

# CURRENT MEDICAL STRATEGIES IN THE PREVENTION OF OVARIAN HYPERSTIMULATION SYNDROME

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**SUMMARY** - The purpose of this review is to analyze current medical strategies in the prevention of ovarian hyperstimulation syndrome (OHSS) during ovarian stimulation for *in vitro* fertilization. Owing to contemporary preventive measures of OHSS, the incidence of moderate and severe forms of the syndrome varies between 0.18% and 1.40%. Although none of medical strategies is completely effective, there is high-quality evidence that replacing human chorionic gonadotropin (hCG) by gonadotropin-releasing hormone (GnRH) agonists after GnRH antagonists and moderate-quality evidence that GnRH antagonist protocols, dopamine agonists and mild protocols reduce the occurrence of OHSS. Among various GnRH agonists, buserelin 0.5 mg, triptorelin 0.2 mg and leuprolide acetate (0.5-4 mg) have been mostly utilized. Although GnRH trigger is currently regarded as the best tool for OHSS prevention, intensive luteal support with exogenous administration of estradiol and progesterone or low-dose hCG on the day of oocyte retrieval or on the day of GnRH agonist trigger are required to achieve optimal conception rates due to early luteolysis. Among currently available dopamine agonists, cabergoline, quinagolide and bromocriptine are the most common drugs that should be used for prevention of both early and late OHSS. Mild stimulation protocols offer attractive option in OHSS prevention with satisfactory pregnancy rates.

**Key words:** *Ovarian hyperstimulation syndrome – prevention and control*

## Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most serious iatrogenic complication of controlled ovarian stimulation (COS), which can vary from mild illness to severe, potentially life-threatening disease. The syndrome almost always occurs a few days after receiving human chorionic gonadotropin (hCG) (early OHSS), or later (late OHSS), which depends on the occurrence of endogenous hCG<sup>1</sup>. Although OHSS

may occasionally occur spontaneously between eight and twelve weeks of pregnancy or with a follicle-stimulating hormone (FSH) producing pituitary adenoma, the great majority of cases are iatrogenic due to ovulation induction in women undergoing assisted reproductive techniques (ART)<sup>2</sup>. According to the latest European Society of Human Reproduction and Embryology (ESHRE) report, the incidence of OHSS ranges from 0.18% to 1.40% of stimulated *in vitro* fertilization (IVF) cycles in European countries<sup>3</sup>. Although the pathophysiology of the syndrome is not entirely clear, it is assumed that the vasoactive substances secreted by ovaries under hCG stimulation may play a key role in increasing capillary permeability observed in OHSS. Of all the different vasoactive cy-

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tokines, vascular endothelial growth factor (VEGF) is the principal mediator and is most responsible for vascular hyperpermeability. A generalized capillary leak and acute shift of protein-rich fluid from the intravascular compartment into the third space may lead to hypoproteinemia, oliguria, acute renal failure and increased blood viscosity with changes in coagulation parameters resulting in severe morbidity and possible mortality due to thromboembolic events<sup>4</sup>.

Therefore, good preventive strategies may be required, which would enable a fair chance to achieve safe pregnancy and to reduce or avoid the occurrence of the syndrome as a life-threatening complication of IVF treatment. Although various strategies have been proposed and have been tried to prevent this serious complication, none was found to be completely effective. The key to prevent OHSS is recognition of risk factors for the syndrome and the experience with ovulation stimulation. Primary prevention includes identification of patients at high risk of OHSS such as younger age, a history of good response to gonadotropins, thin women, polycystic ovary syndrome (PCOS) and history of allergies. Ovulation induction protocols should be individually tailored with minimal dose and duration of gonadotropins combined with gonadotropin-releasing hormone (GnRH) antagonist or *in vitro* oocyte maturation, and carefully monitored. Secondary prevention represents all interventions for the early control of OHSS during ovulation induction including cycle cancellation, coasting, trigger ovulation by low doses of hCG or by alternative agents, cryopreservation of oocytes/embryos and adequate luteal phase support<sup>5,6</sup>. Current evidence demonstrates that age, antral follicle count and anti-müllerian hormone levels have proved as the best methods of predicting high ovarian response before starting COS. Although estradiol (E2) levels were previously less reliable in prediction of OHSS during ovulation stimulation<sup>7</sup>, currently E2 concentrations, the number of medium/large follicles on the day of hCG and the number of retrieved oocytes are regarded as reliable markers of high ovarian response<sup>8</sup>. There is high-quality evidence that replacing hCG by GnRH agonists and moderate-quality evidence that antagonist protocols, dopamine agonists and mild stimulation reduce the occurrence of OHSS. However, evidence for the effect of other interventions is of low/very low quality<sup>8</sup>. Accordingly, the objective of the present review is to analyze the effectiveness and

safety of medical strategies that currently may be justifiably utilized in the prevention of OHSS.

### GnRH Agonists

Gonadotropin-releasing hormone agonists trigger instead of hCG in the context of OHSS prevention has been used for >25 years. In its first decade, it did not gain popularity because it cannot work in GnRH agonist-based ovarian stimulation protocols. Although GnRH agonist initially binds and activates GnRH-receptors inducing a transient rise in gonadotropins, known as a flare-up, this is followed by a state of pituitary desensitization, resulting in a decrease in GnRH receptors and diminished response to GnRH stimulation. However, the GnRH antagonist occupies the GnRH receptor competitively without causing down-regulation. The antagonistic effects of GnRH antagonists may be overcome by GnRH agonists, as GnRH agonists have a greater affinity for the GnRH receptor than GnRH antagonists. By injecting a single bolus of GnRH agonist, the antagonist is displaced from the receptor by the GnRH agonist, which activates the receptor, inducing a flare-up of gonadotropins that accumulate during GnRH antagonist protocols and effectively stimulating the final oocyte maturation and ovulation<sup>9-11</sup>. Although a single bolus of hCG at mid-cycle has been the gold standard for triggering final oocyte maturation and ovulation in ART cycles, it seems that the GnRH agonist trigger may allow a more physiological surge of both luteinizing hormone (LH) and FSH. The short duration of the LH surge with the GnRH agonist trigger of approximately thirty-four hours has been shown to be beneficial for preventing OHSS in GnRH antagonist IVF cycles, when compared with the prolonged elevation of hCG ( $\geq 6$  days) after exposure to an hCG bolus<sup>12</sup>. Although an advantage of the GnRH agonist trigger is the ability to retrieve oocytes in high responders with a markedly reduced risk of OHSS, the induction of early luteolysis after the GnRH agonist trigger represents a problem that requires the use of aggressive steroidal luteal support or low-dose hCG to allow successful fresh embryo transfer (ET) and live birth. Early luteolysis following COS and GnRH agonist is likely due to supra-physiological steroid hormone concentrations inhibiting the LH secretion *via* negative feedback at the level of the hypothalamic-pituitary-gonadal axis and short-

er duration of the endogenously induced LH surge with a potential weaker activation of the LH/hCG receptor<sup>13</sup>.

Although different GnRH agonists have been used in GnRH antagonist cycles for the final oocyte maturation in high-responders, no universal consensus has been defined regarding the optimal agonist kind and dose, and there is no report evaluating the impact of different agonists on cycle outcomes. Among various GnRH agonists, buserelin 0.5 mg<sup>14</sup>, triptorelin 0.2 mg<sup>15,16</sup> and leuprolide acetate (0.5–4 mg)<sup>17,18</sup> have been utilized and almost all studies compared the outcomes of GnRH agonist triggered cycles with the cycles triggered with hCG. Most previous studies have reported successful oocyte maturation with 0.2–0.3 mg triptorelin, 0.5 mg buserelin and 1 mg leuprolide acetate<sup>14–16,19</sup>. Since there is no established triggering dose, GnRH agonists may be effective even at lower doses because 0.1 mg triptorelin effectively induces final oocyte maturation in IVF cycles similarly as standard doses. The rate of retrieved oocytes *per* follicle (89%) and fertilization rate (71%) support the use of lower doses of GnRH agonists in clinical practice<sup>16</sup>. Although higher doses of agonists for the final oocyte maturation have a potential to result in higher gonadotropin surge amplitude and improve the oocyte quantity, the mean number of retrieved oocytes varies and no clear benefit has been demonstrated by this approach<sup>18</sup>.

Since the possible standardization for GnRH agonist trigger criteria that will yield optimal outcomes have not yet been established, some authors used increased estradiol levels as a criterion<sup>20</sup>, whereas others assessed only excess number of available follicles during the late follicular phase of ovarian stimulation<sup>21</sup>. The criteria for GnRH agonist triggering for the patients at high risk of OHSS characterized by a high number of follicles (>12) measuring  $\geq 12$  mm and/or high serum E2 levels ( $\geq 4000$  pg/mL) have been suggested<sup>18</sup>. According to results from several studies in the last decade in OHSS high risk patients, the GnRH agonist for ovulation triggering significantly reduces or almost eliminates the incidence of OHSS and therefore GnRH agonist trigger is the best tool for OHSS prevention<sup>3,22–24</sup>. GnRH agonist triggering is a valid alternative to hCG triggering, resulting in elimination of OHSS and no other prevention strategy comes close to this result<sup>25</sup>. However, several anecdotal

cases of severe OHSS, even after GnRH agonist triggering combined with freezing all embryos in GnRH antagonist cycles have been published and in these cases of extreme hyper-responders other prevention strategies should be considered<sup>26,27</sup>. Therefore, clinicians should be aware that severe early OHSS could rarely occur even after GnRH agonist trigger instead of hCG, despite the fact that induction of final oocyte maturation with GnRH agonist significantly reduces the risk of OHSS. Moreover, an additional risk of late OHSS is possible if pregnancy occurs<sup>28</sup>. Despite acceptable cycle parameters following agonist-triggered cycles, a recently updated Cochrane review has reported that the use of GnRH agonist trigger instead of hCG in fresh autologous cycles was associated with a lower live birth rate, lower ongoing pregnancy rate and higher rate of early miscarriage. However, in donor-recipient cycles, the use of GnRH agonists resulted in a lower incidence of OHSS, with no evidence of difference in live birth rate. Therefore, GnRH agonist could be useful for women who choose to avoid fresh transfers, women who donate oocytes to recipients, or women who wish to freeze their eggs for later use in the context of fertility preservation<sup>29</sup>. Unfortunately, data from studies in the review were not comparable due to different luteal phase protocols used; therefore, the analysis missed the fact that luteal support is the factor which affects pregnancy rate and not the use of GnRH agonist trigger for final oocyte maturation<sup>30</sup>. Therefore, a meaningful comparison between GnRH agonist and hCG trigger must be confined to outcome measures that are not affected by the luteal support used<sup>31</sup>. Unfortunately, standard luteal phase support after GnRH agonist triggering has been reported to be associated with lower conception rates due to corpus luteum dysfunction. Aiming to attain an adequate luteal phase for a fresh embryo transfer and to improve IVF outcomes, the luteal phase support protocols after GnRH agonist trigger have emerged over recent years by using several different concepts. The American concept which relies mostly on intensive luteal support with aggressive exogenous administration of E2 and progesterone is effective in maintaining optimal conception rates in patients with peak E2 levels  $>4000$  pg/mL. The European approach promotes the production of endogenous steroids by the corpus luteum *via* exogenous supplementation of a small dose of hCG on the day of oocyte retrieval or on the day of GnRH agonist

trigger ('dual trigger'). However, patients with peak E2 levels <4000 pg/mL may benefit from dual trigger with GnRH agonist and 1000 IU hCG with intensive luteal phase support to optimize conception rates while still avoiding significant OHSS<sup>32,33</sup>. In patients at risk to develop severe OHSS with less than 20 oocytes retrieved following the ultra-short flare GnRH agonist/GnRH antagonist protocol, GnRH agonist trigger has been offered recently with an intensive luteal support and 1500 IU of hCG in order to improve IVF outcome while eliminating OHSS<sup>34</sup>.

Although the induction of final follicular maturation using GnRH agonist with its advantages over hCG trigger represents a paradigm shift in the ovulation triggering concept in ART, kisspeptins have also been shown to effectively elicit an LH surge, which suggests a completely new, 'natural' pharmacological option and as a new trigger concept<sup>35</sup>. It seems that the risk of OHSS development may be even more decreased following kisspeptin trigger comparing to GnRH agonist, but it is highly speculative because no study so far has been performed in an OHSS risk population and therefore its safety and efficacy remains to be determined<sup>3</sup>.

### GnRH Antagonist Protocols

Gonadotropin-releasing hormone antagonists directly and rapidly inhibit gonadotropin release during COS within several hours without hypo-estrogenic side effects, flare-up or long down-regulation and higher OHSS incidence as compared to GnRH agonists. Three different protocol regimens have been used including multiple-dose fixed (0.25 mg daily from day six or seven of COS) or flexible (0.25 mg daily when leading follicle is 14 to 15 mm) and single-dose regimen (3 mg on day 7 to 8 of stimulation) protocols, with or without the addition of an oral contraceptive pill. Although the probability of clinical pregnancy with GnRH antagonists initially seemed lower than with GnRH agonists, more recent studies were unable to provide any evidence for a difference in the live birth rates by using GnRH antagonists as compared to long GnRH agonist protocols. According to an update of a Cochrane review and forty-five RCTs, the use of GnRH antagonist compared with long GnRH agonist protocols was associated with a significantly lower incidence of OHSS and there was no evidence for a dif-

ference in live birth rates<sup>36-38</sup>. Comparing the effectiveness and safety of GnRH antagonist and GnRH agonist long protocol in supposedly normal ovarian responders undergoing IVF, results of a recent meta-analysis show that the number of stimulation days, gonadotropin amount, E2 value on the day of hCG, number of oocytes retrieved and incidence of OHSS were significantly lower with the GnRH antagonist protocol, whereas the ongoing pregnancy and live birth rates were similar in the two groups<sup>39</sup>. Evaluating the outcomes of IVF utilization of GnRH antagonists for ovarian stimulation in PCOS patients compared with long agonist protocols, the clinical pregnancy rate was similar in the two groups, whereas for severe OHSS, a GnRH antagonist protocol was significantly better in PCOS patients<sup>40,41</sup>.

### Dopamine Agonists

In a rat ovarian hyperstimulation model, it was demonstrated that low-dose dopamine agonist administration blocked VEGF-mediated vascular hyperpermeability without altering VEGF receptor(r) 2-dependent luteal angiogenesis<sup>42</sup>. Targeting the VEGF/VEGFR2 pathway by the administration of pharmacotherapy through low doses of dopamine agonists might be the most appropriate way to prevent OHSS in high-risk patients. The proposed mode of action appears to be through partial blockage of VEGFR2 specific phosphorylation sites involved in the development of vascular permeability without affecting tyrosine sites or activating angiogenic activity<sup>43</sup>. It is likely that decreased VEGF secretion leads to less VEGFR2 activation and lower amounts of phosphorylated VEGFR2 resulting in inhibition of increased vascular permeability and OHSS prevention<sup>44</sup>.

According to guidelines for the use of dopamine agonist, its use should be considered in patients at high risk of OHSS by the presence with one or more of the following findings: >20 growing follicles of more than 12 mm in diameter; E2 >3000 pg/mL; and in patients with a history of previous OHSS even without evident signs of high ovarian response. It would be preferable to start with the treatment a few hours before the injection of hCG, to enable the presence of dopamine agonists before the rise in VEGF production. Cabergoline is currently used at a daily dose of 0.5 mg for eight days despite its long half-life (65-69 h) because

it is the best known effective regimen with good tolerability, in addition to rectal bromocriptine at a daily dose of 2.5 mg for sixteen days as an alternative<sup>45</sup>. In hyperstimulated women undergoing ART, cabergoline successfully reduces hemoconcentration and ascites as a well-established and safe medication in the prevention of OHSS<sup>46</sup>. Although cabergoline is probably not as effective as replacing hCG with a GnRH agonist for decreasing the incidence of OHSS, it can be used as a secondary prevention measure for women at high risk of OHSS undergoing ART and it appears to reduce the risk of the syndrome, especially moderate OHSS. In addition, cabergoline reduces the occurrence of moderate-severe OHSS with no relevant negative effects on the number of retrieved oocytes or implantation rates and clinical pregnancy, without deleterious impact on pregnancy outcome<sup>47,48</sup>. Moreover, evaluating the long-term effects of prophylactic treatment with cabergoline, no negative impact on live birth rates and miscarriage rates without increased rate of congenital malformations of the babies born has been observed<sup>49,50</sup>.

Quinagolide used in a fixed regimen of three oral doses (50, 100 and 200 µg/day), starting on the day of hCG and continued for 17-21 days, significantly reduces the frequency of moderate/severe early OHSS (12% *vs.* 13% *vs.* 4%) as compared with placebo (23%), without compromising pregnancy or treatment outcome. Although the 200-µg dose of quinagolide was most effective in preventing moderate/severe early OHSS in IVF patients, this dose was associated with poor tolerability when administered without dose titration, but also lower doses of quinagolide may be efficacious. The treatment effect is more marked in patients that did not achieve clinical pregnancy and therefore it may be more suitable for oocyte donors or for patients with postponed embryo transfer. However, if quinagolide is used at high doses without dose titration, it is associated with poor tolerability, although the incidence of deleterious events declines after the initial days of treatment<sup>51</sup>.

Bromocriptine is the next dopamine agonist after cabergoline which evokes interest in recent years, owing to its advantages in patients at risk of OHSS, including its shorter half-life and greater experience with this drug in pregnancy, the lack of teratogenicity, despite side effects such as nausea, headaches and orthostatic dysregulation. The incidence of clinically sig-

nificant OHSS was significantly lower (17.5%) as compared to controls (40.9%) due to the beneficial effect of bromocriptine 2.5 mg for rectal insertion, starting on the day of ovum pick up for a period of sixteen days, with no differences between the groups in clinical pregnancy rates<sup>52</sup>.

Although according to a recent meta-analysis the use of dopamine agonists appears to be useful for the prevention, but less effective for the treatment of OHSS, yet so far, no conclusions can be made as for when to start and stop treatment, the most effective drug, the optimal dose, or the most appropriate drug regimen<sup>53</sup>. However, in the light of the new pathogenic and pharmacological evidence, currently dopamine agonists should definitely be considered for prevention of both early and late OHSS. Future prospective randomized studies should compare different modalities in women at high risk of OHSS<sup>54</sup>.

### Mild Stimulation Protocols

Mild ovarian stimulation for IVF uses a low dosage of gonadotropins (100-150 IU), which usually starts in the early follicular phase in combination with a GnRH antagonist five to seven days of stimulation to produce a maximum of ten oocytes. However, minimal stimulation refers to the use of a sequential administration of clomiphene citrate (CC) followed by low-dose gonadotropins and a GnRH antagonist that yields a maximum of five oocytes, with a range from one to five. Both stimulations offer an attractive option to reduce the incidence of OHSS in patients who have experienced this complication in a previous treatment cycle or in high-responders<sup>55</sup>. However, there is only moderate-quality evidence that mild stimulation reduces OHSS without producing a clinically relevant difference in clinical pregnancy rates<sup>8</sup>. Since recently, scientific interest has been increasingly focused on mild approaches for ovarian stimulation in clinical practice because mild stimulations are more physiological, aiming to develop safer and more patient-friendly protocols, less drug use, lower costs and decreased risks of treatment, especially OHSS. A lower incidence of OHSS (4.7%) was observed in patients with a mild/minimal stimulation protocol of recombinant FSH combined with GnRH antagonist than in patients with a standard long protocol (8.4%). Although a significantly higher pregnancy rate (37.7%

*vs.* 23.4%) and delivery rate (32.8% *vs.* 20.1%) were observed in favor of patients with mild stimulation compared to conventional long down-regulation regimen, these data are not evidence based<sup>56</sup>. Comparing the effectiveness of mild ovarian stimulation with GnRH-antagonist and long protocol with low-dose FSH in young, normo-ovulatory responders undergoing IVF, the incidence of severe OHSS, as well as pregnancy and implantation rates were comparable

with the two regimens<sup>57</sup>. Furthermore, there was no evidence indicating that minimal stimulation regimens differed significantly from gonadotropins in GnRH agonist protocols in terms of OHSS incidence and live births or pregnancy rates. According to findings from a Cochrane analysis, the use of CC with gonadotropins (with or without mid-cycle antagonist) led to a reduction in the incidence of OHSS varying between 0.8% and 1.8%, compared with 3.5% preva-

Table 1. Characteristics of current medical strategies in the prevention of ovarian hyperstimulation syndrome

Medical strategies /characteristics	Studies	Advantages	Disadvantages	Quality of evidence
GnRH agonist trigger - buserelin 0.5 mg - triptorelin 0.2 mg - leuprolide acetate 0.5-4 mg	Thomsen <i>et al.</i> <sup>3</sup> Casper <i>et al.</i> <sup>12</sup> Engmann <i>et al.</i> <sup>14</sup> Gülekli <i>et al.</i> <sup>16</sup> Humaidan <i>et al.</i> <sup>21</sup> Griesenger <i>et al.</i> <sup>22</sup> Fatemi <i>et al.</i> <sup>26</sup>	Short duration of LH surge (34 hours) Reduced or almost eliminated OHSS Best tool for OHSS prevention Satisfactory pregnancy rate in fresh cycles with intensive luteal steroidal support or low-dose hCG	Early luteolysis Embryocryopreservation or ET in fresh cycle with aggressive luteal steroidal support or low-dose hCG Several cases of OHSS despite embryocryopreservation Risk of late OHSS with pregnancy	High
GnRH antagonist regimens - single 0.3 mg - multiple 0.25 mg - fixed - flexible	Al-Inany <i>et al.</i> <sup>37</sup> Giliam <sup>38</sup> Xiao <i>et al.</i> <sup>39</sup> Lin <i>et al.</i> <sup>40</sup> Xiaou <i>et al.</i> <sup>41</sup>	Lower number of stimulation days, gonadotropin doses and estradiol levels Lower incidence of OHSS No difference in live-birth rates comparing with GnRH agonist protocols	Lower number of oocytes retrieved	Moderate
Dopamine agonists - cabergoline 0.5 mg - quinagolide 200 mcg - bromocriptine 2.5 mg	Soares <sup>45</sup> Tang <i>et al.</i> <sup>47</sup> Leitao <i>et al.</i> <sup>48</sup> Youssef <i>et al.</i> <sup>49</sup> Alvarez <i>et al.</i> <sup>50</sup> Busso <i>et al.</i> <sup>51</sup> Baumgarten <i>et al.</i> <sup>53</sup>	Lower occurrence of mild-severe OHSS No negative effects on the number oocytes retrieved and pregnancy outcome (miscarriage, congenital malformations and live-birth rate)	Less effective for the treatment of OHSS	Moderate
Mild stimulation - lower doses of gonadotropins - CC with gonadotropins	Nastri <i>et al.</i> <sup>8</sup> Zarek <i>et al.</i> <sup>55</sup> Rinaldi <i>et al.</i> <sup>56</sup> Casano <i>et al.</i> <sup>57</sup> Gibrel <i>et al.</i> <sup>58</sup> Figueiredo <i>et al.</i> <sup>59</sup>	Mild ovarian response Less drug use and lower cost Lower incidence of OHSS Satisfactory pregnancy rates and pregnancy outcome	Higher risk of miscarriage rates is correlated with poor ovarian response comparing to hyper-response to ovarian stimulation	Moderate

OHSS = ovarian hyperstimulation syndrome; LH = luteinizing hormone; GnRH = gonadotropin-releasing hormone; ET = embryo transfer; CC = clomiphene citrate

lence of OHSS using a GnRH agonist regimen<sup>58</sup>. It is likely that CC with gonadotropin and GnRH antagonist decreases the risk of OHSS because in a recent meta-analysis there was a significant reduction in OHSS (0.5%) as compared with conventional controlled ovarian hyperstimulation (4.1%)<sup>59</sup> (Table 1).

## Conclusion

Although among currently available medical strategies none is completely effective, there is high-quality evidence that replacing hCG by GnRH agonists and moderate-quality evidence that antagonist protocols, dopamine agonists and protocols with a mild ovarian response reduce the occurrence of OHSS. GnRH agonist trigger is the best tool for OHSS prevention due to significant decrease in the incidence of OHSS, however, the use of intensive steroidal luteal support or low-dose hCG is required to achieve optimal conception rates. The incidence of OHSS was significantly lower in the GnRH antagonist protocol than in GnRH agonist long regimen, whereas live birth rates were similar in the two groups. Among dopamine agonists used, cabergoline, quinagolide and bromocriptine are the most common drugs that should be considered for OHSS prevention, especially for moderate forms of the syndrome, without adverse effects on pregnancy outcome. Furthermore, protocols with a mild ovarian response represent an attractive option to reduce the incidence of OHSS in patients who have experienced this complication in a previous treatment cycle or in high-responders with satisfactory pregnancy outcome.

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## Sažetak

## MEDIKAMENTNA PREVENCIJA SINDROMA HIPERSTIMULACIJE JAJNIKA

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Svrha ovoga rada bila je analizirati današnje medikamentne strategije u prevenciji sindroma hiperstimulacije jajnika za vrijeme stimulacije ovulacije u postupku izvantjelesne oplodnje. Zahvaljujući suvremenim metodama prevencije pojavnost sindroma hiperstimulacije se kreće od 0,18% do 1,40%. Premda se nijedna preventivna strategija nije pokazala u potpunosti djelotvornom, postoje čvrsti dokazi da zamjena humanog korionskog gonadotropina gonadotropnim otpuštajućim hormonom nakon antagonista gonadotropnog otpuštajućeg hormona te umjereni dokazi da protokoli antagonista gonadotropnog otpuštajućeg hormona, agonisti dopamina i blagi protokoli smanjuju pojavnost sindroma hiperstimulacije. Između nekoliko agonista gonadotropnog otpuštajućeg hormona najčešće se koriste buserelin 0,5 mg, triptorelin 0,2 mg i leuprolid (0,5-4 mg). Premda se danas smatra da je gonadotropni otpuštajući hormon najuspješniji u prevenciji sindroma hiperstimulacije jajnika, zbog rane luteolize potrebna je intenzivna potpora žutom tijelu primjenom estradiola i progesterona ili sniženim dozama humanog korionskog gonadotropina na dan aspiracije jajnih stanica da bi se postigle optimalne stope zanošenja. Između danas dostupnih agonista dopamina kabergolin, kinagolid i bromokriptin su lijekovi koji se najčešće primjenjuju i koje bi trebalo primjenjivati u prevenciji ranog i kasnog oblika sindroma hiperstimulacije. Blagi stimulacijski protokoli predstavljaju privlačan izbor u prevenciji sindroma hiperstimulacije sa zadovoljavajućim stopama trudnoće.

*Ključne riječi: Sindrom hiperstimulacije jajnika – prevencija i kontrola*