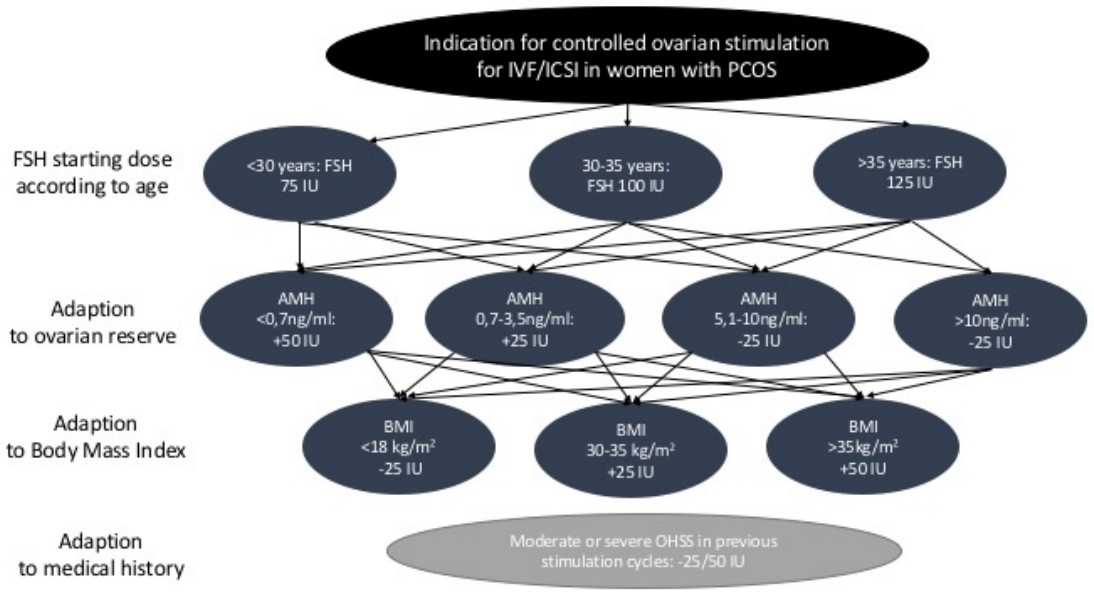

Figure 3: Careful and individual dosage-finding pathway in women with PCOS [36].

and oligo- or anovulation (1,3% of all women, n=3). Most women with PCOS had three positive criteria (6% of all women, n=14). Especially the group with hyperandrogenemia, high ovarian reserve, and suspected sensitive response to gonadotropin-stimulation had the highest risk for OHSS. We propose a careful individual dosing strategy for women with PCOS with the intent of reducing the risk of OHSS without impairing the pregnancy rates (Figure 3).

Conclusion

In spite of multiple approaches to avoid ovarian hyperstimulation syndrome, it constitutes still a common and potentially life-threatening complication in controlled ovarian stimulation for ART. Careful and individual dosing of gonadotropins either in long agonist or in antagonist protocols are a useful technique to minimize the risk. Individual ovarian reserve, age of the women, BMI, diagnosis of PCOS and the history of previous OHSS may help to find the starting dose. Although the antagonist protocol offers the possibility to trigger the ovulation with GnRH-a instead of hCG, the long agonist protocol still is a good option for COS in women with elevated OHSS risk. Many other effective secondary preventive strategies exist to reduce the OHSS risk. Future research is needed to identify patients, in which those risk reductive strategies fail to eliminate OHSS.

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