RBMO

COUNTERCURRENT

Why ovarian stimulation should be aimed to maximize oocyte yield

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ABSTRACT

The ultimate measure of success of assisted reproductive technology (ART) is the cumulative live birth rate (CLBR) per ovarian stimulation cycle, which increases with every oocyte collected. However, the adverse effects of ovarian stimulation on endometrial receptivity, as well as the risks of ovarian hyperstimulation syndrome (OHSS) and adverse obstetric and neonatal outcomes, are observed to increase with ovarian response to stimulation. To mitigate these risks, mild stimulation has been hailed as the safer patient-friendly approach with the additional benefit of cutting the cost of gonadotrophins. Yet accumulating data demonstrate the absence of an adverse effect of ovarian stimulation on oocytes as well as on obstetric and neonatal outcomes, and multiple preventive strategies have been introduced for OHSS. The widespread use of vitrification revolutionized ART by enabling the liberal use of cycle segmentation to minimize the risk of OHSS and avoid impaired endometrial receptivity due to ovarian stimulation. Vitrification also allowed every oocyte to contribute to the CLBR. Thus, it is questionable whether the cost savings from gonadotrophins during the index ovarian stimulation offset the cost saving by preventing repeat ovarian stimulation and repeat laboratory procedures per live birth. This paper aims to prove by contradiction that ovarian stimulation should be aimed to maximize oocyte yield.

THE GOAL OF ASSISTED REPRODUCTIVE TECHNOLOGY

Cumulative live birth rate (CLBR) per ovarian stimulation cycle is the ultimate measure of success in contemporary assisted reproductive technology (ART). Even family completion by having more than one child with one ovarian stimulation cycle is an achievable goal for women with an adequately high ovarian reserve. Since CLBR continuously increases in parallel with the number of oocytes collected (*Fanton et al., 2023*; *Law et al., 2021*), stimulating every woman to her full potential seems to be the rational approach. This paper aims to prove this by contradiction.

EFFECTIVENESS CONCERNS

If ovarian stimulation were to grow follicles of lower quality, which would be destined to atresia in a natural cycle, or exogenous gonadotrophins were harmful to follicles or oocytes, one could expect that the additional oocytes from such follicles would not significantly contribute to live birth rate (LBR). Then no stimulation or, if the suggested adverse effect of ovarian stimulation were dose dependent, 'mild stimulation' rather than maximal stimulation would be the logical approach that would decrease the risk of ovarian hyperstimulation syndrome (OHSS) and cut the costs of gonadotrophins. This argument resembles the maxim 'less is more' for ovarian stimulation. However, consistent evidence from multiple observational studies suggests otherwise.

Studies cumulatively involving more than 20,000 embryos from over 4000 ovarian stimulation cycles have reported similar age-adjusted euploidy rates across the number of embryos available for comprehensive chromosome screening or the number of oocytes collected (*Ata et al., 2012*; *Barash et al., 2017*; *Irani et al., 2020*). Moreover, blastulation and euploidy rates were not affected by cumulative gonadotrophin exposure (*Barash et al., 2017*; *Irani et al., 2020*). An earlier trial that reported a higher aneuploidy rate with conventional ovarian stimulation than mild ovarian stimulation was limited by the application of blastomere biopsy from cleavage-stage embryos and testing for a limited number of chromosomes by fluorescent in-situ hybridization and was prematurely terminated based on an unplanned interim analysis (after including only 111 women), which downgrades the evidence provided (*Baart et al., 2007*). Since the findings of this trial have not been corroborated in any of the much larger observational studies, evidence against the harm of ovarian stimulation on euploidy rate seems to be overwhelming.

If the oocytes from the salvaged follicles would not contribute to the LBR, one

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would expect to see a plateau in CLBR across the number of oocytes collected. While a landmark paper published more than a decade ago suggested that LBR indeed plateaued around 15 oocytes, the analysis was limited to fresh embryo transfers and did not reflect the CLBR (*Sunkara et al., 2011*). More recent studies have consistently demonstrated the absence of such a plateau in CLBR, the ultimate measure of effectiveness (*Fanton et al., 2023*; *Law et al., 2021*). While the finding of a plateauing LBR per fresh embryo transfer was persistent, this is clearly due to the adverse effect of supraphysiological sex steroid concentrations on the endometrium, rather than decreased oocyte potential above a certain number of oocytes collected. A number of studies on the freeze-all approach suggest that the magnitude of multifollicular growth is positively correlated with endometrial dysfunction in fresh transfer cycles (*Ata and Seli, 2017*).

Returning to 'less is more', whether a maxim holds true is context dependent, and the counter-maxim 'less is only more when more is no good' seems to better fit the current ART paradigm with the advent of vitrification, the cryopreservation technique that provided reproducibly high embryo cryo-survival. Vitrification did not only bring about a liberal use of cycle segmentation with the freeze-all option to avoid endometrial dysfunction when indicated but also allowed surplus embryos after a fresh transfer to increasingly contribute to the CLBR in parallel with the increasing number of oocytes collected (*Scaravelli et al., 2019*).

SAFETY CONCERNS

The risk of OHSS is proportionate to the number of growing follicles, and thus maximal stimulation can come at the expense of an increased risk of OHSS, which could be regarded against the maxim 'primum non nocere'. Yet this controversial maxim has multiple aspects and a distinct type of its usage is the risk–benefit ratio (*Smith, 2005*). The question then becomes one of how to balance the risk of OHSS with the benefit of collecting as many oocytes as possible.

Today, there are multiple effective strategies to prevent OHSS, which act synergistically through different mechanisms (*Dahan et al., 2018*). The use of a gonadotrophin-releasing hormone (GnRH) agonist rather than the conventional human chorionic gonadotrophin (HCG) trigger not only avoids the prolonged luteinizing effect of the latter on granulosa cells, but also generates an LH surge that is even shorter in duration than in the natural cycle. As a result, the corpora lutea undergo rapid atresia, curbing the production of vascular endothelial growth factor (VEGF), the main culprit responsible for increased vascular permeability, the hallmark of OHSS. The administration of a GnRH antagonist for a few days into the luteal phase would also further decrease endogenous LH and, arguably, further accelerate the demise of the corpora lutea, which are dependent on LH stimulation. Moreover, administration of the dopamine agonist cabergoline deactivates VEGF-2 receptors and diminishes the effect of any remaining VEGF on endothelial cells. Forfeiting a fresh embryo transfer to avoid the endogenous HCG of pregnancy is essential in preventing OHSS.

The author has not observed a single case of moderate to severe OHSS that required admission or ascites drainage in longer than the last 10 years of his practice with over 5000 ovarian stimulation cycles, despite never intending to limit the oocyte yield of an ovarian stimulation cycle. A similar experience has been reported in a series of 5599 GnRH agonist-triggered freeze-all cycles, where the incidence of OHSS that required ascites drainage was 0.05% (3/5599) despite an average collected oocyte count of 24.9 (*Berkkanoglu et al., 2019*). Whether a dopamine agonist had been used in addition to the agonist trigger and freeze-all approach was not mentioned.

Ovarian torsion is another rare risk brought about by enlarged ovaries after ovarian stimulation, yet a freeze-all approach coupled with other OHSS prevention methods would be expected to rapidly shrink the ovaries and further decrease the risk of torsion. In the same series of 5599 agonist-triggered freeze-all cycles only a single case of ovarian torsion (0.02) was reported (*Berkkanoglu et al., 2019*).

While a large registry study including 65,868 singleton live births that occurred between 1991 and 2008 suggested an increased risk of preterm birth (PTB) and low birthweight following a fresh embryo transfer in women with more than 20 oocytes collected, the analyses were not adjusted for important confounders such as smoking, body mass index and concurrent medication (*Sunkara et al., 2015*). In contrast, another registry study including 27,359 singleton deliveries after fresh embryo transfer that occurred between 2002 and 2015 did not corroborate these findings in analyses adjusted for the above-mentioned factors. Moreover, the latter study demonstrated an independent association between OHSS and PTB and small for gestational age, as well as between anovulation/polycystic ovary syndrome (PCOS) and PTB and very-preterm birth (*Magnusson et al., 2018*).

While the latter study provided more reliable and reassuring estimates with adjusted analyses, it should be noted that both studies exclusively involved fresh embryo transfer cycles that were conducted up to three decades ago. Today, it would be wise to avoid fresh embryo transfers when the number of oocytes collected exceeds 15 for both safety and effectiveness purposes (*Ata, 2020*). Studies investigating an independent association between the number of oocytes and the obstetric and neonatal outcomes following frozen embryo transfers are needed for definitive conclusions. While studies investigating PTB and other obstetric complications are not yet available, a recent registry study including 575,107 frozen embryo transfer cycles culminating in a singleton live birth reassuringly reported that number of oocytes collected in the ovarian stimulation cycle was not associated with large for gestational age in analyses adjusted for age, race and ethnicity, body mass index, maximum FSH, parity, gravidity, reason for ART, year of cycle start, clinic region, oocyte source, use of a gestational carrier, assisted hatching, preimplantation genetic testing, stimulation protocol, number of oocytes retrieved, sperm source, semen collection method, number of fetal heartbeats or infant sex (*Roshong et al., 2022*).

COST-EFFECTIVENESS CONCERNS

A lower cost of gonadotrophin injections has been suggested as a possible advantage of 'mild stimulation' when a fresh embryo transfer regardless of the number of oocytes collected was the norm due to an unpredictable and relatively lower

effectiveness of cryopreservation. However, in the current ART paradigm it is unknown whether a relatively small saving from the cost of gonadotrophins in the index ovarian stimulation cycle, for example 150 IU/day versus 225 or 300 IU/day over a period of 8–12 days of ovarian stimulation, justifies an expected decline in CLBR due to the collection of a lower number of oocytes and offsets possible cost savings through the prevention of repeat ovarian stimulation cycles and repeat laboratory procedures including fertilization, embryo culture and preimplantation genetic testing (if applied). This would require a complex cost-effectiveness analysis, but the author's hunch is that the use of lower gonadotrophin doses to limit the number of oocytes collected would not prove more cost-effective per live birth when a woman can yield a higher number of oocytes.

THE HYPERRESPONDER DILEMMA

Nobody doubts that women with decreased ovarian reserve should be stimulated to their maximal potential. While the so-called normo-responders are unlikely to provide an excessive number of oocytes that would significantly risk OHSS or other complications when proper preventive measures are taken, the debate would be about so-called hyperresponders including women with PCOS. Patients with PCOS are at the highest risk of OHSS, not only because they are prone to developing a higher number of oocytes, but also due to decreased dopaminergic tonus (*Gomez et al., 2011*).

The difference between FSH dosages that provide monofollicular and multifollicular growth is menacingly narrow in women with PCOS. An attempt to limit the number of growing follicles at the outset of ovarian stimulation significantly risks ending up with fewer oocytes, sometimes even too few, far below the true potential, with implications for CLBR. It would be pretentious to claim than one can tailor ovarian stimulation and gonadotrophin starting dosage to exactly yield a desired number of oocytes. Indeed, the recognition of this fact has led to abandonment of the term controlled ovarian stimulation, which was used to define the process of ovarian stimulation during the earlier days of ART. Acknowledging our limitations and cautiously erring on the side of over-stimulation rather than under-stimulation is probably in the best interest of these patients.

CONCLUSION – THE MORE THE BETTER

Available evidence suggests that every oocyte contributes to CLBR and gonadotrophin stimulation is not harmful to follicle or oocyte reproductive potential. Multiple preventive methods enable a minimization of the risk of OHSS to close to null. Obstetric and neonatal outcomes of ovarian stimulation cycles with a high oocyte yield so far seem reassuring, even though more data for frozen embryo transfers would be appreciated.

Indeed, the facts that CLBR increases with every additional oocyte and that our failure to precisely tailor ovarian stimulation seem to be recognized by the proponents of 'mild stimulation', hence the description of 'mild stimulation' has been changed from ovarian stimulation that aims to collect 2–7 oocytes, to ovarian stimulation with a daily gonadotrophin dosage of 150 IU or less (*Datta et al., 2021*; *Fauser et al., 2010*). The current paper is about neither daily gonadotrophin dosages nor the choice of ovarian stimulation protocols; it is about ovarian stimulation aiming to cautiously maximize oocyte yield. The ovarian stimulation protocol should be designed to this end with adequate gonadotrophin dosage, and clinical experience and common sense should be used to take proper preventive measures as indicated.

DATA AVAILABILITY

No data was used for the research described in the article.

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