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EDITORIAL

Mild ovarian stimulation for IVF is the smartest way forward

The aim of IVF treatment is to achieve a healthy full-term baby, with minimal health risks to the woman and her child, and at reasonable cost to allow this treatment option to be within financial reach for many women around the world. Ovarian stimulation – which contributes a considerable proportion of the overall cost of IVF – aims to generate multiple follicle development, allowing for the retrieval of multiple oocytes to improve success rates. Complex ovarian stimulation regimens have become an integral part of most IVF programmes. However, after nearly four decades of experience in developing and evaluating numerous strategies for ovarian stimulation (*Macklon et al., 2006*), controversy continues concerning the optimal number of oocytes to be retrieved, and whether 'more is better' or 'less is more'. It is widely acknowledged that the duration and extent of ovarian stimulation, the need for intensive monitoring and related frequent clinic visits, the avoidance of treatment complications such as ovarian hyperstimulation syndrome (OHSS), overall cost and achieving better health outcomes for mother and baby, are all crucial considerations for both patients and society.

However, when it comes to measuring the 'success' of IVF treatment, for example in national or international registries, there tends to be a uni-dimensional approach, using merely the live birth rate per cycle of treatment (mostly only involving fresh embryo transfer) without any measure of OHSS, dropout rates and related cumulative success rates per started treatment, health outcomes for the woman and her baby, and the ultimate cost of IVF and its sequelae (*Fauser, 2019*).

In our view, such measurement of success is not only incomplete but also short-sighted, resulting in suboptimal clinical practice. Like any other medical intervention, any protocol used during IVF treatment should aim at optimising a well-defined indicator of 'success' in relation to safety, burden of treatment and cost. This is more relevant now than ever before because a significant and increasing proportion of women who undergo ovarian stimulation for IVF treatment are healthy fertile women; many of these women will have a partner with male-factor subfertility, are trying to conceive as single women or as same sex-partners to start families, are only freezing their oocytes for possible future use, or are acting as oocyte donors. Moreover, access to IVF treatment still varies greatly around the globe, and a significantly reduced cost may facilitate the coverage of IVF treatment by health insurance companies or by public health systems, or render IVF more affordable if patients have to pay themselves. With this in mind, we examined the published evidence concerning the relationship between the extent of ovarian stimulation (i.e. related oestrogen serum concentrations and oocyte numbers) and embryo quality, pregnancy chances, pregnancy complications and perinatal outcomes.

Recently, a systematic review published in *RBMO* fuelled the view 'more is better', by demonstrating a direct positive correlation between the number of oocytes retrieved and the number of high-quality/euploid embryos (*Vermey et al., 2019*). This meta-analysis did not include any properly designed prospective trials and consisted mainly of retrospective studies of diverse designs and populations, with no meaningful information on stimulation dose and with variable definitions for low and high responses. This clinical complexity resulted in low-quality evidence. The authors do not comment on the incidence of OHSS, cost, and live birth rate in relation to oocyte numbers and admit that a better ovarian response is probably a reflection of a better prognostic profile of patients treated.

A Swedish group (*Magnusson et al., 2018*) studied the balance between safety and efficacy based on the number of oocytes retrieved. They reported that live birth rates (in fresh embryo transfer IVF cycles only) increased when up to 11 oocytes were retrieved and then evened out. Cumulative live birth rates per oocyte retrieval (including fresh and all subsequent frozen embryo transfer cycles) increased up to approximately 20 oocytes, but the incidence of severe OHSS increased significantly with the number of oocytes retrieved, particularly if more than 18 oocytes were retrieved. Patient discomfort, side effects, cumulative cycle outcomes and cost were not addressed.

It should be stressed once more that a higher oocyte yield may primarily reflect adequate ovarian reserve (i.e. good response to ovarian stimulation) rather than the stimulation protocol or dose used. This is often ignored, and an observed relationship between high oocyte yield and favourable IVF outcomes is often mistakenly used as argument to stimulate hard. Hence, high response to ovarian stimulation usually represents good prognosis patients, who will present with high IVF success rates no matter how you stimulate. Evidence from prospective studies indicating that a dose increase will actually improve IVF success rates is lacking.

For the 'more is better' believers, the answer to an increase in OHSS is to trigger final oocyte maturation with GnRH agonist and freeze all embryos or to provide luteal support allowing for a fresh embryo transfer. However, with luteal support the benefit of reduction in the risk of OHSS is compromised (*Youssef et al., 2014*). With these strategies, the risk of OHSS is significantly reduced, but it is certainly not eliminated. Such interventions mean additional cost and an increasing time to pregnancy. The complacency induced by the 'reassurance' given by the GnRH agonist trigger has made many clinicians less concerned about the stimulation dose and duration, consequently a

persistent residual incidence of OHSS remains in many European countries (*Calhaz-Jorge et al., 2017*).

It is now established that the strategy to freeze all embryos may improve pregnancy chances only in a select group of women (e.g. high responders), when compared with fresh embryo transfer, but it does not improve cumulative live-birth rates (*Roque et al., 2019*). Moreover, the idea to freeze all embryos was initially put forward to circumvent detrimental effects of supraphysiological steroid levels during the stimulation phase on endometrial receptivity, allowing the transfer of frozen-thawed embryos in subsequent unstimulated cycles. Few studies directly addressed the effects of mild (with consequently less abnormal follicular phase steroid concentrations) compared with conventional stimulation on endometrial receptivity and related embryo implantation rates.

When it comes to comparing embryo quality between mild and conventional stimulation, the only randomized controlled trial (RCT) available to date showed a significantly higher proportion of good quality euploid embryos with mild stimulation (*Baart et al., 2007*). A relationship between ovarian stimulation and aneuploidy rates of embryos has also been proposed based on a large sample size, multi-centre, cross-sectional data set (*McCulloh et al., 2019*). In a review that analysed published RCTs comparing mild and conventional stimulation protocols in poor and normal responders, no difference was found in the mean number of high-grade embryos (*Nargund et al., 2017*). A recent retrospective cohort study (*Irani et al., 2020*) suggested that there was no difference in euploidy rates and live birth rates following the transfer of euploid embryos between cycles with higher and lower stimulation dosages, regardless of number of oocytes retrieved. The authors did not include any fresh embryo transfer cycles and did not comment on the absolute number of euploid embryos obtained per cycle or on the risk of OHSS and the cost of reaching an embryo transfer. The authors also warn that the study should not be misinterpreted as a promotion of aggressive stimulation protocols because high response is linked to increased risk of OHSS and its related complications.

A large cross-sectional study suggested an inverse relationship between gonadotropin dosage and live birth rates (*Baker et al., 2015*). In addition, a recent RCT comparing individualised FSH dosing (based on pre-treatment Anti-Müllerian Hormone concentrations and body weight) with conventional stimulation, demonstrated a similar clinical pregnancy rate, but higher amounts of exogenous FSH used and increased OHSS rates in conventional stimulation (*Nyboe Andersen et al., 2017*; *Fernandez-Sanchez et al., 2019*). A recent Cochrane review demonstrated live birth rates to be no different, whether a standard 150 IU daily dose was used or the dose was adjusted according to ovarian reserve; however the incidence of OHSS was less when a stimulation dose of <150 IU was applied in hyper-responders (*Lensen et al., 2018*).

Although far from conclusive yet, it should be noted that several preliminary reports suggest an inverse relationship between the extent of ovarian stimulation and pregnancy complications, perinatal outcomes (*Kamath et al., 2018*) and even blood pressure in IVF off-spring (*Seggers et al., 2014*). In addition, multiple studies reported a negative association between supraphysiological oestradiol concentrations during ovarian stimulation (*Liu et al., 2017*; *Pereira et al., 2017*; *Zhang et al., 2019*) or number of oocytes retrieved (*Sunkara et al., 2015*) and neonatal birth weight. These studies, however, should be interpreted cautiously, because many confounders may have influenced outcomes, such as characteristics of patients treated, compromised endometrial receptivity and placental formation in relation to fresh or frozen embryo transfer, and so forth.

Even today, many clinicians still believe that higher stimulation doses improve outcomes in poor responders, despite much recent data challenging this view. The American Society for Reproductive Medicine recommended that in patients who are considered to be poor responders, 'strong consideration' should be given to a mild ovarian stimulation protocol (≤ 150 IU FSH) due to lower costs and comparable pregnancy rates (*ASRM, 2018*). Our recent meta-analysis which included all published RCTs observed no difference in the mean number or proportion of high-grade embryos and pregnancy outcomes comparing mild and conventional IVF among poor responders (*Datta, 2020*).

As discussed recently in this journal (*Fauser, 2019*), the goalposts for the outcome of IVF treatment have moved over the last decade from live birth rate per cycle to cumulative live birth rate per oocyte retrieval. To date, no consensus exists regarding the optimal number of oocytes required to balance cumulative live birth rates per oocyte retrieval [let alone per started IVF treatment which may include multiple IVF cycles (*Heijnen et al., 2007*)] with patient discomfort, safety and overall cost. Some clinicians argue that a single stimulated cycle with high number of oocytes could help patients to complete a 'family' rather than achieve a single live birth, but this contention represents wishful thinking rather than reality, with no prospective study to back up this concept. In addition, 'time to pregnancy' should also be considered, but again no prospective studies are available to date.

Looking at the bigger picture, the currently available evidence base does not support the concept 'more is better' when it comes to balancing cumulative live birth rate with safety, treatment burden and the cost to patient and society. We have a responsibility not to expose healthy women to unnecessarily high stimulation and potential harm and to achieve the best long-term health outcomes for the mother and baby. We also have a responsibility to focus on the health economics of both IVF treatment itself and its health sequelae such as pregnancy complications and compromised perinatal outcomes, in addition to potential long-term health implications for the offspring. Developing cost-effective and affordable IVF will increase access to treatment in many parts of the world where patients have to self-fund their care, and may also convince more health insurance companies to cover IVF expenses. The true real-world cost of IVF should take into account not only the actual cost of treatment but also resources required for the management of complications such as OHSS, and added costs related to pregnancy complications and additional perinatal care, including any long-term healthcare costs for the mother and her offspring.

The current COVID-19 crisis has been a 'wake-up call' for us to reduce OHSS and related complications in order to avoid hospital admissions and any increased burden on public healthcare services.

Moreover, with the current significant increase in unemployment, fewer patients, even in relatively prosperous societies, will be able to pay for high-priced IVF treatment themselves. Now that we are entering a worldwide economic recession, affordability of IVF becomes even more vital. It is a time to reflect on what is best for our patients and for society.

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