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REVIEW

The case for mild stimulation for IVF: recommendations from The International Society for Mild Approaches in Assisted Reproduction

BIOGRAPHY

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KEY MESSAGE

Mild ovarian stimulation for IVF should be considered in all clinical scenarios, as it is as effective as conventional IVF in terms of pregnancy outcome but safe, better tolerated and less expensive.

ABSTRACT

The practice of ovarian stimulation for IVF is undergoing a fundamental re-evaluation as recent data begin to successfully challenge the traditional paradigm that ovarian stimulation should be aimed at the retrieval of as many oocytes as possible, in the belief that this will increase pregnancy rates. An opposing view is that live birth rate should not be the only end-point in evaluating the success of IVF treatment and that equal emphasis should be placed on safety and affordability. The International Society for Mild Approaches in Assisted Reproduction (ISMAAR) committee has carried out an up-to-date literature search, with the evidence being graded according to the University of Oxford's Centre for Evidence-Based Medicine. The recommendations were formulated taking into account the quality of evidence on the efficacy, risk and cost of each intervention. ISMAAR recommends adopting a mild approach to ovarian stimulation in all clinical settings as an increasing body of evidence suggests that mild stimulation is as effective as conventional stimulation, while being safer and less expensive. Mild ovarian stimulation could replace conventional stimulation, thus making IVF safer and more accessible worldwide.

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KEYWORDS

ISMAAR
IVF
Mild IVF
Mild ovarian stimulation

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Declaration: The authors report no financial or commercial conflicts of interest.

INTRODUCTION

Recommendations on ovarian stimulation from different authorities published over recent years have differed widely: for example, guidelines from the American Society for Reproductive Medicine (ASRM) on ovarian stimulation for poor responders undergoing IVF, published in 2018 (*Practice Committee of the American Society for Reproductive Medicine, 2018*) are not reflected in the more recent recommendations of the European Society of Human Reproduction and Embryology (ESHRE) (*Bosch et al., 2020*). Among other guidelines, a review of evidence with drafted recommendations was provided to the World Health Organization (WHO) for global guideline development (*Farquhar et al., 2017*). In addition to these reviews and statements, a considerable amount of high-quality literature comparing mild and conventional approaches in ovarian stimulation for IVF have been published, which have the potential to change practice (TABLE 1). Hence, The International Society for Mild Approaches in Assisted Reproduction (ISMAAR) feels that a re-evaluation of its previous recommendations (*Nargund et al., 2007*) is required.

Furthermore, a reappraisal of mild stimulation IVF (MS-IVF) in the light of recent data is particularly relevant at a time when the WHO has recognized infertility as a global health issue and has outlined proposals to deliver standard and affordable fertility care (https://www.who.int/news-room/fact-sheets/detail/infertility). More and more attention is being shifted towards a more global perspective to make infertility treatment (especially IVF) universally available and affordable (*Chambers and Fauser, 2021*; *Fauser, 2019*; *Nargund and Fauser, 2020*; *Ombelet, 2020*; *Ombelet and Campo, 2007*, *Paulson et al., 2016*). The absence of a standardized and safe protocol, along with variations in the treatment cost and funding opportunities, have caused gross inequalities in access to IVF treatment across nations (*Chambers and Fauser, 2021*).

REVIEW METHODS

This is a narrative review that is the basis for ISMAAR recommendations on ovarian stimulation. The search method, period, search terms and data extraction process have been described in previous systematic reviews on the efficacy and safety of MS-IVF (*Datta et al., 2020*, *2021b*). An electronic search was performed in MEDLINE, Embase, PubMed and Cochrane Central using the search terms detailed elsewhere (*Datta et al., 2021b*). The search period was extended until December 2021 and in the context where randomized controlled trials (RCT) were lacking, retrospective cohort studies were included. In this review, 'mild stimulation' has been defined as a gonadotrophin daily dose of ≤150 IU, with or without an oral agent, usually in a gonadotrophin-releasing hormone (GnRH) antagonist cycle (*Datta et al., 2020*). The outcomes were compared with conventional IVF where a dose >150 IU/day was used in GnRH agonist or antagonist cycles.

The risk of bias, sample size and the range of confidence intervals (precision) were taken into consideration to evaluate the quality of evidence of individual studies. In addition, the clinical and statistical heterogeneity were taken into account in order to assess the overall quality in previous meta-analyses (*Datta et al., 2020*, *2021b*). The grade of recommendation was determined following guidance from the University of Oxford's Centre for Evidence-Based Medicine (CEBM) (*OCEBM Levels of Evidence Working Group 2011*), taking efficacy (pregnancy outcomes) as well as risks (e.g. cycle cancellation, ovarian stimulation, cost) into account (TABLE 2). In this review we first critically appraise the principles of ovarian stimulation with reference to both conventional IVF and MS-IVF, define what the target of modern-day IVF programmes should be and give recommendations on ovarian stimulation in different clinical situations, highlighting the place of MS-IVF based on current evidence.

VARIATIONS IN RECOMMENDATIONS ON OVARIAN STIMULATION BY DIFFERENT AUTHORITIES

The ESHRE guideline on ovarian stimulation accepted that mild stimulation significantly reduces the risk of ovarian hyperstimulation syndrome (OHSS) and recommended GnRH antagonist protocols in predicted high responders (*Bosch et al., 2020*). This guideline has commented that it is unclear whether a higher gonadotrophin dose (over 300 IU per day) is justified in predicted poor responders. The guideline group stated that a reduced (lower than standard) gonadotrophin dose is probably not recommended in predicted normal responders as it could potentially compromise cumulative live birth rate (LBR) in this group. However, the main focus of the ESHRE guideline was the efficacy of individual compounds and dosages used for ovarian stimulation on pregnancy outcomes with no discussion of cost implications, accessibility, treatment burden and health outcomes of mother and baby. The ASRM guideline, on the other hand, advised using no more than 150 IU/day in poor responders because this dose appeared to be as effective as any higher dose, with less physical and economic burden on the patients (*Practice Committee of the American Society for Reproductive Medicine. Electronic address: ASRM@asrm.org, 2018*). The evidence from our systematic reviews published in 2020–21 supersedes the ESHRE guideline on mild stimulation (*Datta et al., 2020*, *2021b*). The other contemporary review by *Farquhar et al. (2017)*, intended to guide the WHO, stated: 'Mild stimulation IVF cycles with low dose gonadotrophins in women with a good prognosis can be used as an alternative to standard IVF treatment for couples to achieve acceptable cumulative LBR and reduced risk of OHSS', and they found insufficient evidence to use minimal IVF for poor responders (*Farquhar et al., 2017*). However, a targeted stimulation dose was not specified.

ARE MANY OOCYTES NEEDED FOR A SUCCESSFUL IVF PROGRAMME?

The conventional approach is that the more oocytes retrieved, the higher will be the cumulative chance of having a baby (*Drakopoulos et al., 2016*; *Polyzos et al., 2018*; *Venetis et al., 2019*). This concept in the mainstream of IVF thinking has been backed by data from a few widely quoted national databases that show a direct correlation between the number of oocytes and LBR (*Steward et al., 2014*; *Sunkara et al., 2011*). However, the authors of these papers noted that this association was not linear with regards to fresh cycle outcomes and that there was little or no association at high oocyte yield (*Sunkara et al., 2011*); even LBR has been shown to have an inverse

TABLE 1 SYSTEMATIC REVIEWS COMPARING MILD/LOW DOSE AND CONVENTIONAL/HIGH-DOSE PROTOCOLS

Systematic review	Intervention	LBR	CLBR	CPR	OHSS	CCR
Poor responders						
Song et al., 2016	CC ± Gn versus C-IVF	↔	#	↔	#	↔
Practice Committee of the American Society for Reproductive Medicine. Electronic address ASRM@asrm.org, 2018	Gn ± CC/let versus C-IVF	↔	#	↔	#	#
Youssef et al., 2018	Lower versus higher dose IVF	↔	#	↔	#	↔/↑[a]
Datta et al., 2020, *2021b*	Gn ± CC/let versus C-IVF	↔	↔	↔	#	↔
		***	***	***		*
Montoya-Botero et al., 2021	Gn ± CC/let versus C-IVF	↔	↔	↔	#	↑
		**	***	**		**
Normal and poor responders						
Bechtejew et al., 2017	CC/let + Gn versus C-IVF	↔	#	↔	↓	#
		**		****	*	
Fan et al., 2017	CC ± Gn versus C-IVF	↔	#	↔	↔	↑↔[b]
Kamath et al., 2017	CC/let ± Gn versus C-IVF	↔	#	↔	↓	↑
		*		*/**	*	*
Normal responders						
Sterrenburg et al., 2011	Gn only low versus high-dose IVF	#	#	↔	↔	↔/↑[c]
Gibreel et al., 2012	CC + Gn versus C-IVF	↔	#	↔	↓	↑[b]
		*		**	*	**
Matsaseng et al., 2013	Gn only/CC + Gn versus C-IVF	↓[d]	#	#	↓	↑
Datta et al., 2021b	Gn ± CC/let versus C-IVF	↔	↔	↔	↓	↑
		***	**	***	***	*
Normal and high responders						
Datta et al., 2021b	Gn only low versus high-dose IVF	↔	↔	↔	↓	↔
		***	**	***	***	***

↔ = similar; # = not mentioned; ↑ = high with MS-IVF; ↓ = low with MS-IVF; – = not mentioned; * very low quality of evidence; ** low quality evidence; *** moderate quality of evidence (as stated by the authors); CC = clomiphene citrate; CCR = cycle cancellation rate; C-IVF = conventional IVF; CLBR = cumulative live birth rate; CPR = clinical pregnancy rate; Gn = gonadotrophin; LBR = live birth rate; let = letrozole; MS-IVF = mild stimulation IVF; OHSS = ovarian hyperstimulation syndrome; RCT = randomized controlled trial.

[a] No difference with Gn only protocol, high with oral agent incorporated protocol.

[b] No difference if antagonist was used.

[c] High with 100 IU dose versus 200 IU dose, no difference between 150 IU versus 225 IU dose.

[d] Based on one RCT.

relationship when the oocyte numbers exceeded 20 (*Steward et al., 2014*). Other more recent papers confirmed these findings (*Magnusson et al., 2018*); the general consensus being that the LBR graph in fresh cycles flattens when an optimal number of oocytes (12–15) is collected (*Law et al., 2021*).

The explanations as to why the LBR plateaus, other than a compromised endometrial receptivity, can be derived from the studies demonstrating an increasing number of oocytes with chromosomal abnormality with high oocyte yield (*Haaf et al., 2009*) and a direct correlation between cytoplasmic dysmorphism and the number of mature oocytes (*Figueira Rde et al., 2011*).

Furthermore, analysis of a large database showed a declining oocyte utilization rate (i.e. cumulative LBR per mature oocyte) with increasing oocyte yield in younger women (*Stoop et al., 2012*). This may suggest that even if the absolute number of competent oocytes rises, the ratio of competent embryos to oocytes appears to drop as the number of oocytes increases [unpublished results]. As far as embryo yield is concerned, fresh cycle LBR have been shown to become static, or even decline, once four embryos (*Datta et al., 2021a*) or five blastocysts are obtained (*Smeltzer et al., 2019*).

Cumulative LBR has been recognized as a better benchmark for IVF success, as it represents the total potential of achieving a baby from one cycle of ovarian stimulation, overcoming the influence of the number of embryos transferred or efficiency of embryo selection. Cumulative LBR has been shown to rise steadily with increasing oocyte number (*Drakopoulos et al., 2016*); while some studies found it plateauing at a higher oocyte yield, as with fresh cycle LBR (*Magnusson et al., 2018*). In an analysis of large multicentre databases, *Polyzos et al. (2018)* showed no decline in the cumulative LBR with rising oocyte number. However, this study reported a slowing of the increment, leading to a rise from 60% to 70% LBR, as the oocyte number rose from 18–20 to ≥25, with a steady rise in the incidence of moderate to severe OHSS, reaching 2.96%, even

TABLE 2 RECOMMENDATIONS WITH LEVEL AND GRADE OF EVIDENCE

ISMAAR recommendations	Level of evidence	Grade of recommendations[a]	References
Poor responders: MS-IVF with gonadotrophin dose of ≤150 IU/day ± CC/letrozole should be considered. Justification: MS-IVF is associated with comparable pregnancy outcomes and similar CCR but less stimulation medication and cost.	1a Multiple RCTs and systematic reviews. Moderate QoE for pregnancy outcomes, low QoE for CCR due to clinical heterogeneity.	A Consistent pregnancy and cycle cancellation outcomes from level 1 studies; large live birth data; low cost.	*Datta et al., 2020*; *Montoya-Botero et al., 2021*; *Song et al., 2016*; *Youssef et al., 2018*
Natural/natural-modified IVF may be considered for older women with low ovarian reserve. Justification: Natural IVF appears to result in comparable pregnancy outcomes and is better tolerated with fewer dropouts in this group of patients.	1b Two small RCTs with wide CI and retrospective studies; low QoE.	B Consistent pregnancy outcomes from RCT, insufficient live birth data.	*Kim et al., 2009*; *Morgia, et al., 2004*
Normal responders: MS-IVF with gonadotrophin dose of ≤150 IU/day ± CC/letrozole should be considered. Gonadotrophin dose modification according to BMI may be required. Justification: MS-IVF is associated with comparable pregnancy outcomes and similar CCR with lower risk of OHSS, less gonadotrophin requirement and cost.	1a Moderate QoE (low for CCR) due to clinical heterogeneity.	A/B Consistent pregnancy outcomes but data on OHSS rate and CCR not consistent.	*Datta et al., 2021b*; *Sterrenburg et al., 2011*
High responders: MS-IVF with gonadotrophin dose of ≤150 IU/day ± letrozole and agonist trigger with FAE in presence of high response need to be considered. Justification: MS-IVF results in comparable pregnancy outcomes and similar CCR with lower risk of OHSS. In-vitro maturation of oocytes could be a potential alternative to conventional ovarian stimulation in selected cases.	1b+ Two RCTs with narrow CI. Moderate QoE (clinical heterogeneity). 1b (for in-vitro maturation) One RCT (narrow CI in LBR).	A Consistent level 1 study outcomes in terms of efficacy, lower risk. B	*Datta et al., 2021b*; *Vuong et al., 2020*
Oocyte cryopreservation: Probability of a live birth depends on the number of oocytes cryopreserved. More than one cycle with MS-IVF is preferred to intensifying stimulation in one cycle in low responders. Justification: Mild stimulation may generate the same proportion of euploid embryos without the adverse effects associated with high stimulation.	2b Prospective or retrospective prognostic studies.	B Consistent outcomes from level 2 studies. Anticipated lower risk profile.	*Doyle et al., 2016*; *Goldman et al., 2017*; *Maslow et al., 2020*
Oocyte donation cycles: Oocyte donors do not need to produce a high number of oocytes to donate to a single recipient to achieve a success. Justification: Mild stimulation results in a sufficient number of oocytes required for a single recipient, while protecting the donors from the risks of high stimulation.	2b Large prospective or retrospective prognostic studies.	B Multiple large level 2 studies on the pregnancy outcomes. Risks derived from both level 1 and level 2 studies.	*Cobo et al., 2015*; *Hariton et al., 2017*; *Martin et al., 2010*

[a] Grade of recommendation according to the University of Oxford's Centre for Evidence-Based Medicine (OCEBM Levels of Evidence Working Group, 2011).

BMI = body mass index; CC = clomiphene citrate; CCR = cycle cancellation rate; CI = confidence interval; FAE = freeze-all embryos; LBR = live birth rate; MS-IVF = mild stimulation IVF; OHSS = ovarian hyperstimulation syndrome; QoE = quality of evidence, as described in Cochrane Handbook (*Schünemann et al., 2022*); RCT = randomized controlled trial.

with GnRH agonist trigger (*Polyzos et al., 2018*).

Two highly discussed laboratory-based papers challenge the concept of MS-IVF. *Venetis et al. (2019)* in their article 'Is more better?...' showed more day 3 euploid embryos were associated with higher oocyte yield and *Labarta et al. (2012)* found that 'moderate' ovarian stimulation does not increase the aneuploidy rate in embryos when compared with embryos obtained from unstimulated cycles. However, in a later paper, *Labarta et al. (2017)* demonstrated that not only euploid embryos, but the number of aneuploid embryos, rises steadily with increasing ovarian response, with no change in the euploidy rate. This is reflected in other recent studies involving trophectoderm biopsy (as opposed to cleavage-stage embryos examined by *Venetis et al. (2019)*), showing that the proportion of euploid blastocysts did not change with the number of oocytes retrieved or with total gonadotrophin dosage in any given age group (*Barash et al., 2017*; *Irani et al., 2020*). In an RCT, *Arce et al. (2014)* demonstrated a greater oocyte yield with increasing gonadotrophin dose; however, they found no changes in the proportion of high-grade blastocysts with increasing oocyte yield in both women with good and low ovarian reserve.
A dose-finding study testing a novel recombinant FSH demonstrated that although a higher FSH stimulation dose resulted in more oocytes being retrieved, pregnancy chances remained unaltered (*Nyboe Andersen et al., 2017*). In a head-to-head comparison between MS-IVF and conventional IVF, systematic reviews of RCTs found that the number (mean or proportion) of good-quality embryos was no different, notwithstanding more oocytes being retrieved with conventional IVF (*Datta et al., 2020*, *2021b*). None of the individual RCTs found a difference among the poor responders (n = 7 RCTs) or normal responders (n = 6 RCTs); however, the quality of evidence is low due to small sample size and clinical heterogeneity (*Datta et al., 2021b*).

It can be appreciated that women with good ovarian reserve usually produce high numbers of oocytes, despite low stimulation dose, and those with low reserve are less likely to elicit the desired response regardless of the stimulation dose. It was evident from the study by *Sunkara et al. (2011)* that LBR in fresh cycles peaks at fewer oocytes in younger women while older women needed a higher oocyte yield to optimize live birth. The woman's age influences the pregnancy outcome independent of the intensity of ovarian stimulation; a large

study with 'natural cycle IVF', where no ovarian stimulation was used, found that an increasingly higher number of oocytes was needed to achieve a live birth as the woman's age increased (*Silber et al., 2017*). In the paper by *Polyzos et al. (2018)*, a woman's age and body mass index (BMI) were found to be significant variables influencing cumulative LBR. Subsequently, a systematic review on the number of oocytes optimizing pregnancy outcome reported that the oocyte yield and live birth may not have a direct causal relationship and individual prognostic factors also influence the pregnancy outcome (*Law et al., 2021*). The study by *Labarta et al. (2017)* quoted above also found the gonadotrophin requirement per oocyte (i.e. 'ovarian sensitivity index') was inversely related to the number of euploid embryos. In other words, a high ovarian response with a low dose of gonadotrophins (low gonadotrophin use per oocyte), positively correlates with the number of euploid embryos. A good ovarian response despite low ovarian stimulation (high ovarian sensitivity index) has also been shown to correlate positively with LBR (*Huber et al., 2013*). Therefore, targeting a high oocyte number by increasing the stimulation dose by itself does not improve the prospect of conception.

DIFFERENT OVARIAN STIMULATION APPROACHES

The practice of ovarian stimulation has recently become more diverse, and alongside conventional IVF and its variations, some contemporary thoughts and strategies have emerged; some of which seemingly oppose the concept of MS-IVF, with others developed with the intention of reducing the treatment burden. The 'one and done' approach, for example, favours the maximum possible ovarian stimulation, aiming to create one or more children to 'complete a family' from one single oocyte collection (*Vaughan et al., 2017*). However, it is currently unknown how many couples would like to have more than one child and how many couples will be capable of achieving this goal. It has been shown that only 1 in 5 women might be able to produce more than one child through a single ovarian stimulation (*Vaughan et al., 2017*). More worrying is that, according to a study, around 15–20 oocytes are required to achieve two children and around 40 oocytes for more than two children from one oocyte collection; the same study reported around 1% incidence of severe OHSS, even with GnRH agonist ovulation trigger (*Connell et al., 2019*). Another approach is termed as 'one dose for all', which has been supported by RCTs that compared a fixed 150 IU daily gonadotrophin dose with 'individualized dosing' according to the ovarian reserve (*Oudshoorn et al., 2017*; *van Tilborg et al., 2017*). Subsequently, a Cochrane review did not find an advantage of ovarian reserve-dependent dose calculation over a fixed stimulation dose (150 IU/day) in terms of pregnancy outcomes (*Lensen et al., 2018*). In contrast, another group emphasized the concept of 'personalized dosing' according to ovarian reserve and a woman's age to optimize ovarian response (*La Marca et al., 2018*). Interestingly, both 'fixed dosing' and 'personalized dosing' have been found to make no difference when it comes to pregnancy outcomes, but both strategies identified an advantage of further lowering the stimulation (<150 IU/day) for high responders to reduce the risk of OHSS (*La Marca and Sunkara, 2014*; *Lensen et al., 2018*). In addition, 'personalized dosing' claims to prevent 'under-response' and thereby, cycle cancellation by increasing the stimulation dose (*La Marca and Sunkara, 2014*). It is also important to note that, in line with MS-IVF, the main intention of both 'one dose for all' and 'personalized' dosing is to optimize outcome without inflicting an 'unnecessarily' high stimulation dose that only increases the risk, treatment burden and cost (*La Marca and Sunkara, 2014*; *Lensen et al., 2018*). Of note, MS-IVF does not mean a 'fixed mild dose' either, as the protocol also favours reducing the dose further in predicted high responders and slightly adjusting the dose according to BMI to avoid over- or under-response linked to BMI (see below). Thus, MS-IVF differs from the 'one dose for all' policy by allowing further lowering of the intensity of stimulation for high responders and differs from 'personalized dosing' in that MS-IVF does not recommend increasing the dose in women with low ovarian reserve or advanced age.

SHOULD LIVE BIRTH RATE BE THE ONLY MEASURE OF A SUCCESSFUL IVF PROGRAMME?

Understandably, achieving a baby is the ultimate target of any IVF treatment. The cumulative LBR, which is widely considered to be the actual targeted outcome of an IVF programme, has been reported to keep rising over and above the oocyte cohort, which optimizes the per-cycle LBR (*Drakopoulos et al., 2016*; *Polyzos et al., 2018*). This has often been cited as an argument against the practice of mild ovarian stimulation, which does not produce as many oocytes as with conventional IVF (*Bosch et al., 2020*). In reality, however, so far there is no evidence that MS-IVF compromises the cumulative LBR, whether in poor responders undergoing IVF (*Montoya-Botero et al., 2021*), or in normal or high responders (*Datta et al., 2021b*). Another yardstick of cumulative live birth is the total number of childbirths achieved in a given period of time: one of the largest RCTs confirmed cumulative LBR in 1 year was no different while MS-IVF was associated with a lower incidence of OHSS and cost compared with conventional IVF (*Heijnen et al., 2007*).

Importantly, not only the cumulative LBR but also the complications of IVF treatment, including incidence of OHSS, thromboembolic events, bleeding and pain following the oocyte retrieval procedure, also rise in parallel with an oocyte yield of above 15–20 (*Levi-Setti et al., 2018*; *Magnusson et al., 2018*). Consequently, the outlook is now changing: the outcome of a successful IVF programme should be to achieve a full-term, healthy baby following a safe and uncomplicated IVF cycle with reduced treatment burden and cost (*Nargund and Datta, 2022)*. A GnRH agonist ovulation trigger does not give licence to stimulate the ovary indiscriminately, as around a 1–3% incidence of severe OHSS has been reported even with an apparently 'safe' agonist trigger (*Connell et al., 2019*; *Polyzos et al., 2018*) and it does not prevent the other complications of high response described above. *Magnusson et al. (2018)* reported cumulative LBR per aspiration increased up to 20 oocytes retrieved and then slowed down, while the incidence of severe OHSS increased rapidly from around 18 oocytes and thromboembolic events, although rare, occurred in particular if 15 or more oocytes are retrieved. As a result, these authors called for a balance between an optimum cumulative LBR, and the risks associated with high response (*Magnusson et al., 2018*). A cumulative LBR of 53.1% per started cycle, with judicious use of freeze-all embryos

(FAE) in the event of high ovarian response, was obtained with MS-IVF, with no recorded cases of severe OHSS, thus achieving an acceptable trade-off between success and risks (*Datta et al., 2021a*). It is becoming increasingly clear that the definition of success should not be LBR or cumulative LBR per started cycle alone but should include other factors, especially the woman's safety and wellbeing; but most national 'success rate tables' concentrate solely on pregnancy and LBR. A scoring system that accounts for live birth outcome, significant complications, neonatal outcome and the cost would be necessary to evaluate the performance of an IVF programme holistically (*Nargund and Datta, 2022)*.

WHAT IS MILD OVARIAN STIMULATION FOR IVF?

Mild ovarian stimulation for IVF is defined as 'a protocol in which the ovaries are stimulated with gonadotrophins, and/or other pharmacological compounds, with an intention of limiting the number of oocytes following stimulation for IVF' (*Zegers-Hochschild et al., 2017*). In practical terms, it denotes ovarian stimulation for IVF at a daily gonadotrophin dose of ≤150 IU, with or without oral medication (clomiphene citrate or letrozole) in a GnRH antagonist cycle. The principle of MS-IVF is neither rigidly guided by the oocyte number, nor a fixed daily dose of 150 IU. It is well recognized that high responders or good prognosis patients can easily produce more than seven oocytes despite having very low stimulation dose; on the other hand, poor responders are unlikely to yield seven oocytes regardless of the intensity of stimulation. Dose adjustment may be required according to BMI, which influences the bioavailability of administered medication (*Howles et al., 2006*; *Ledger et al., 2011*). Good prognosis women with low BMI (<20 kg/m^2) or women with very high ovarian reserve such as PCOS may require a dose of <150 IU, while those with high BMI of >30 may need a higher dose (up to 225 IU/day) in order to provide an equivalent response (*Borini and Dal Prato, 2005*; *Yovich et al., 2012*). The concept of mild stimulation is to achieve a mild response from the ovaries to encourage healthy, more competent follicles to develop.

Ovarian reserve has been proposed to be taken into account while considering the starting stimulation dose (*La Marca and Sunkara, 2014*). While it is evident that inclusion of anti-Müllerian hormone (AMH) or antral follicle count (AFC) improves the age-related prediction of ovarian response (*Broer et al., 2013*), neither is a good predictor of pregnancy outcome (live birth) (*Broer et al., 2013*; *Iliodromiti et al., 2014*). As shown in the OPTIMIST trial, dose adjustment according to ovarian reserve does not alter the LBR (*Oudshoorn et al., 2017*; *van Tilborg et al., 2017*). Whether AMH- or AFC-based dose adjustment can reduce the risk of cycle cancellation is controversial at present; failure to increase the gonadotrophin dose with high BMI or setting up a relatively high dominant follicle number as the cancellation criterion (<3) might influence the cycle cancellation rate. The cut-off number of follicles for cycle cancellation is rather arbitrary at present, as there is insufficient evidence to expect poor pregnancy outcomes if ≤3 follicles develop following ovarian stimulation (*Biljan et al., 2000*).

Various oral compounds that augment endogenous FSH secretion have been tried in combination with gonadotrophins in IVF cycles, with the aim of reducing the total amount of gonadotrophin used. Clomiphene citrate and letrozole are the two most commonly used compounds. Several systematic reviews and meta-analyses of RCT have confirmed that the addition clomiphene citrate or letrozole reduces the gonadotrophin consumption in women with predicted normal, poor or high response, with an added advantage of a reduction in the incidence of OHSS (*Bechtejew et al., 2017*; *Datta et al., 2021b*; *Kamath et al., 2017*) and treatment cost (*Aleyamma et al., 2011*; *Mukherjee et al., 2012*; *Ragni et al., 2012*). These systematic reviews did not find any reduction in the LBR per randomization by the addition of clomiphene citrate or letrozole (**TABLE 1**). One RCT with only clomiphene citrate showed similar LBR when compared with a high-dose gonadotrophin regimen in predicted poor responders in IVF (*Ragni et al., 2012*). Despite fewer oocytes being collected with mild stimulation protocols using oral compounds (*Kamath et al., 2017*), the high-grade embryo yield (*Datta et al., 2021b*), as well as the cumulative LBR (*Liu et al., 2020*), have been found to be similar. Concern has been expressed that the risk of cycle cancellation is higher with a stimulation protocol using oral medications (*Gibreel et al., 2012*; *Kamath et al., 2017*). However, the cycle cancellation rates are found to be no different from conventional IVF when data from the early studies that did not use antagonist to suppress spontaneous LH surge were excluded from the meta-analyses (*Datta et al., 2021b*; *Gibreel et al., 2012*).

OVARIAN STIMULATION FOR WOMEN WITH DIFFERENT RESPONSE CATEGORIES IN IVF

Normal responders

Both GnRH agonist and antagonist protocols seem to be equally effective, but antagonist cycles are associated with a lower risk of OHSS in the event of unexpected high response (*Lambalk et al., 2017*). An earlier systematic review and meta-analysis (*Sterrenburg et al., 2011*) indicated 150 IU/day as the optimal daily dose of recombinant FSH (rFSH) in presumed normal responders younger than 39 years undergoing IVF. Based on evidence from this systematic review, which found a higher cycle cancellation rate (CCR) with 100 IU daily dose, the ESHRE guideline recommended a gonadotrophin dose of 150 IU or higher for this category of women, to improve the cumulative pregnancy outcomes (*Bosch et al., 2020*). However, the same meta-analysis by *Sterrenburg et al. (2011)* found no difference in pregnancy rates, CCR or mean number of cryopreserved embryos when daily 150 IU was compared with any higher dose. Apart from one (*Matsaseng et al., 2013*), subsequent systematic reviews and meta-analyses of all RCTs (**TABLE 1**) comparing between ≤150 IU daily gonadotrophin with or without oral medications and a higher gonadotrophin dose found the latter offered no advantage (moderate quality of evidence), including in cumulative pregnancy outcomes, while the lower dose (≤150 IU/day) was associated with comparable CCR (low quality of evidence), but lower risk of OHSS, less requirement for gonadotrophins (moderate quality of evidence) (**TABLE 2**) and lower treatment cost (**TABLE 3**).

Poor responders

There is no standard universally accepted treatment protocol for poor responders in IVF (*Patrizio et al., 2015*); despite different modifications of conventional stimulation protocols that have been attempted, there is no evidence of consistent improvement in the pregnancy outcomes (*Vaiarelli et al., 2018*). Various

TABLE 3 TREATMENT COST: MILD VERSUS CONVENTIONAL IVF

Study	Cost: MS-IVF	Cost: Conventional IVF
Poor responders		
Ragni et al., 2012	€81,294 per live birth	€113,107 per live birth
van Tilborg et al., 2017	€5289	€6397
Normal responders		
Heijnen et al., 2007	€8333	€10,745
Lou and Huang, 2010	€136	€2160
Mukherjee et al., 2012	Mild stimulation: 34% cost saving	
Aleyamma et al., 2011	IVF with CC continued until trigger without GnRH antagonist/agonist costs: $675	
High responders		
Oudshoorn et al., 2017	€4622	€4714

CC = clomiphene citrate; GnRH = gonadotrophin-releasing hormone; MS-IVF = mild stimulation IVF.

definitions to select the 'poor responder' population, as well as variations in the treatment protocols including the adjuvant therapies, have only introduced heterogeneity across the studies.

Different high doses of gonadotrophins have been tried with no apparent benefit on the pregnancy outcomes (moderate quality of evidence) (TABLE 2). The evidence on cycle cancellation is conflicting (TABLE 1): some meta-analyses of RCT showed higher CCR with mild IVF (*Kamath et al., 2017*; *Montoya-Botero et al., 2021*; *Youssef et al., 2018*), while other meta-analyses found no difference (*Datta et al., 2021b*; *Fan et al., 2017*, *Song et al., 2016*). The gonadotrophin requirement was less with MS-IVF (*Datta et al., 2021b*; *Kamath, et al., 2017*; *Youssef et al., 2018*); the RCT by *Ragni et al. (2012)* reported a clomiphene citrate only regimen to be less expensive with no difference in LBR. The other RCT that compared the cost between MS-IVF and conventional IVF found the same (TABLE 3).

Natural/natural-modified (N/NM) protocols have a role in treating poor responders, particularly in older women with low ovarian reserve. It is thought that the pregnancy outcome of this prognostic group remains poor, regardless of the treatment protocols or any addition of adjuvants (*Vaiarelli et al., 2018*). N/NM-IVF has been found to achieve pregnancy rates or LBR comparable to those of conventional high-dose regimens in women with previous poor response in randomized trials available till date (*Kim et al., 2009*; *Morgia et al., 2004*), with the former being less intense, and these protocols are better tolerated by patients (*Hojgaard et al., 2001*) and can be repeated for 'embryo banking' to try to improve the pregnancy outcome.

High responders

The GnRH antagonist protocol is preferred to agonist down-regulation, not only because the antagonist protocol requires less gonadotrophin and reduces the risk of OHSS (*Al-Inany et al., 2016*; *Lambalk et al., 2017*), but it also leaves the option of GnRH agonist trigger open, in case of high ovarian response. Two large RCT compared milder versus standard dose IVF in high responders: one defined a delayed start with 150 IU gonadotrophin in an antagonist protocol as 'mild' and a 150 IU dose on a long down-regulation protocol as conventional IVF (*Casano et al., 2012*); the other RCT compared daily doses of 150 IU and 100 IU, both in antagonist protocols (*Oudshoorn et al., 2017*). Individually, these trials found no difference in LBR and cumulative LBR; a meta-analysis of the pooled data also confirmed the same (moderate quality of evidence); however, the milder stimulation was associated with a lower incidence of OHSS, lower gonadotrophin use and the number of oocytes retrieved was not significantly different (*Datta et al., 2021b*) (TABLE 2). The only RCT comparing the cost reported no difference in the expense when the <150 IU dose was used (*Oudshoorn et al., 2017*).

Letrozole has been employed in expected hyper-responders, including women with PCOS or in women with oestrogen-sensitive cancer. Two small RCT with varied letrozole-based protocols found the addition of letrozole to the standard antagonist protocol resulted in comparable LBR with no incidence of moderate to severe OHSS (*Tshzmachyan and Hambartsoumian, 2020*; *Yang et al., 2019*). The RCT by *Tshzmachyan and Hambartsoumian (2020)* reported a reduced gonadotrophin requirement when letrozole was added to 150 IU daily gonadotrophin. One retrospective study with PCOS patients (n = 181) found no difference in pregnancy rate and OHSS by adding letrozole when serum oestradiol concentration exceeded 4000 pg/ml (*Chen et al., 2018*), while another retrospective study of 125 women with PCOS reported improved pregnancy outcomes with no occurrence of OHSS in either group (*D'Amato et al., 2018*). Addition of letrozole increases the likelihood of having fresh embryo transfers (*D'Amato et al., 2018*).

GnRH agonist trigger followed by 'freeze-all' has been shown to reduce OHSS by multiple RCTs and meta-analysis of the pooled data from those trials (*Mourad et al., 2017*; *Youssef et al., 2014*). If agonist trigger is used, FAE seems to be essential: not only because the pregnancy rate has been shown to be compromised with fresh embryo transfer (*Roque et al., 2019*; *Youssef et al., 2014*), but also the risk of OHSS is not reduced when a small dose of HCG (such as a 1500 IU single dose) is added to reinforce luteal phase support (*Youssef et al., 2014*). A gonadotrophin dose of ≤150 IU/day and lower than standard dose of HCG (*Nargund et al., 2007*) could be a safer way when a fresh embryo transfer is contemplated.

In-vitro maturation (IVM) can be a useful alternative in high-responder groups. An approach referred to as 'natural cycle IVF with IVM for immature oocytes collected (natural IVF/M)' or 'mild stimulation IVF with IVM for immature oocytes collected (mild IVF/M)' reported acceptable pregnancy rates and LBR (*Chian et al., 2004*; *Lim et al., 2007*, *2009*). A recent RCT reported comparable LBR and cumulative ongoing pregnancy rates when IVM was compared with conventional ovarian stimulation (*Vuong et al., 2020*). IVM could be the first line of treatment before considering ovarian stimulation for women who have a genetic predisposition to developing OHSS (as noted among cases who were reported to have had OHSS despite agonist trigger and freeze-all) and in those who are undergoing IVF with oestrogen-sensitive cancer (*Chian et al., 2013*, *2019*).

OVARIAN STIMULATION FOR OOCYTE/EMBRYO CRYOPRESERVATION

The aim of oocyte or embryo cryopreservation for social or medical reasons is to obtain a targeted number of oocytes that could give a reasonable probability of at least one child in the future. The probability of live birth correlates with ovarian 'response', which is not synonymous with the ovarian 'stimulation' dose. For example, a good oocyte yield despite a low stimulation dose would indicates high 'ovarian sensitivity index' (see above). Both ovarian response and the absolute number of euploid embryos relate to the age of the woman, her ovarian reserve and ovarian stromal blood flow, but not to stimulation dose (*Popovic-Todorovic et al., 2003*; *Venetis et al., 2019*). As mentioned earlier, neither euploidy rates nor pregnancy rates correlate with gonadotrophin dose (*Barash et al., 2017*; *Irani et al., 2020*; *Sekhon et al., 2017*; *Venetis et al., 2019*).

The survival of mature oocytes following thawing is now estimated to be approximately 95% for women <35 years of age and around 82–85% in women aged 36 years or older (*Cobo et al., 2016*). Age and ovarian reserve need to be taken into account when counselling women prior to oocyte cryopreservation (*Maslow et al., 2020*). To achieve the same chance of live birth, younger women require fewer oocytes (*Goldman et al., 2017*; *Maslow et al., 2020*); data from multiple studies found that 10 mature vitrified oocytes give 60–70% probability of a baby in the future in women <35 years of age (*Doyle et al., 2016*; *Goldman et al., 2017*). With advancing age, as the quantity and quality of oocytes drop, women may require more than one cryopreservation cycle to achieve the targeted oocyte number for their age (*Maslow et al., 2020*). The use of agonist trigger and freeze-all should not encourage adoption of a 'one and done' policy and attempting to obtain as many oocytes as possible from one cycle by increasing the stimulation dose, as cases of OHSS have been reported even after agonist trigger and FAE (*Santos-Ribeiro et al., 2015*).

OVARIAN STIMULATION FOR OOCYTE DONORS

Oocyte donors are a unique subset of women who generally come from a young and fertile population. Hence, the oocyte quality of the donors is regarded as optimal, with the highest LBR per oocyte or 'oocyte to baby rate' (*Patrizio and Sakkas, 2009*). A large dataset reported 6.5% LBR per oocyte among oocyte donors; about 15 oocytes were needed to achieve a live birth in a setting of conventional ovarian stimulation (*Cobo et al., 2015*). Some oocyte donors with a proven fecundity (more than one baby born from the donated oocytes) represent the best prognosis donors, with even higher LBR per oocyte than the average of oocyte donors (*Martin et al., 2010*). These donors do not need a high number of oocytes to ensure a reasonable success in the recipient (*Martin et al., 2010*). Like oocyte cryopreservation (*Maslow et al., 2020*), the number of oocytes needed to maintain the same probability of live birth rises with advancing age of the donor. A study reported significantly improved LBR when >10 mature oocytes or embryos were obtained, but no further increase in the LBR with the yield of >20 mature oocytes (compared with 10–15 mature oocytes) (*Hariton et al., 2017*). Another study of almost 3500 donor cycles found the cumulative LBR ranged between 65% and 82% when the donors produced 15–20 oocytes (*Cobo et al., 2015*). The same study showed the increment in the overall LBR slowed down, approximately 5% for every five oocytes, when in excess of 20 oocytes were obtained (*Cobo et al., 2015*); hence, it appears that targeting an oocyte number above 15–20 oocytes in one cycle would certainly expose the oocyte donors to the risk of OHSS (*Magnusson et al., 2018*) and other risks of over-stimulation mentioned above, for little extra benefit. It is of utmost importance to protect oocyte donors from untoward events of over-stimulation as they choose to undertake treatment altruistically (*Pennings, 2020*). As far as the stimulation dose is concerned, a recent analysis of 8627 'donor-recipient' cycles from the Society for Assisted Reproductive Technology (SART) database confirms a negative correlation between the stimulation doses and LBR (*Shaia et al., 2020*).

An ideal donor cycle also needs to be simple and convenient for the donor, without incurring high cost to the recipient. Use of a moderate dose of long-acting gonadotrophin appears to be as effective as daily gonadotrophin (*Pouwer et al., 2015*) in autologous oocyte cycles; a single injection of corifollitropin alfa (150–180 µg) in the first week of stimulation has been shown to increase donor satisfaction (*Requena et al., 2013*). Oral progestogens have been introduced to replace GnRH antagonist injections, both in donor cycles (*Begueria et al., 2019*; *Martinez et al., 2019*) and in treating infertile couples and have been found to be a more convenient and less expensive method for endogenous LH suppression with equivalent efficacy (*Cui et al., 2021*). Although a recent systematic review found a lower incidence of OHSS with progesterone priming, higher requirement of gonadotrophin stimulation (*Cui et al., 2021*), and RCT evidence of lower pregnancy rate among the oocyte recipients (*Begueria et al., 2019*) has cast doubt on the use of progesterone-primed protocols at present (*Martinez et al., 2021*).

Properly selected oocyte donors usually produce sufficient oocytes to give a good chance of success for one recipient and mild ovarian stimulation can meet this target; donors are often subjected to high stimulation aimed at producing a large number of oocytes in order to distribute them between more than one recipient. This strategy could be detrimental to the donor's wellbeing (*Pennings, 2020*).

CONCLUSION

In 2010, a review was published adopting a SWOT (strength–weakness–opportunity–threat) analysis of mild IVF and a prediction was made about which direction it would go over the next 10 years (*Fauser et al., 2010*). Of note, most of the weaknesses of MS-IVF perceived 10 years ago have not been proved to be weaknesses: for example, despite lower oocyte yield, the number of good-quality embryos has been shown to be equivalent to that of conventional IVF and there are emerging data that the per-cycle or cumulative LBR are not compromised with MS-IVF (*Datta et al., 2021b*; *Montoya-Botero et al., 2021*). It is yet to be confirmed whether CCR is higher with MS-IVF, bearing in mind that what is classed as 'too low' a response for a conventional IVF programme may be deemed as an acceptable response for MS-IVF. The laboratory technologies have improved over the last decade and the clinics are now comfortable in managing antagonist cycles. However, most of the

'threats' of MS-IVF described 10 years ago (*Fauser et al., 2010*) still exist: many clinicians are still keen to collect a large number of oocytes and as a result patient expectations are often focused on egg numbers rather than egg quality. The literature has been enriched by more convincing data from multiple RCTs and analyses of large databases that support the use of mild ovarian stimulation in all clinical settings, including for oocyte preservation and oocyte donation cycles.

Our recommendation of mild approaches in ovarian stimulation is based on the evidence of equivalent success rate to conventional high stimulation with a higher safety profile, better patient experience and lower cost, which is now thought to be the *sine qua non* of a successful IVF programme. If adequate response is not achieved, repeated IVF cycles could be a safer and a better way of increasing the success rates.

A recent Italian survey noted a slight change in practices of stimulation doses, in the direction from high to medium range, since the publication of the OPTIMIST trial (*Papaleo et al., 2021*). We hope, with recent evidence and recommendations from scientific bodies, this change will gain momentum. The mild approach to ovarian stimulation appears to be the way forward to bring IVF within the reach of vast economically underprivileged populations around the globe, and its better safety profile could be an added advantage in situations where high levels of cycle monitoring are not feasible.

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Received 3 June 2022; received in revised form 25 July 2022; accepted 29 July 2022.