Mild stimulation for in vitro fertilization

Geeta Nargund, F.R.C.O.G.,[a] Adrija Kumar Datta, M.R.C.O.G.,[a] and Bart C. J. M. Fauser, M.D., Ph.D.[b]

[a] Create Fertility, London, United Kingdom; and [b] Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, Utrecht, the Netherlands

It has been proven that the use of high gonadotropin dose does not necessarily improve the final outcome of IVF. Mild ovarian stimulation is based on the principle of optimal utilization of competent oocytes/embryos and endometrial receptivity. There is growing evidence that the pregnancy or live birth rates with mild-stimulation protocols are comparable to those with conventional IVF; the cumulative pregnancy outcome has been shown to be no different, despite having fewer numbers of oocytes or embryos available with milder ovarian stimulation. Although equally effective, mild-stimulation IVF is associated with a greater safety profile, in terms of the incidence of ovarian hyperstimulation syndrome and venous thromboembolism. It is also found to be better tolerated by patients and less expensive. Emerging research evidence may lead to widespread acceptance of mild IVF, by both patients and IVF providers, and make IVF more accessible to women and couples worldwide. (Fertil Steril® 2017;108:558–67. ©2017 by American Society for Reproductive Medicine.)

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In vitro fertilization is performed with oocytes collected in natural and stimulated cycles. Different approaches to ovarian stimulation are used worldwide. The introduction of GnRH antagonists has given an opportunity to reduce the duration and burden of ovarian stimulation protocols and to make them more woman-friendly. The need to reduce multiple births and to improve health outcomes for women and babies has led to the revival of milder and a more physiologic approach to ovarian stimulation in IVF cycles.

However, pituitary down-regulation (desensitization) with a GnRH agonist, followed by controlled ovarian hyperstimulation (COH), is still the most commonly used IVF protocol worldwide. This so-called "long down-regulation" is often described as "conventional" IVF (C-IVF) to distinguish it from the mild-stimulation IVF (MS-IVF) protocols. Terminologies of different types of MS-IVF have been defined in a proposal statement from the International Society for Mild Approaches in Assisted Reproduction (1). The term "mild-stimulation IVF" is denoted as "a method when follicle stimulating hormone (FSH) or human menopausal gonadotropin (hMG) is administered at a lower dose and or for a shorter duration in a gonadotropin releasing hormone (GnRH)-antagonist co-treated cycle, or when oral compounds, anti-estrogens or aromatase inhibitors (AIs) are used either alone or in combination with gonadotropins (Gn) with the aim of collecting fewer oocytes" (1).

Despite obvious advantages described below, widespread acceptance of MS-IVF has been hindered by an insecurity among clinicians regarding obtaining fewer oocytes/embryos, with its implications as to the success rate and alleged increased risk of cycle cancellation (2). Over the last few years, however, several high-quality publications have added convincing data in favor of natural and mild IVF, necessitating a re-evaluation to define its current position and future prospects.

IS MS-IVF AS EFFECTIVE AS C-IVF?

Mild-stimulation IVF has gained recognition as a safer, less-expensive, and patient-friendly IVF option. Yet by and large there is a resistance among providers of assisted reproductive technology (ART) in incorporating this approach into their practice, mainly due to doubt as to its clinical effectiveness.

Scientific Basis of Effectiveness

Conventional COH aims to retrieve a large number of oocytes to maximize

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Reprint requests: Geeta Nargund, F.R.C.O.G., Create Fertility, 150 Cheapside, St. Paul's, London EC2 V6ET, United Kingdom (E-mail: geetanargund@gmail.com).

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the number of embryos available for transfer and cryopreservation. The basic concept underpinning the success of MS-IVF is that, because of gentle stimulation, only the healthier follicle(s) with more competent egg(s) are encouraged to develop (3). The physiologic hormonal milieu inside the follicles of a natural cycle is disturbed when the follicles are exposed to a high dose of gonadotropins (Gns) (4). Follicular antimüllerian hormone, which is a marker of a good intrafollicular environment, has been shown to be significantly higher in natural cycles compared with that with ovarian stimulation (4). A landmark randomized controlled trial (RCT) (n = 111) found that the number of euploid embryos with C-IVF was no higher than that with MS-IVF, despite twice the number of embryos being obtained with the former (5). A more recent, large RCT (n = 265) found incremental doses of FSH to have a direct correlation with the number of oocytes recovered, with no increment in the number of good-quality blastocysts; indeed, the blastocyst/oocyte ratio and fertilization rate demonstrated an inverse relationship with the dose of stimulation (6). Several other RCTs on a population of normal/high responders also found a trend toward a higher proportion of good-quality embryos/blastocysts with MS-IVF (7–9).

There is growing laboratory evidence to support the concept that MS-IVF creates a physiologic milieu consistent with a normal menstrual cycle and optimizes endometrial receptivity. A basic science study demonstrated progressively less adhesiveness of mouse embryos to human endometrium from fertile oocyte donors as they were exposed to increasing concentrations of estradiol (E_2) (10). It has been recognized that supraphysiologic levels of serum E_2 could affect implantation (11, 12). More recently, natural endometrial gene expression has been shown to be disrupted during C-IVF cycles, owing to associated high serum E_2 or follicular P rise (13, 14).

Clinical Evidence of Effectiveness

Despite this convincing scientific evidence, there is ongoing skepticism among clinicians concerning pregnancy outcomes of MS-IVF in terms of live births. Two meta-analyses on normal responders, in which all but one RCT were underpowered for pregnancy outcomes, reported lower ongoing pregnancy rates (OPRs) with MS-IVF as compared with C-IVF (3, 15). In contrast, another meta-analysis of 10 RCTs found no difference in pregnancy rates between ovarian stimulation with a low (150 IU/d) and high (>200 IU/d) Gn dose (16). The debate has been further enlivened by the findings that retrieval of 13–15 oocytes is required to optimize the live birth rate (LBR) (17, 18) in C-IVF cycles; whereas Verberg et al. (3), analyzing data from three RCTs, demonstrated that only 6 oocytes would be adequate to yield the best OPRs by adopting a milder approach. In a recent article Baker et al. (19) reported an analysis of 658,519 fresh IVF cycles from the Society for Assisted Reproductive Technology database in the United States, which demonstrated an inverse relationship between Gn dose and LBRs across all age groups, irrespective of the number of oocytes retrieved or prognosis of patients. Another trial on poor responders that randomized patients to three different daily Gn doses (150 IU, 300 IU, and 450 IU) in antagonist, cycles found no difference in the clinical pregnancy rates (CPRs) per cycle whether 150 or 450 IU/d (20).

Individual RCTs comparing MS-IVF and C-IVF have been summarized in Tables 1 and 2. The meta-analysis by Verberg et al. (3) that included three RCTs with normal responders found lower OPRs per cycle with MS-IVF than with a down-regulation protocol (15% vs. 29%). Another meta-analysis, by Matsaseng et al. (15), comprising five RCTs also found significantly better OPRs per cycle with C-IVF (26% vs. 20%; odds ratio [OR] 0.72, 95% confidence interval [CI] 0.55–0.93, P=.01). However further scrutiny of both these meta-analyses identified that the difference in the pooled OPR was mainly contributed from a single large RCT (n = 404) by Heijnen et al. (24), in which participants in the MS-IVF group had compulsory single embryo transfer (SET), whereas those in the long down-regulation group underwent double embryo transfer (DET); other smaller RCTs included in the meta-analyses reported no difference in OPRs (5, 9, 26). Not included in the above meta-analyses was an equally large and adequately powered RCT (n = 412) on normal/high responders that reported equal LBRs per ET (both 28.6%) with either approach (7).

With regard to administration of oral agents, three systematic reviews, including a Cochrane review of 11 RCTs and one with poor responders, concluded that LBRs or CPRs from clomiphene citrate (CC)+Gn IVF cycles were not significantly different from those of C-IVF (36–38). The only available RCT that used a strategy of administering CC+Gn until the day of GnRH agonist for ovulation trigger reported a lower cumulative LBR when compared with C-IVF (49% vs. 63%; relative risk 0.76, 95% CI 0.64–0.89) in normal responders. Again, a SET policy was applied to CC+Gn arm, whereas women on the long down-regulation protocol had DET (25). In contrast, two adequately powered RCTs mentioned above reported cumulative LBRs with MS-IVF to be comparable to C-IVF among normal/high responders (7, 24). A recent retrospective study (n = 163) with sequential CC+Gn in good-prognosis patients achieved 40.4% CPR per ET in first fresh cycles, with a cumulative (four fresh and vitrified–thawed cycles) LBR of 70% (39).

Mild-stimulation IVF has gained wider acceptance in the treatment of poor responders. In this group of women, the majority of the RCTs reported LBRs or CPRs with mild IVF to be equal to, or in some cases, better than high-dose C-IVF (20, 32–35). A recent meta-analysis of four RCTs concluded that CC+Gn mild stimulation and C-IVF were associated with similar LBR and CPR (38). In a retrospective study Lazer et al. (40) (n = 141) found that letrozole plus low-dose Gn in poor responders was actually associated with a higher LBR (21.4% vs. 7.0%; P<.05) when compared with a high-dose antagonist protocol. Thus, there is growing evidence that in good-prognosis patients as well as in poor responders, administration of lower than

TABLE 1

RCTs comparing MS-IVF with C-IVF: normal responders/unselected population.

Authors (year) (reference), population (n), power	Inclusion criteria	MS-IVF protocol (n)	C-IVF protocol (n)	PR/CPR/OPR/LBR (MS-IVF vs. C-IVF)	OHSS rate, CCR (MS-IVF vs. C-IVF)	Other significant findings (MS-IVF vs. C-IVF)
Baart et al. (2007) (5) n = 111	Age <38 y. BMI 19-29 kg/m^2. Regular cycle. Sperm count >5 × 10^6/mL. No uterine/ovarian abnormalities. No previous cycle resulting in failed ET. No recurrent miscarriages.	FSH fixed 150 IU/d from D5. GnRH-ant when leading follicle(s) 14 mm. (n = 67)	Long GnRH agonist down-regulation, then fixed FSH doses of 225 IU/d. (n = 44)	OPRs/cycle: 19.0% vs. 17.1% (NS) OPRs/ET: 34.3% vs. 22.6% (NS)	OHSS: 0% vs. 2% (NS) CCR (under-response): 11% vs. 0%	Proportion of good-quality embryos: 51% vs. 35% (*P*=.04) Euploid embryos: 50% vs. 38% (*P*=.05)
Casano et al. (2012) (7) n = 412 Adequately powered	Age <38 y. D3 FSH <8 IU/L, AMH >2 ng/mL, and AFC >16. 1st IVF attempt.	FSH 150 IU/d from D4, adjusted if needed from D8. GnRH-ant from D8. (n = 205)	Long GnRH agonist down-regulation, then FSH 150 IU/d (increased if needed). (n = 207)	LBR/cycle: 24.8% vs. 26.6% (NS) Cumulative (fresh + frozen) LBRs: 42.7% vs. 41.7% (NS)	OHSS: 1.6% vs. 2.0% (NS) CCRs: 1% vs. 0% (NS)	No. oocytes, embryos, FR and IR: no significant difference
		Canceled if <2 follicle >10 mm on D5.				
Dhont et al. (1995) (21) n= 303 Adequately powered	No age/ovarian reserve criterion. 1st IVF attempt. Treatment also included ZIFT and GIFT.	COCP pretreatment. CC 100 mg/d × 5 days, then hMG 150 IU/d. No GnRH-ant. (n = 151) Canceled if <3 follicles	OCP pretreatment. Long-acting GnRH agonist. hMG 300 IU/d (increase if required). (n = 152)	PR/cycle: 24.5% vs. 36.8% (*P*=.02) LBRs/cycle: 18.5% vs. 25.7% (NS)	OHSS: 0% vs. 4.1% CCR: 20.5% vs. 2.6% (*P*<.001)	No. oocytes/embryo/surplus embryos and miscarriage rate significantly more with long agonist protocol
Ghosh Dastidar et al. (2010) (8) n = 116	Good-prognosis patients. 1st IVF attempt.	CC 100 mg/d on D2–6 + r-FSH 100-150 IU on D3, D5, and daily from D7. GnRH-ant @ leading follicle(s) 13–14 mm.	Long GnRH agonist down-regulation, then r-FSH 200–225 IU/d.	PR/cycle: 1st: 35.7% vs. 40.0% 2nd: 42.9% vs. 43.7% (NS) Cumulative PRs: 60.0% vs. 58.0% (NS)		IR: 20.3% vs. 17.2% (*P*<.05) Top-quality embryo: 64% vs. 48% (*P*<.05) Drop-out: 7.1% vs. 25.9% (*P*<.05)
Grochowski et al. (1999) (22) n = 324 Adequately powered	Age <36 y. Regular cycles. Cause of infertility solvable by IVF/ICSI, 1st IVF/ICSI attempt.	CC 100 mg/d on D2–7 + hMG 150 IU/d on D4, D6, and D8. No GnRH-ant. (n = 164)	Long GnRH agonist down-regulation, then hMG 150–225 IU/d (n = 160)	PRs/ET: 29.7% vs. 25.5% (NS)	OHSS: 0% vs. 3.1% (NS)	FR: 73.1 vs. 60.9% (*P*<.05). IR: 19% vs. 13.5% (NS) Cost: CC 1/5 less.
Harrison et al. (1994) (23) n = 150	Unselected, not specified	CC 100 mg/d on D2–7 + hMG 150 IU/d from D4. No GnRH-ant. (n = 50)	GnRH-agonist long-acting down-regulation, then hMG 225 IU/d. (n = 50)	LBRs/cycle: 24% vs. 22% (NS) LBR/ET: 34% vs. 31% (NS)	CCR: 22% vs. 18% under-response (NS)	No. oocytes/embryos: no difference
Heijnen et al. (2007) (24) n = 404 Adequately powered	Age <38 y. BMI 18–28 kg/m^2. Regular 25–35 days' cycle. 1st IVF/ICSI attempt/no previous healthy LB from IVF.	FSH fixed dose 150 IU/d from D5. GnRH-ant @ leading follicle(s) 14 mm. SET. (n = 205)	Long GnRH agonist down-regulation, then FSH fixed 150 IU/d. DET. (n = 199)	LBRs (term)/cycle: 15.8% vs. 24.0% OR 0.59 (95% CI 0.41–0.85) Cumulative 1-y LBRs: 43.4% vs. 44.7% (NS)	OHSS: 1.4% vs. 4% (*P*=.04) CCRs: 18% vs. 8% (*P*<.001)	Mean total costs: €8,333 vs. €10,745 (*P*=.006) Drop-out rates: lower with MS-IVF (*P*=.04)

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TABLE 1

Continued.

Authors (year) (reference), population (n), power	Inclusion criteria	MS-IVF protocol (n)	C-IVF protocol (n)	PR/CPR/OPR/LBR (MS-IVF vs. C-IVF)	OHSS rate, CCR (MS-IVF vs. C-IVF)	Other significant findings (MS-IVF vs. C-IVF)
Hohmann et al. (2003) (9) n = 142	Age 20-38 y. BMI 19–29 kg/m^2, regular cycle. No severe endometriosis/ uterine/ovarian anomaly. <3 previous IVF. No previous poor response/OHSS	FSH fixed dose 150 IU/ d from D5. GnRH-ant @ leading follicle(s) 14 mm. (n = 49)	Long GnRH agonist down-regulation, then fixed 150 IU/ d FSH. (n = 45) Canceled if <3 follicles	OPRs/cycle: 16% vs. 18% (NS) OPR/ET: 36% vs. 39% (NS)	Premature ovulation: 2% vs. 0%	No. grade 1 embryos: 61% vs. 29% (*P*=.008)
Zhang JJ et at (2016) (25) n = 564 (non-inferiority) Adequately powered	Age 18–38 y. BMI 18.5–32 kg/m^2. Regular cycle, FSH <12 IU/L, 1st IVF attempt. No medical conditions.	COCP pretreatment. CC 50 mg/d from D3 until the day before GnRH agonist trigger. FSH/hMG 75–150 IU/ d. Later vitrified–thawed SET (n = 285)	Long GnRH agonist down-regulation, then hMG or FSH @ 150–300 IU/d. Fresh DET (blastocyst), remaining vitrified and transferred later. (n = 279)	Cumulative LBR: 49% vs. 63% (0.76; 95% CI 0.64–0.89)	OHSS: 0% vs. 5.7% (*P*< .001)	Multiple pregnancy: 6.4% vs. 32% 0.25 (0.14–0.46) Less Gn use
Karimzadeh et al. (2010) (26) n = 243	Age 18–35 y, BMI 18–30 kg/m^2. FSH <10 IU/L. Regular 26–35 days' cycle. 1st IVF attempt.	CC 100 mg on D3–D7. FSH fixed 75 IU/ d from D5. GnRH-Ant @ leading follicle(s) 12 mm + hMG 75 IU/d (n = 100)	Long GnRH agonist for 2 wk and then flexible 150–225 IU/ d dose of FSH. (n = 100)	OPRs/ET: 32% vs. 26% (NS)	OHSS: 0% vs. 6% (*P*=.02) CCR: 4% vs. 0%	No. oocytes/embryo significantly less with MS-IVF. No. top-quality embryo: similar
Lin et al. (2006) (27) n = 120	Age 20-38 y, BMI 18.5-24.9, FSH <10 IU. Couples with male factor infertility. 1st ICSI cycle.	CC 100 mg/d on D3–7 + hMG 150–300 IU/ d on D4, D6, and D8. GnRH-ant @ follicle 14 mm. (n = 60)	Long GnRH agonist down-regulation. Then hMG 150–300 IU/d. (n = 60)	LBR/cycle: 36.7% vs. 35% (NS) CPR/cycle: 41.7% vs. 40.0% (NS)	OHSS: 1.7% vs. 5% (NS) CCR: 23.5% vs. 10.9%	FR: 87.7% vs. 81.3% (*P*=.03) IR: No difference. Less Gn use.
Long et al. (1995) (28) n = 70	Age 25–45 y. 1st IVF cycle.	CC 50 mg/d on D2–6 + hMG 150 IU/d from D3. No GnRH-ant. (n = 34)	GnRH agonist flare 0.25 mg/d from D2, along with hMG 150 IU/d. (n = 36) Canceled if < 3 follicles 15 mm or more	CPR/cycle: 14.7% vs. 13.8% (NS) LPR/cycle: 11.8% vs. 8.3% (NS)	CCR: 17.6% vs. 16.7% (NS)	Mean number of oocytes/embryos: No difference
Lou et al. (2010) (29) n = 60	Age <35 y. BMI 18–28 kg/m^2. FSH <10 IU/L. Regular cycle. Tubal factor, 1st IVF attempt.	hMG-fixed 150 IU/d from D3 if E_2 <50 pg/mL. No GnRH-ant. (n = 30)	Long GnRH agonist down-regulation, then r-FSH 150–300 IU/d. (n = 30) Canceled if <2 follicles	OPR/cycle: 26.7% vs. 23.3% (NS) CPRs/cycle: 30% vs. 30%	OHSS: 0% vs. 6.7% (NS) CCR: None	Reduced cost (*P*< .001)
Tummon et al. (1992) (30) n = 408 Adequately powered	Any couple who need IVF treatment, except severe male factor.	CC 100 mg/d on D5-D9 + hMG 75 IU/d from D6. No GnRH-ant. (n = 229)	Long GnRH-agonist down-regulation+ hMG dose adjusted with body weight. (n = 179) Canceled if <2 follicles	PRs/cycle: 10.7% vs. 9.2% (NS) PRs/ET: 19.2% vs. 17.5% (NS)	CCR: 30.8% vs. 10.1% (*P*< .001)	No. oocytes/embryo significantly less with MS-IVF. IR: No difference

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TABLE 1

Continued.

Authors (year) (reference), population (n), power	Inclusion criteria	MS-IVF protocol (n)	C-IVF protocol (n)	PR/CPR/OPR/LBR (MS-IVF vs. C-IVF)	OHSS rate, CCR (MS-IVF vs. C-IVF)	Other significant findings (MS-IVF vs. C-IVF)
Weigert et al. (2002) (31) n = 294	Age 20–39 y. No previous IVF cycles, Normal ovulatory cycles, tubal/male factor/ unexplained infertility.	COCP pretreatment. CC 100 mg/d for 5 days + rFSH 225 IU + 75 IU of rLH on alternate days. No GnRH-ant. (n = 154) Canceled if no follicular development by D8	Long GnRH agonist down-regulation, then rFSH 150 IU/d. (n = 140)	PRs/cycle: 35.1% vs. 29.3% (NS) PRs/ET: 42.9% vs. 36.6% (NS)	OHSS: 3% vs. 10% (P=.02) CCR: 16.9% vs. 15.7% (NS)	No. oocytes/embryo significantly less with MS-IVF. No. embryos IR: no difference

Note: Criteria for included/excluded RCTs: RCTs that compared low-dose (<225 IU/day) gonadotropin ± oral agents with long down-regulation protocol, high-dose 'flare' or antagonist protocol were included; and RCTs that compared natural/natural modified cycles with another MS-IVF or between two types of mild-stimulation protocols were excluded. RCTs that used conventional high daily gonadotropin doses along with oral agents–clomiphene/aromatase inhibitors were also excluded. AFC = antral follicle count; AMH = antimüllerian hormone; BMI = body-mass-index; COCP = combined oral contraceptive pill; D = day (eg, D3 = day 3); FR = fertilization rate; GIFT = gamete intrafallopian transfer; GnRH-ant = GnRH antagonist; IR = implantation rate; NS = not significant (statistically); PR = pregnancy rate; r-FSH = recombinant FSH; ZIFT = zygote intrafallopian transfer.

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standard stimulation dose with or without oral agents does not compromise LBR.

ADVANTAGES OF MS-IVF

Higher Safety Profile

Ovarian hyperstimulation syndrome (OHSS) and multiple birth are recognized as two major risks of ART. The above-mentioned meta-analysis by Matsaseng et al. (15) from two RCTs found a significantly lower incidence of OHSS with MS-IVF compared with C-IVF (OR 0.27, 95% CI 0.11–0.66). Other systematic reviews, including the Cochrane review quoted earlier, also reported a significantly reduced risk of OHSS with a CC+Gn regimen, when compared with the long down-regulation protocol or a standard-dose GnRH antagonist protocol (36, 37). A GnRH agonist as a "trigger" for ovulation has now been shown to be very effective in preventing OHSS. However, sporadic cases of OHSS have been reported despite GnRH agonist trigger when a standard dose of Gn was used (41, 42). No cases of OHSS occurred by applying a protocol comprising CC+Gn administration until the day of GnRH agonist trigger followed by elective freezing of embryos in large studies on unselected populations (25, 43). It is yet to be determined whether MS-IVF in high responders with GnRH agonist trigger could be a further improvement in the current drive of establishing an "OHSS-free" clinic.

Elective SET is an effective strategy for prevention of multiple pregnancies in ART. Higher-quality embryos produced by MS-IVF could lead to a successful SET program without the need for preimplantation genetic screening, which is frequently recommended in C-IVF. The RCT by Heijnen et al. (24) found the cumulative LBR of MS-IVF with SET to be equivalent to that with C-IVF followed by DET over the course of 1 year, with a significantly lower incidence of multiple pregnancy (0.5% vs. 13.1%; P<.001). In the study by Kato et al. (43), single blastocyst transfer was associated with a very low incidence of twin gestation (0.9%) and ectopic pregnancy (0.36%; 9 of 2,523), with comparable LBRs. These incidences were even lower than those in the background population.

Higher Birth Weight

Live birth rate has traditionally been regarded as the benchmark for success in IVF. In recent years, a healthy singleton live birth at term has been suggested to be the goal of any IVF program (44). The mean birth weight of the babies born out of natural cycle IVF has been shown to be higher than that of C-IVF (45, 46). An analysis of a large dataset of 63,686 singleton births revealed a direct correlation between number of oocytes retrieved and the incidence of perinatal complications, including preterm and low birth weight babies (47). Mak et al. (46) (n = 364) also found a significantly lower incidence of premature birth and low birth weight singletons with natural cycle IVF, although there was no significant difference in the number of growth-restricted newborns. The association between stimulation dose, number of oocytes collected, and adverse

TABLE 2

Randomized controlled trials comparing MS-IVF with C-IVF: poor responders.

Authors (year) (reference), population (n), power	Inclusion criteria	MS-IVF protocol (n)	C-IVF protocol (n)	PR/OPR/LBR (MS-IVF vs. C-IVF)	OHSS rate CCR (MS-IVF vs. C-IVF)	Other significant findings (MS-IVF vs. C-IVF)
Bastu et al. (2016) (20) n = 95 Powered for no. oocytes	Poor ovarian reserve by Bologna criteria. BMI 19.3–28.9 kg/m^2. Normal uterine cavity. ICSI with ejaculated sperm only.	Letrozole 5 mg/d × 5 days + daily hMG 75 + rFSH 75 IU/d from D2. GnRH ant from D6. (n = 33)	GnRH-ant. fixed start of on D6 + hMG 225 IU and rFSH 225 IU/d from D2. (n = 31)	CPR/cycle: 15% vs. 13% (NS) CPR/ET: 20% vs. 18% (NS)	CCR: 24% vs. 29% (NS)	Mean no. of oocytes/embryos, FR, IR: no difference Less Gn use
Mohsen et al. (2013) (32) n = 60	Previous 1 or more failed cycles. BMI <30 kg/m^2. Regular cycle.	Letrozole 5 mg/d D2–6; hp hMG 150 IU/d from D7. GnRH-Ant @ follicle(s) 14 mm. (n = 30)	GnRH agonist "short flare" from D2 until hCG trigger; hp hMG 300 IU/d. (n = 30)	CPR/cycle: 13.3% vs. 16.6% (NS)	CCR: 20% vs. 16.6% (NS)	Mean no. of oocytes/embryos: no difference. Less Gn use
Ragni et al. (2012) (33) n = 304 Underpowered for LB	Age 18–42 y. D3 FSH >12 IU/L × 2 times. Previous poor response (≤3 oocytes with C-IVF) on 1–3 cycles.	CC 150 mg/d on D3–7 No Gn; no GnRH-ant. (n = 148)	GnRH-agonist "short flare" from D2; ovarian rFSH 450 IU/d (n = 156)	LBR/cycle: 3% vs. 5% (NS) LBR/ET: 9% vs. 9%	CCR: 14% vs. 14%	Lower cost/patient with CC + FSH: €2,803 vs. €5,423
Revelli et al. (2014) (34) n = 640 Adequately powered	Age <43 y. D3 FSH 10-20 IU/L with E^2 <80 pg/mL; AMH between 0.14 and 1.0 ng/mL AFC 4–10.	CC 100 mg/d on D2-6 and hMG/Pergoveris 150 IU/d from D5. GnRH-ant from D8. (n =309)	Long GnRH agonist down-regulation; half the dose at hMG, starting 300 IU/d, max. 450 IU/d. (n = 331)	CPR/cycle: 13.2% vs. 15.3% (NS) OPR/ET: 17.8% vs. 16.8% (NS)	CCR: 13% vs. 2.7% (P< .01)	Mean metaphase II oocytes: 2.2 ± 1.9 vs. 4.0 ± 2.8 (P< .01). Top-grade embryo: no difference Less Gn use
Youssef et al. (2017) (35) n = 394 Adequately powered	Age ≥35 y or basal FSH >10 IU, or AFC <5 or previous poor response (oocyte ≤5)/cancellation irrespective of age.	COCP Pretreatment; fixed FSH 150 IU/d from D5 of last pill; GnRH-ant fixed D6 start. (n = 195) Canceled if <2 follicles 15 mm after 7 d	GnRH agonist long down-regulation; hMG 450 IU/d fixed dose. (n = 199)	OPR/woman: 12.8% vs. 13.6% (NS) CPR/women: 15.3% vs. 15.5% (NS)	CCR: 26% vs. 18% (NS)	No. oocytes/embryo significantly less with MS-IVF. No. top-quality embryos: similar

Note: Abbreviations and criteria for included RCTs in this table are the same as detailed in Table 1.

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perinatal outcomes seems to be consistent, but this needs to be confirmed in RCTs.

Higher Patient Satisfaction

A systematic review of 22 studies (21,453 patients) found physical or psychological stress to be the most common causes of discontinuation of fertility treatment (48). Being associated with lower stimulation and lower E_2 levels, MS-IVF has long been found to be tolerated better by patients. An earlier study that specifically addressed women's attitudes toward the acceptability of two different IVF protocols found more treatment-related stress with C-IVF compared with MS-IVF (49). The RCT by Heijnen et al. (24) reported lower dropout rates after MS-IVF, with the level of anxiety and discomfort in MS-IVF not significantly different from that with C-IVF; however, a further analysis of the same RCT found significantly fewer symptoms of depression after a failed MS-IVF cycle (50). Mild-stimulation IVF cycles have been reported to reduce the anxiety score and dropout rate by more than 50% compared with C-IVF cycles (51). Another large RCT on normal/high responders observed increased tolerance to medications in the "mild-stimulation" group (7). None of the 163 recruited women dropped out when followed through to a maximum of three cycles with a CC+Gn protocol (39).

Lower Financial Cost

Cost is an important consideration in IVF treatment, whether it is public or self-funded. Although it required one more treatment cycle (four vs. five) to achieve equivalent LBRs in a 1-year period, the RCT by Heijnen et al. on normal responders reported the overall cost of MS-IVF to be less than that of C-IVF with long down-regulation (€8,333 vs. €10,745; $P=.006$) (52). A subsequent detailed cost analysis of this trial identified that higher multiple pregnancy rates, the cost of consumed medications, and other laboratory procedures all had a significant impact in raising the cost in C-IVF cycles (52). A few retrospective non-RCTs showed no cost savings comparing CC+Gn cycles with GnRH agonist down-regulation cycles (53, 54). However, many RCTs, including the one previously mentioned here, found MS-IVF to be significantly less expensive (22, 23, 29). Extending CC until the trigger day has been shown to prevent premature ovulation by suppressing the LH surge and avoids the need for the more-expensive GnRH antagonist (25, 43, 55). The few studies that performed economic analysis estimated a lower per-cycle cost with this regimen (56). There is emerging evidence that a CC+Gn mild-stimulation regimen may not require luteal phase support (57). It is therefore possible that the overall cost of an MS-IVF cycle may decrease further in time.

A distinct financial advantage MS-IVF offers is in the treatment of poor responders, who frequently receive the highest dose of Gn in C-IVF cycles. A large noninferiority RCT among poor responders identified significant cost reduction with a sequential CC+Gn protocol compared with a high-dose GnRH agonist protocol (33). A recent retrospective cohort study comparing letrozole+Gn with standard-dose Gn in an antagonist protocol had similar conclusions (40). Assisted reproductive technology remains a costly affair and beyond the reach of many couples, especially in low-resourced communities and in countries where there is no or inadequate public funding. A recent review proposed consideration of MS-IVF or natural IVF, to make treatment more accessible to people who require IVF but find it difficult to afford treatment (58).

POTENTIAL LIMITATIONS OF MS-IVF

Higher Cycle Cancellation Rate

Mild-stimulation IVF has been found to be associated with higher cycle cancellation rate (CCR), predominantly owing to lower response. However, many studies inappropriately adopted the cancellation criterion of development of few than three dominant follicles, whereas development of one to three follicles is not regarded as under-response in MS-IVF (9, 21, 28). The systematic review by Matsaseng et al. (15) reported a significantly higher CCR with MS-IVF among normal responders (16% vs. 9%; OR 2.55, 95% CI 1.62–4.02). However, many other RCTs, not included in this meta-analysis, found no difference in CCRs when MS-IVF was compared with C-IVF in normal responders (7, 23, 26, 28, 29). Interestingly, the Cochrane review that included CC+Gn as a "mild stimulation" regimen found higher CCR mainly in those RCTs in which a GnRH antagonist was not used to suppress endogenous LH, implying a decline in CCRs with antagonist cotreatment (36). Not a single cycle was canceled owing to premature ovulation in an RCT comprising 60 normo-responders undergoing mild IVF with a CC+Gn protocol (27).

The majority of recent RCTs on poor responders found CCRs in MS-IVF to be similar to that of C-IVF (20, 32, 33, 35), with a few exceptions (34). A meta-analysis that incorporated recent large RCTs with CC+Gn and high-dose IVF protocols in this population showed no difference in CCR (38). A low CCR (4.2%) has been reported in a retrospective study on poor responders with a letrozole plus Gn protocol (40).

Few methods have been shown to effectively reduce the incidence of premature ovulation. The nonsteroidal anti-inflammatory drug indomethacin, by limiting the preovulatory intrafollicular inflammatory process (59, 60), and the administration of CC throughout the follicular phase, by suppressing the LH surge (55), are effective in preventing premature ovulation. Indeed, a very low CCR (approximately 2%–3%) has been reported in large retrospective as well as randomized studies with the administration of CC+Gn until ovulation trigger (25, 43). Cycle cancellation rate seems to be linked with ovarian reserve, women's age, and the study protocols used: further large well-designed trials may clarify this further.

Fewer Embryos for Cryopreservation

The aim of MS-IVF is to achieve "quality" and not "quantity" in terms of oocytes and embryos in the stimulated cycle. Two meta-analyses of RCTs in normal responders demonstrated a lower number of retrieved oocytes in MS-IVF (3, 15). However, the evidence is currently inconsistent, with several RCTs reporting no difference in the mean number of

transferred or cryopreserved embryos between high and mild stimulation (7, 20, 23, 28, 32), which contradicts the findings of other RCTs (21, 26, 30). The study by Casano et al. (7) on good-prognosis women found a similar number of retrieved oocytes, top-quality embryos, and cryopreserved embryos between MS-IVF and C-IVF. The meta-analysis on poor responders has also reported that the mean number of oocytes retrieved with a CC+Gn protocol to be no different from that with a high-stimulation strategy (38). Similarly, another meta-analysis mentioned earlier reported a comparable number of created embryos whether a low dose (150 IU/d) or high dose (>200 IU/d) of Gn was used (16). Notably, several RCTs identified the number of high-grade embryos from MS-IVF to be equivalent to, if not better than, those from C-IVF, regardless of total number of embryos created (5, 8, 9). Whether MS-IVF leads to acquisition of fewer embryos or not, good and comparable cumulative pregnancy rates from combining fresh and frozen–thawed ETs have been reported (7, 39).

WHERE DOES MS-IVF STAND TODAY AND WHAT IS THE FUTURE?

Mild-stimulation IVF has been proven to be a safer, better tolerated, more woman-friendly and affordable way of conducting ovarian stimulation in IVF cycles. There is also growing evidence that gentle stimulation is associated with better perinatal outcomes. Mild-stimulation IVF has gained acceptance in the treatment of poor responders by virtue of its cost-saving and avoidance of unnecessarily high-stimulation drugs. Mild-stimulation IVF incorporating tamoxifen or aromatase inhibitors has secured a place in treatment of women with estrogen-sensitive malignancies (breast or endometrial) (61). Milder protocols could be an option in providing low-cost IVF and thereby making it more accessible (58).

At the time of writing this review, approximately 20 RCTs were identified to have compared one of the MS-IVF protocols with conventional long down-regulation or high-dose antagonist protocol; more than half were large trials (9 claimed to be adequately powered; Table 1 and 2); and approximately a dozen editorials and opinion papers have been published in scientific journals, with no clear conclusion. Except for two RCTs (24, 25), all reported MS-IVF to be equally successful in terms of pregnancy outcomes per ET. An RCT that found lower per-cycle pregnancy rates in the MS-IVF group did not find a significant difference in LBRs per ET (21) (Table 1). The majority of RCTs that analyzed cumulative pregnancy (CPRs/LBRs) found no difference in these outcomes between the two approaches. The current weight of evidence points to comparable LBRs between MS-IVF and C-IVF in good responders and a trend toward better outcomes in poor responders. An updated meta-analysis and systematic review, adding the data from recent RCTs and stratifying them by different MS-IVF regimens and prognostic groups, may provide better-quality evidence, reassuring the efficacy of MS-IVF.

Many clinicians argue that with increased efficacy with vitrification, it would be better to collect a high number of oocytes after GnRH analogue trigger in a single C-IVF cycle and to cryopreserve all embryos, to prevent OHSS and to transfer cryopreserved embryos "one at a time" at a later stage. The modern trend of overstimulating the ovaries to obtain large numbers of oocytes, which are then fertilized and the embryos vitrified at blastocyst stage and stored in embryo banks in IVF laboratories to be used when the patient chooses, is the stuff of dystopian nightmares. Yet we are being persuaded that this development is a normal progression of the IVF process instead of being a reaction to the complications of this unphysiologic approach. The process of high stimulation causes a massive rise in E_2 levels, which is linked to adverse endometrial conditions for implantation and potentially chromosomally abnormal embryos. The former is an incentive to freeze, and the latter creates a need to perform preimplantation genetic screening. Laboratories with huge banks of embryos represent a logistic problem, which will ultimately lead to a need to store embryos off site, increasing costs and constituting a further risk to the embryos. Doctors in reproductive medicine should take a step back and consider the advantages of a more physiologic and milder stimulation in IVF that reduces the physical, emotional, and economic burden for women and promotes better health outcomes for mothers and babies.

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