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Towards complication-free assisted reproduction technology

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Assisted reproductive technology (ART) has vastly improved over the last 40 years, from a frequently unsuccessful and complicated procedure requiring hospital admission and routine laparoscopy to a fairly simple outpatient technique with relatively high success rates. However, it is important to stress that ART is not without risk and medical complications may still occur. The incidence of most of these ART-related complications is associated with how women undergo ovarian stimulation. For this reason, physicians should be aware that a carefully thought-out ovarian stimulation protocol and cycle monitoring are of paramount importance to maximise the success of the treatment while avoiding potentially life-threating complications to occur in this frequently otherwise healthy patient population. This review discusses the rationale and evolution of ovarian stimulation strategies over the years and the

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current developments towards finding a balance between the retrieval of a sufficient number of oocytes and ART-related complication prevention.

Ovarian stimulation (OS) is historically regarded as a milestone for the treatment of infertility [1], as it allowed physicians to bypass the natural phenomena of follicular dominance and atresia by artificially overcoming the *follicle-stimulating hormone (FSH) threshold* and inducing multi-follicular (instead of mono-follicular) development [2]. The generalized use of exogenous gonadotropins during assisted reproductive technology (ART) has led to a substantial increase in pregnancy rates, from the typical 3–10% range (using no or minimal stimulation) to 20–50% [3]. While there is a clear advantage in using OS in routine ART, one must be aware that its administration requires a comprehensive knowledge of how the ovaries react to hyperstimulation, as an unsuspecting user may fail to adequately avoid a premature luteinizing hormone (LH) surge, or worse, cause ovarian hyperstimulation syndrome (OHSS) or other potentially lethal complications.

Over the last years, a fervid discussion regarding OS dosing and the "sweet spot" which may maximize ART pregnancy outcome without affecting the safety of the procedure has been ongoing. Most of the discussion has circulated around whether an increasing number of oocytes retrieved is always associated with better pregnancy outcomes or not. The two first large registry studies which analysed the outcome of only the first embryo transfer both concluded that live birth rates plateau as soon as at least 10–15 oocytes are collected [4,5]. However, these studies did not account for the potential benefit of the transfer of supernumerary frozen embryos in subsequent cycles – *i.e.* the cumulative live birth rate after one oocyte retrieval cycle – which is considered by many to be the most accurate benchmark for ART success [6]. When assessing the relationship between oocyte retrieval rates and cumulative ART outcomes, the results seem conflicting, with some studies proposing that there is a plateau as soon as approximately 15–20 oocytes are retrieved [7], while others conclude that cumulative live birth rates continue to increase with the number of oocytes collected [8–10]. These contrasting results have led to a frequent debate among physicians who question what the best approach for their patients may be, namely to either (a) perform a tailored stimulation and thrive to obtain between 15 and 20 oocytes per oocyte retrieval in order to minimize potential complications as much as possible or (b) to allow for the development of more retrievable oocytes and apply secondary preventive measures to ensure patient safety whenever an excessive response occurs.

What are the main complications of ovarian stimulation and how can we prevent them?

ART has vastly improved over the last 40 years, from a highly unsuccessful and complicated procedure that required hospital admission and consecutive laparoscopies for oocyte retrieval and/or embryo transfer to an outpatient technique with relatively high success rates of 50–80% [11]. Moreover, owing to progressive advances in the gonadotropin arsenal available for OS and procedures performed during OS cycle monitoring, complications associated with ART have gradually reduced over time [12]. However, it is important to stress that ART is not without risk and medical complications may still occur. Specifically, following ovarian hyperstimulation, serious complications such as OHSS, thromboembolism and ovarian torsion may occur at a rate which should not be deemed insignificant, especially in view of the fact that one should expect these complications to be underreported [13]. Moreover, despite the increased safety measures, the rate of these specific ART complications has remained relatively stable since the year 2000 [14]. In this sense, adequate stimulation is of paramount importance, given that the most relevant ART-related complications are determined by how patients are stimulated [15].

Ovarian hyperstimulation syndrome

OHSS is an exaggerated response to OS characterized by cystic enlargement of the ovaries, abdominal distention and fluid shift from the intravascular space to the third space which can result in

ascites, pericardial and pleural effusions, and even generalized oedema [16]. Although this syndrome has been extensively studied, its pathophysiology remains rather elusive. Until now, there is sufficient evidence to believe that OHSS results from an excessive secretion of vasoactive substances during OS, namely vascular endothelial growth factor (VEGF) and factors that derive from the renin–angiotensin system [17]. VEGF is produced by the granulosa cells after stimulation with gonadotropins and increases sharply following the administration of human chorionic gonadotropin (hCG) due to a hypersensitivity to this latter hormone [18]. This vasoactive substance over-secretion seems to be almost entirely dependent on the activity of LH, which is present for only a short period in the natural cycle. During ART, however, final oocyte maturation and ovulation are frequently triggered with hCG, which, in comparison to LH, has a substantially longer half-life [19].

While its general incidence is approximately 2%–3% per cycle, OHSS can occur in up to a third of all cases of high-risk patients [20], namely in those with a previous history of OHSS or polycystic ovaries. In its most severe forms, this syndrome has the potential to cause serious morbidity or mortality, mainly due to the increased occurrence of ovarian torsion and thromboembolism [21]. In fact, OHSS in the most frequent complication of ART [14] and, with it, comes an increase in the risk of many other potential complications of ART. For this reason, the largest step towards a complication-free ART era entails thriving to develop an OHSS-free clinic [22], given that between 72% and 83% of all ART complications are OHSS-related (Table 1).

The key discovery that led to the first drastic reduction in ovarian hyperstimulation syndrome – gonadotropin-releasing hormone antagonists

In the early days of ART, researchers were evaluating the use of exogenous gonadotropin-releasing hormone (GnRH) agonists in women with hypogonadotropic hypogonadal anovulation [23]. These investigators noted that a continuous administration of GnRH agonist would cause a GnRH receptor depletion with subsequent pituitary desensitization and the abolition of LH and FSH production. What was initially perceived as a failure in treatment for hypogonadotropic hypogonadal women eventually led to the development of the long-agonist GnRH protocol [24], the mainstream co-treatment modality for at least the first 20 years of ART [2]. By adding GnRH analogues to OS, physicians were able to reduce cycle cancellation rates by 67% while increasing clinical pregnancy rates by 70% [25]. However, since the year 2000, a new approach has been developed with the advent of GnRH antagonists [26]. Conversely to GnRH agonists, GnRH antagonists cause immediate pituitary suppression, obviating the need for a more prolonged and cumbersome administration of GnRH analogues. This more patient-friendly approach has shown to have comparable pregnancy outcomes, leading many to recommend that it become the new “standard” in IVF [27,28]. More importantly, head-to-head trials have shown that the use of GnRH antagonist is associated with a significantly lower incidence of OHSS. Specifically, when pooled together in a recent meta-analysis [29], the studies evaluating the use of GnRH antagonist co-treatment revealed that it was associated with a decreased odds-ratio of 0.61 (95% confidence interval 0.51–0.72) for OHSS, which, in absolute terms, resulted in a reduction from 11% (after GnRH agonist) to 6–9% (following GnRH antagonists).

With GnRH antagonists being recognized as the principal weapon to prevent OHSS, several researchers have postulated whether extending its administration beyond OS in women with an increased risk for OHSS may not be of added value. While the concept may be of interest, a recent

Table 1
OS-related complication and the association with OHSS.

ART-related complication	Overall risk	With OHSS
Thromboembolism [93]	0.04–0.2%	4%
Adnexal torsion [93]	0.08–0.11%	3%
Lobar pneumonia [94]	Unknown	4%
ARDS [94]	Unknown	2%
Pulmonary embolism [94]	Unknown	2%
Death [95]	0.001%	Present in ±50% of the cases of death

ART, assisted reproductive technology, OHSS, ovarian hyperstimulation syndrome; ARDS, Acute respiratory distress syndrome.

systematic review has highlighted that this approach still requires validation and, for now, should not be considered a first-line option for the prevention and/or treatment of OHSS [30].

Tailoring the approach to ovulation triggering and embryo transfer following excessive ovarian response – the GnRH agonist trigger and "freeze-all" strategies

Even though GnRH antagonist therapy is associated with a significant reduction in the occurrence of severe OHSS, the syndrome continues to exist, especially when hCG is used for final maturation and ovulation triggering [22]. The reason for this seems to stem from the fact that hCG has a sustained luteotropic effect, which continues for up to 6 days following the administration of the drug, even when a dose of 5000 IU is administered [31]. Consequently, many authors have proposed that women with a high risk of developing OHSS should perform OS under GnRH antagonist suppression and use a GnRH agonist for triggering instead [20,32]. When administered, the GnRH agonist will cause the displacement of the GnRH antagonist from the pituitary receptors, resulting in the induction of an LH flare-up that lasts only for approximately 24–36 h in total [19]. Although this approach has effectively reduced the incidence of OHSS [33], it has not eliminated the risk completely [34–38].

GnRH agonist triggering has been increasingly acknowledged as a worthy strategy to minimize the risk of OHSS [22]. However, while seeming equally efficient in terms of oocyte competence [39], the generalized use of GnRH agonist triggering has remained thus far limited by the fact that this approach seems to cause an artificially shortened luteal phase with abrupt luteolysis which significantly reduces ART pregnancy outcomes [40,41]. In light of these reduced clinical pregnancy rates, several possible strategies have been proposed.

The first strategy is intensive luteal phase support with either an alternative supplementation of progesterone and oestradiol [42] or a low-dose administration of hCG immediately after oocyte retrieval [43]. While this approach seems to increase pregnancy rates after GnRH triggering, this improvement may potentially come at the cost of once more increasing the risk of OHSS [44,45].

A second strategy (*i.e. freeze-all strategy*) is to electively cryopreserve all embryos and then replace them in a subsequent frozen embryo transfer cycle [22], which, until now, has been shown to be the method most effective at reducing the occurrence of severe OHSS [46].

Although both these approaches to resolve the low pregnancy rates after agonist triggering seem reasonable, there is no consensus on which is the most adequate since no comparative trial has ever been published. To that extent, an RCT comparing the efficiency and safety of both strategies has recently recruited its last patient and is in its final stages of data accrual (further information on the trial is available at https://clinicaltrials.gov/ct2/show/NCT02148393).

Finally, another ovulation triggering drug – kisspeptin – is also currently under investigation as a potential alternative to both hCG and GnRH agonist triggering [47]. When administered, kisspeptin induces a dose-dependent release of LH and FSH, thus mimicking the effect obtained by the administration of a GnRH agonist. However, concerns on the post-trigger endocrine profile of this relatively unstudied drug [48] deem further studies necessary to confirm whether its routine use does not decrease ART pregnancy outcomes.

The new "rule number 1" of the ART complication-free era: one cannot "go wild" on stimulation just because we have efficient OHSS secondary prevention measures!

The systematic review of Youssef et al. [44] has shown that, in comparison to hCG, women who perform GnRH agonist triggering have a 20-fold reduction in OHSS risk, with a mere 2 cases reported (0,3%) in the 689 women studied. These surprising results may give the false impression that one no longer needs to care for safety during OS and that we can now finally consider ART clinics to be OHSS-free [22]. Moreover, the fact that the first-ever reported case of severe OHSS after GnRH agonist triggering and freeze-all [35] was met with controversy [49] led further to a false sense of "absolute" safety in modern-day OS. This information when taken together with recent evidence that cumulative live birth rates could increase linearly with the number of oocytes retrieved [8–10], may also lead physicians to believe that the days of "wild stimulation" have finally arrived.

Shortly following the first case of severe OHSS after a freeze-all strategy [35], another seven were reported, the last of which the patient agreed to undergo whole exome sequencing in order to exclude genetic causes of OHSS [38]. However, the fact that in none of these reports there was an apparent

genetic predisposition for OHSS are a testament that caution during OS is still warranted to avoid not only OHSS, but other complications associated with OS such as ovarian torsion and thromboembolism.

Cycle monitoring and secondary predictive factors for OHSS

Physicians frequently monitor women under OS using consecutive transvaginal ultrasound and blood hormones evaluations in order to detect unexpected poor or excessive ovarian response and to optimise timing for ovulation triggering [50]. Moreover, cycle monitoring is also an important tool to assess the patient's risk for OHSS and to prevent its' occurrence. Regarding the latter, the number of follicles with a mean diameter above 10–11 mm is currently the best predictor during cycle monitoring. Specifically, one of the first studies to evaluate this finding, performed by Papanikolaou et al. [51], concluded that detecting $\geq$18 follicles above 10 mm on the day of ovulation triggering was a reasonable predictor of severe OHSS, with an estimated sensitivity and specificity of 83% and 84%, respectively. These results were confirmed recently in a post-hoc analysis [52] of 3 randomized controlled trials (sensitivity and specificity 74.3% and 75.3%, respectively), albeit using a slightly different threshold ($\geq$19 follicles above 10 mm).

Although oestradiol levels above 2500–3500 pg/mL have also been traditionally considered as a reliable predictor of OHSS [50], it seems to deliver very little added-value when evaluated in combination with the number of developing follicles [51,52]. Most importantly, up to 70% of all cases of OHSS may be missed when oestradiol is used as the sole risk predictor [52]. Thus, basing the decision to perform additional OHSS preventative strategies solely on oestradiol levels is not advisable.

Other OHSS prevention strategies

Severe OHSS is, fortunately, an uncommon iatrogenic complication of OS today. Nevertheless, as this is an iatrogenic complication of a non-vital treatment with a potentially fatal outcome, it remains a severe problem for specialists performing ART. Although the major advantage of the freeze-all strategy is its potential to practically eliminate OHSS, several other strategies can also be applied, especially by paying appropriate attention to the risk factors for OHSS development and considering tailoring OS.

Primary prevention. Although there is currently no method that can completely abolish OHSS, its prevention can be lifesaving and is highly preferred over its treatment. Thus, the prevention of OHSS is based greatly on its risk prediction. The first method to prevent OHSS is a strategic planning of the stimulation regimen according to the circulating levels of anti-Mullerian hormone (AMH), antral follicle count (AFC) and historical background of the patient. A recent Cochrane review showed no difference in the type of gonadotropin used for outcomes including live birth, OHSS, clinical pregnancy and multiple pregnancy rates [53]. However, the minimum gonadotropin dose should be used for OS in patients with polycystic ovaries and step-down regimes should be considered whenever necessary.

Many studies have investigated how the suppression of insulin levels with metformin might reduce hyperinsulinemia and its effect on ovarian response. In fact, the results of a meta-analysis including 8 RCT concluded that metformin significantly reduced the risk of OHSS by 63% and increased clinical pregnancy rates, with no effect on live birth rates [54].

Secondary prevention. Other alternative secondary preventive measures could be considered in patients with an exaggerated response to OS. Firstly, cycle cancellation before final follicular maturation with hCG is a simple and safe alternative to avoid OHSS. However, as it associated with significant emotional and financial burden for the couple, it is, therefore, a difficult decision for clinicians [55]. Another possible option is withholding daily gonadotrophins prior to administration of hCG in IVF cycles (*i.e. coasting*) has also been used to reduce this risk of OHSS. However, results of a systematic review revealed that there was no difference in the incidence of moderate and severe OHSS between patients who underwent this technique [56].

Based on the pathophysiological explanation of OHSS, where VEGF is responsible for an increase in the capillary permeability by binding to VEGF receptor 2, dopamine agonists have been shown to be able to antagonize VEGF-dependent vascular permeability by inhibiting VEGFR-2 phosphorylation and signaling. In the prevention of OHSS, cabergoline successfully reduced the incidence of moderate OHSS

with no significant effect on clinical pregnancy and miscarriage rates [53]. Thus, the administration of oral cabergoline, starting on the day of hCG triggering at a dose of 0.5 mg for 8 days, can also be recommended [57]. Furthermore, as supraphysiological OS may cause platelet hyperstimulation, some studies have shown that low-dose aspirin therapy (100 mg daily, starting on the first day of OS) may reduce further the risk of severe OHSS [58]. However, this strategy requires more extensive validation prior to widespread use [53].

Lastly, in-vitro maturation can be considered as another alternative method for fertility treatment in patients who are at high risk for OHSS. This simple and more economical procedure may be less stressful for women [59] and has not had a reported case of early-onset OHSS thus far.

Ovarian torsion

Ovarian torsion is a surgical emergency which can lead to the loss of the ovary, peritonitis and even death [60]. The incidence of ovarian torsion during ART has been reported to be between 0.08% and 0.2% [61,62]. This increased risk after OS is assumed to be due to resulting ovarian enlargement and is seen more frequently in cases of OHSS [63]. Among women taking gonadotrophins, an association between the increased risk of ovarian torsion, peak oestradiol levels and ovarian diameter has also been reported [64]. Moreover, those who become pregnant following fresh embryo transfer are especially prone to adnexal torsion as hCG continues to support the lutein cysts. During pregnancy, this complication is generally encountered during the first trimester, although it may also sporadically occur later in pregnancy [65].

The diagnosis strongly relies on the patient's symptoms and signs, including unilateral lower abdominal pain, nausea, vomiting and progressive leucocytosis and/or anaemia. The most consistent imaging finding is asymmetric enlargement of a twisted ovary [66]. Although ultrasound with doppler may confirm the diagnosis in case there is an absence of flow at the level of the ovarian vessels, the presence of flow does not exclude torsion and may be normal in up to 60% of all cases [60]. During OHSS, the diagnosis of ovarian torsion is more difficult as the symptoms are less specific for torsion [21] and during early pregnancy a differential diagnosis with an extra-uterine pregnancy is necessary.

Follow-up management for patients with an ovarian torsion should take into account that adhesions around the adnexal lesion might occur [67]. Moreover, when surgery for adnexal torsion needs to be performed during pregnancy, a miscarriage rate of 16.6% has been reported [65].

To prevent ovarian torsion, women undergoing OS should be advised to avoid strenuous physical activity and, in case of OHSS, a freeze-all embryo approach should be considered, knowing that the occurrence of a pregnancy can further increase the risk of late-onset OHSS and adnexal torsion [21].

Thromboembolism

A thromboembolic event is a rare ART complication, however, one associated with significant morbidity and even mortality. It is well known that women during pregnancy and in puerperium are at risk to develop venous thromboembolism (VTE) – *i.e.* deep vein thrombosis or pulmonary embolism [68]. In the ART setting, successful cycles are more prone to VTE [69] and, although arterial thromboembolic events are even rarer than VTE, this latter complication has been reported following ART as well [70].

Initially, the overall VTE risk in women pregnant following IVF has been reported to be between 0.08% and 0.11% [71]. However, a more recent VTE risk of 0.42% after ART has been reported versus a 0.25% risk following natural conceptions [72]. To assess whether and how this elevated risk is related to the ART procedure, confounder-adjustment strategies were of utmost importance, given that the incidence of thromboembolic events is known to increase with age, multiple pregnancies and over time [73,74].

In women with OHSS, an even more significant risk of VTE has been described from 0.78% up to 11% [75], even after excluding the potential confounding risk of pregnancy [69]. The exact mechanism predisposing to excessive clotting is unclear but is likely to involve multiple concomitant factors associated with hyperstimulation such as abnormal oestradiol and VEGF levels, third-space fluid shifting with haemoconcentration and other hypercoagulable changes [75].

There is broad agreement that a women's VTE risk should be assessed preconceptionally and again during pregnancy [76], however, the recommendations guiding thromboprophylaxis are not uniform [77] and there is even less evidence guiding in the context of ART. Thromboprophylaxis should be considered in patients with known thrombophilia and in cases of moderate or severe OHSS [70]. A selective thrombophilia screening based on a history of a thromboembolic event is also recommended and has been shown to be cost-effective prior to other high-risk situations such as oral oestrogen administration, pregnancy and major orthopaedic surgery [78].

Long-term risks

As the use of ART steadily rises [79], an increasing number of researchers have shown potential concern regarding the risk of exogenous gonadotropin use and long-term female health. These fears are rooted in the fact that infertile women have multiple factors (*e.g.* anovulation, endometriosis and nulliparity) which are frequently also associated with an increased risk of cardiovascular disease [80] and cancer [81] and also since many cancers (*e.g.* breast, ovarian and uterine cancers) can be hormone-dependent [82]. Although some studies did posit an increased risk for (borderline) ovarian [83,84], breast [85] and endometrial [86] cancers, and melanoma [87], these concerns have been relatively assuaged for now by large registry analyses in which special care was taken to untangle the potential effect of OS from the confounding factors involved in infertility itself [88–92].

Summary

The vast majority of the couples performing ART are generally young and otherwise healthy. While this apparent absence of co-morbidities may mitigate the possibility of complications, ART can still be followed by iatrogenic events. Among these, OHSS in the most frequent complication and, with it, comes an increase in the risk of many other potential complications such as ovarian torsion and VTE. That said, the use of GnRH antagonist co-treatment is the most important OS-related strategy to minimize the incidence of OHSS, followed by GnRH agonist triggering and the elective deferral of a fresh embryo transfer. Collectively, these secondary preventive strategies have practically abolished the modern-day risk of OHSS.

Conflicts of interest

SSR declares that he has received research grants from Ferring Pharmaceuticals, MSD and Merck Serono, and consultancy fees from MSD and Besins. All other authors have no conflicts of interest to declare pertaining to this article.

Practice points

- Although ART is fairly a safe and simple outpatient technique generally performed in relatively young and otherwise healthy women, it is not without risk and medical complications may still occur.
- OHSS in the most frequent complication of ART and, with it, comes an increase in the risk of many other potential complications such as ovarian torsion and VTE. Since up to 83% of all ART complications are OHSS-related, the largest step towards an era of complication-free ART will be achieved by efforts towards attaining an OHSS-free ART clinic.
- The use of GnRH antagonist co-treatment is the most important OS-related strategy to minimize ART complications, followed by GnRH agonist triggering and the elective deferral of a fresh embryo transfer. Collectively, these secondary preventive strategies have practically abolished the modern-day risk of OHSS. However, careful cycle monitoring and gonadotropin dosing are still recommended and "wild" stimulation should not be performed.

Research agenda

- To determine the long-term complication associated with ART
- To compare the pregnancy outcomes and OHSS rates of the "*freeze-all*" and luteal phase rescue strategies after GnRH agonist triggering
- Validate the clinical usefulness of alternative drugs for final oocyte maturation such as kisspeptin

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