GYNECOLOGY

Minimal stimulation IVF vs conventional IVF: a randomized controlled trial

John J. Zhang, MD, PhD; Zaher Merhi, MD; Mingxue Yang, MD, PhD; Daniel Bodri, MD, PhD; Alejandro Chavez-Badiola, MD; Sjoerd Repping, PhD; Madelon van Wely, PhD

BACKGROUND: Minimal stimulation in vitro fertilization (mini—in vitro fertilization) is an alternative in vitro fertilization treatment protocol that may reduce ovarian hyperstimulation syndrome, multiple pregnancy rates, and cost while retaining high live birth rates.

OBJECTIVE: We performed a randomized noninferiority controlled trial with a prespecified border of 10% that compared 1 cycle of mini—in vitro fertilization with single embryo transfer with 1 cycle of conventional in vitro fertilization with double embryo transfer.

STUDY DESIGN: Five hundred sixty-four infertile women (<39 years old) who were undergoing their first in vitro fertilization cycle were allocated randomly to either mini—in vitro fertilization or conventional in vitro fertilization. The primary outcome was cumulative live birth rate per woman over a 6-month period. Secondary outcomes included ovarian hyperstimulation syndrome, multiple pregnancy rates, and gonadotropin use. The primary outcome was cumulative live birth per randomized woman within a time horizon of 6 months.

RESULTS: Five hundred sixty-four couples were assigned randomly between February 2009 and August 2013 with 285 couples allocated to mini—in vitro fertilization and 279 couples allocated to conventional in vitro fertilization. The cumulative live birth rate was 49% (140/285) for mini—in vitro fertilization and 63% (176/279) for conventional in vitro fertilization (relative risk, 0.76; 95% confidence interval, 0.64-0.89). There were no cases of ovarian hyperstimulation syndrome after mini—in vitro fertilization compared with 16 moderate/severe ovarian hyperstimulation syndrome cases (5.7%) after conventional in vitro fertilization. The multiple pregnancy rates were 6.4% in mini—in vitro fertilization compared with 32% in conventional in vitro fertilization (relative risk, 0.25; 95% confidence interval, 0.14-0.46). Gonadotropin consumption was significantly lower with mini—in vitro fertilization compared with conventional in vitro fertilization (459 ± 131 vs 2079 ± 389 IU; $P < .0001$).

CONCLUSION: Compared with conventional in vitro fertilization with double embryo transfer, mini—in vitro fertilization with single embryo transfer lowers live birth rates, completely eliminates ovarian hyperstimulation syndrome, reduces multiple pregnancy rates, and reduces gonadotropin consumption.

Key words: IVF, mini-IVF, clomiphene citrate, OHSS, multiple pregnancy

The current standard of in vitro fertilization (IVF) treatment involves ovarian hyperstimulation with high doses of gonadotropins in combination with transfer of ≥1 embryos.[1] The major safety issues of conventional IVF are ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Women with OHSS are at serious risk of potentially life-threatening conditions that involve hospitalization in 1.8% of the cases.[2] Multiple pregnancies are associated with a high risk of preeclampsia, gestational diabetes mellitus, antepartum hemorrhage, anemia, preterm delivery, and cesarean delivery.[3-7] Preterm birth is associated with a high risk of bronchopulmonary dysplasia, necrotizing enterocolitis, and cerebral palsy.[6,8-10] Additionally, all these complications often lead to expensive hospital admissions,[11] which impose a steep burden on societal expenses and health services.[12]

One of the most important factors that influences the rate of multiple births is the number of embryos that are transferred.[13] Single embryo transfer (SET) not only reduces the incidence of multiple pregnancies effectively but also decreases pregnancy rates per transfer.[14] Given this reduction in pregnancy chances, most physicians and patients in the United States are reluctant to practice a SET policy; the percentage of SET in IVF cycles ranged from 8.9-14% among women who were <38 years old in 2012.[15] This resulted in 25-29% multiple pregnancy rates among all pregnancies that were achieved during the same period of time.[15]

Minimal stimulation IVF (mini-IVF) combined with SET has the potential to reduce OHSS and multiple pregnancy rates without significantly lowering live birth rates. Mini-IVF entails the use of clomiphene citrate (CC), which allows an endogenous rise in follicle-stimulating hormone (FSH) to be added to the ovarian stimulation with low doses of gonadotropins.[16,17] By triggering ovulation, mini-IVF frequently makes use of a gonadotropin-releasing hormone agonist (GnRHa), instead of human chorionic gonadotropin, to prevent OHSS. A final contentious feature of mini-IVF is a freeze-all-embryo policy to prevent any negative effect of ovarian stimulation on endometrial receptivity.[18] In observational studies, mini-IVF has been shown to lead to high pregnancy rates, low multiple pregnancy rates, low OHSS rates, and low cost.[19,20]

The aim of this noninferiority randomized trial was to compare the effectiveness and safety of the mini-IVF strategy with the use of the freeze-all policy and SET with conventional IVF with the use of fresh double embryo transfer.

Cite this article as: Zhang JJ, Merhi Z, Yang M, et al. Minimal stimulation IVF vs conventional IVF: a randomized controlled trial. Am J Obstet Gynecol 2016;214:96.e1-8.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2015.08.009

Materials and Methods

Study oversight

This minimal ovarian stimulation trial was designed by investigators at the Academic Medical Center (Amsterdam, The Netherlands) and the New Hope Fertility Center (NHFC; New York, NY). All the participants received IVF treatments in a single center (NHFC). The noninferiority trial was approved by the Institutional Review Board of New York Downtown Hospital and was registered before its start at clinicaltrials.gov: NCT 00799929.

The trial protocol was approved by a protocol review committee and a data and safety monitoring board, both appointed by NHFC and by the institutional review boards of the New York Downtown Hospital and the Biomedical Research Alliance of New York. Randomization, monitoring, and data analysis were coordinated at the Academic Medical Center in the Netherlands.

Study design and patients

Women were recruited between February 2009 and August 2013 via printed and online media. Participants were responsible to pay for their own medications; they were provided free services (ie, oocyte retrieval and embryo transfer) as compensation for participation. Inclusion criteria included women between 18-38 years of age, having normal menstrual cycles, undergoing first IVF treatment and having infertility diagnoses of male, unexplained, and tubal factors. Exclusion criteria included preexisting medical conditions (such as diabetes mellitus, hypertension, hypothyroidism, and hyperprolactinemia), a body mass index of <18.5 or >32 kg/m^2, and day-3 FSH >12 mIU/mL. Screening tests before initiation of treatment included complete blood count, varicella and rubella titer, Papanicolaou smear, syphilis, HIV 1 and 2, hepatitis B, hepatitis C, chlamydia, gonorrhea, prolactin, thyroid-stimulating hormone, cycle day 3 FSH and estradiol. Ultrasound testing was performed at baseline, and women with any submucosal or large intramural fibroid tumors that required surgery were excluded from the study.

Informed consent and randomization

After we obtained written informed consent, women were allocated randomly to mini-IVF or conventional IVF at a 1:1 ratio. The randomization was done at the start of the cycle with the use of sequentially numbered opaque envelopes that had been prepared on the basis of a computer-generated list at the Academic Medical Center in the Netherlands and sent to NHFC in New York. Women and medical staff were not blinded for treatment allocation. Outcome data were not disclosed to participants or investigators until completion of the trial.

Mini-IVF

After oral contraceptive pill pretreatment for 10-14 days, adequate suppression was confirmed with an estradiol level of <75 pg/mL. Minimal ovarian stimulation was started with an extended regimen (from day 3 until the day before triggering) of CC (50 mg/d orally) in conjunction with gonadotropin injections (Bravelle and/or Menopur, Ferring, Parsippany, NJ; Follistim, Merck, White House Station, NJ; or Gonal F, EMD Serono, Rockland, MA) starting on cycle days 4-7 with 75-150 IUs daily. No hypothalamic-pituitary suppression was performed, and the final maturation of oocytes was induced by a GnRHa nasal spray (Synarel nasal spray, Pfizer, New York, NY) when the lead follicle reached a diameter of $\geq$18 mm (Figure 1). Oocyte retrieval was performed most often with local anesthesia; follicular flushing was performed as needed. Retrieved oocytes were fertilized by conventional IVF or ICSI, as indicated, and subsequently cultured until the blastocyst stage. All blastocysts were vitrified with the CryoTop method (Kitazato Biopharma, Fuji, Japan).[21] A single thawed blastocyst was transferred in a subsequent natural or artificially prepared cycle with oral Estrace (Actavis Pharma, Inc, Parsippany, NJ).[20]

Conventional IVF

Conventional ovarian stimulation consisted of a long GnRHa protocol with mid-luteal down-regulation (Leuprolide Acetate, Teva, Sellersville, PA) followed by stimulation with daily gonadotropins injections (Bravelle and/or Menopur, Ferring; Follistim, Merck; or Gonal F) at a dose of 150-300 IUs daily starting in the early follicular phase (cycle day 3). The final maturation of oocytes was induced with the standard human chorionic gonadotropin (Novarel, Ferring; Pregnyl, Merck; or Ovidrel, EMD Serono, Rockland, MA), rather than GnRHa, when at least 2 follicles reached $\geq$18 mm. Oocyte retrieval was performed mostly with general anesthesia because of the presence of a large number of mature follicles. Retrieved oocytes were fertilized by conventional IVF or ICSI according to the same indications as in the mini-IVF protocol and subsequently cultured until the blastocyst stage. Two or 1 blastocysts (the latter if 2 embryos were not available or if there was a medical contraindication for double embryo transfer) were transferred in the fresh cycle. Remaining supernumerary blastocysts were vitrified, and 2 thawed blastocysts or 1 blastocyst (if 2 were not available) were transferred in subsequent naturally or artificially prepared cycles with oral Estrace.

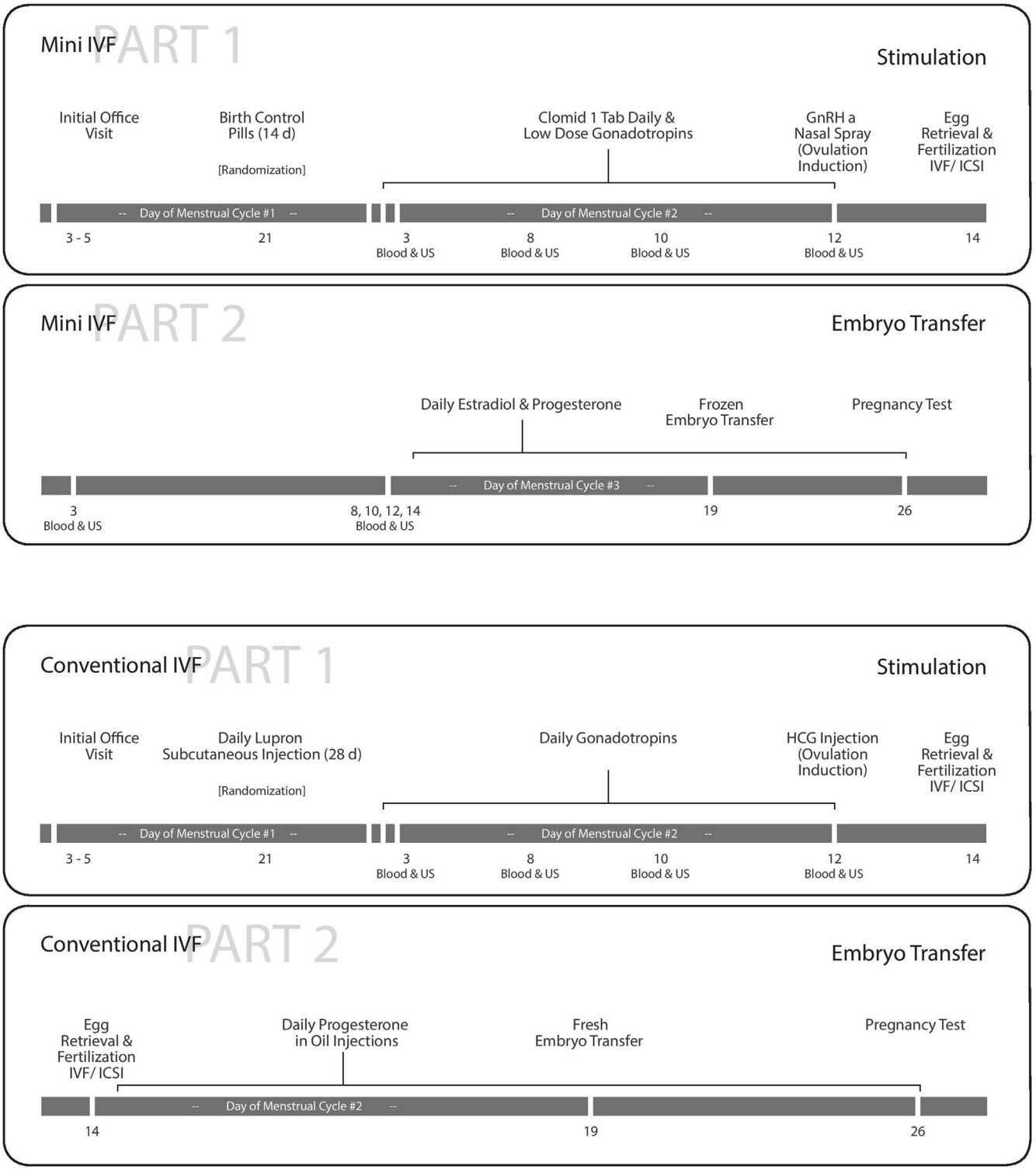
Outcomes

The primary outcome was cumulative live birth per randomly assigned woman (which included fresh and subsequent frozen embryo transfers [FET]) within a time horizon of 6 months. Secondary outcomes were clinical pregnancy rate; OHSS; multiple pregnancy rate; gonadotropin usage; the number of retrieved, mature, and fertilized oocytes; implantation rate; cancellation rate, and failed fertilization. A *clinical pregnancy* was defined as at least 1 intrauterine sac at 6 weeks gestation; *live birth* was defined as a child born after 22 weeks of gestation or who weighed at least 500 g.

Sample size calculation and statistical analysis

Sample size calculation was based on an expected cumulative live birth rate of 65% in women who were $\leq$38 years old after conventional IVF based on US Society for Assisted Reproductive Technology registry data from 2007 because recruitment started in 2009.[15]

FIGURE 1
Schematic diagrams of mini–in vitro fertilization and conventional in vitro fertilization protocols

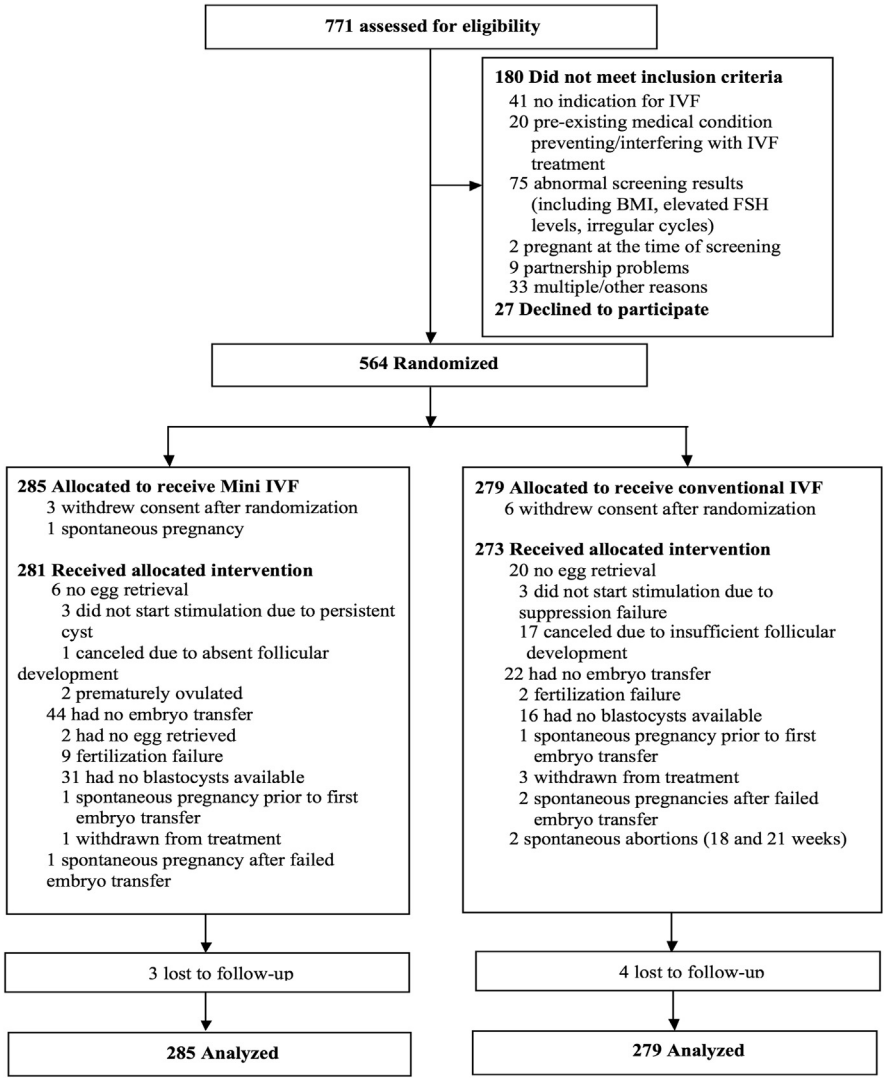


In the artificially prepared frozen embryo transfer of the mini–in vitro fertilization protocol, oral estradiol treatment was started on day 3 and was given daily; progesterone treatment was added on day 13 onward to the estradiol pills.

GnRHa, gonadotropin-releasing hormone agonist; *HCG*, human chorionic gonadotropin; *ICSI*, intracytoplasmic sperm injection; *IVF*, in vitro fertilization; *US*, ultrasound.

Zhang et al. Mini-IVF vs conventional IVF. Am J Obstet Gynecol 2016.

FIGURE 2
Trial profile



Screening, eligibility, randomization, and follow-up are addressed.

BMI, body mass index; *FSH*, follicle-stimulating hormone; *IVF*, in vitro fertilization.

Zhang et al. Mini-IVF vs conventional IVF. Am J Obstet Gynecol 2016.

A noninferiority margin of −10% was considered a clinically significant difference. Thus, 564 women were needed to assure that, with a power of 80%, the lower limit of a 1-sided 95% confidence interval (CI) was within a prespecified border of −10%.

The effectiveness of mini-IVF vs conventional IVF was expressed as a risk ratio for cumulative live birth, with the corresponding 95% CI. The risk difference and 95% CI for live birth and the relative risks and 95% CI for all binary secondary outcomes were calculated. For continuous outcomes, data were expressed as means ± standard deviation, and the difference between both arms was compared with the use of *t*-test. Chi-square and Fisher exact tests were used for categoric data, as appropriate. The analysis of all outcomes was on an intention-to-treat basis. A probability value of $<.05$ was considered statistically significant. SPSS software (version 22.0; SPSS Inc, Chicago, IL) was used to perform all statistical analyses.

Results

A total of 771 women were assessed for eligibility (Figure 2). Of these, 180 women did not fulfill the inclusion criteria (41 women had no indication for IVF; 20 women had preexisting medical conditions interfering with IVF treatment; 75 women had abnormal screening results; 2 women were pregnant at the time of screening; 9 women had personal problems, and 33 women had multiple reasons) and 27 women did not give informed consent. A total of 564 women were allocated randomly to the mini-IVF strategy or to conventional IVF. Four women in the mini-IVF arm and 6 women in the conventional IVF arm did not receive the allocated intervention because of withdrawal before starting treatment. Additionally, 3 women in the mini-IVF arm and 6 women in the conventional IVF arm dropped-out after starting treatment for reasons that are detailed in Figure 2. Cancelled cycles, failed fertilization, and blastocyst developmental failure in each arm are shown in Figure 2. In the mini-IVF arm, of the 281 participants who received the allocated intervention, 6 women did not make it to the oocyte retrieval stage (3 women had ovarian cyst at the baseline ultrasound scanning; 1 woman had no follicular development, and 2 women prematurely ovulated), and 44 women had no embryo transfer for reasons such as failed fertilization, failed blastocyst formation, and spontaneous pregnancy before embryo transfer. In the conventional IVF arm, of the 273 participants who received the allocated intervention, 20 women did not make it to the oocyte retrieval stage (3 women failed to have ovarian suppression, and 17 women did not have appropriate follicular development), and 22 women did not have embryo transfer for similar reasons as those in the mini-IVF arm.

Baseline characteristics did not differ between both arms (Table 1). Most women (68%) were <35 years old. Primary and secondary outcomes are listed in Table 2. The cumulative live birth rate per randomly assigned woman (including live births from frozen-thawed embryo

transfers in both arms of the study) was 49% in the mini-IVF arm and 63% in the conventional IVF arm, which resulted in a relative risk of 0.78 (95% CI, 0.67–0.90). The average absolute difference of mini-IVF vs conventional IVF was −14% (95% CI, −6 to −22%). None of the women in the mini-IVF arm experienced OHSS because of the use of GnRHa; moderate/severe OHSS occurred in 16 women (5.7%) in the conventional IVF arm. Seven of these women were hospitalized and underwent transvaginal paracentesis for symptomatic relief. The multiple pregnancy rate was significantly lower in the mini-IVF arm (6.4% vs 32%; relative risk, 0.25; 95% CI, 0.14–0.46); they were all monozygotic twins because only 1 embryo was transferred in this arm. Women in the mini-IVF arm required significantly lower total doses of gonadotropins per cycle (459 ± 131 vs 2079 ± 389 IU; $P < .0001$).

Laboratory outcome data are summarized in Table 3; details on the transfer procedures and their outcomes are summarized in Table 4. In total, 340 and 334 fresh and/or frozen embryo transfers procedures were performed in the mini-IVF and conventional IVF arms, respectively. In the mini-IVF arm, strict SET was performed; in the conventional IVF arm, 1.7 embryos on average were transferred in either fresh or subsequent frozen cycles (Table 4). After the first FET cycle, the implantation rate was significantly higher in the conventional IVF arm (58%) compared with the mini-IVF arm (47%; $P = .02$; Table 4). However, the implantation rate declined in subsequent FET cycles in the conventional IVF arm but increased in subsequent FET cycles in the mini-IVF arm to have tendency towards statistical significance in the third FET cycle (30% in the conventional IVF vs 54% in the mini-IVF; $P = .1$; Table 4). Additionally, the clinical pregnancy rate dropped in subsequent FET cycles in the conventional IVF arm (68% in the first FET cycle then 49%, 40%, and 33% in subsequent cycles), although it remained constant in subsequent FET cycles in the mini-IVF arm (47% in the first FET cycle then 48%, 54%, and 50% in subsequent cycles; Table 4).

TABLE 1
Demographics and baseline characteristics of the participants

Variable	In vitro fertilization	
	Mini	Conventional
Randomly assigned patients, n	285	279
Age, y[a]	32.4 ± 3.6	31.9 ± 4
Body mass index, kg/m^2[a]	24.7 ± 3.8	24.9 ± 3.8
Baseline follicle-stimulating hormone, mIU/mL[a]	8.6 ± 2.2	8.5 ± 2.3
Infertility duration, y[a]	2.4 ± 1.5	2.5 ± 1.5
Primary infertility, n (%)	127 (45)	132 (47)
Nulliparous, n (%)	207 (73)	207 (74)
Ethnicity, n (%)		
White	143 (50)	126 (45)
Black	55 (19)	70 (25)
Hispanic	42 (15)	46 (16)
Asian	35 (12)	29 (10)
Mixed/other	10 (4)	8 (3)
Infertility diagnoses, n (%)		
Tubal	78 (27)	101 (36)
Unknown	69 (24)	66 (24)
Male	70 (25)	48 (17)
Mixed male/female	21 (7)	29 (10)
Other (polycystic ovary syndrome, diminished ovarian reserve, endometriosis, multiple)	47 (16)	35 (12)

[a] Data are given as mean ± SD. $P > .1$ for all comparisons between the mini and the conventional in vitro fertilization arms.
Zhang et al. Mini-IVF vs conventional IVF. Am J Obstet Gynecol 2016.

Comment

This randomized trial compared the mini-IVF strategy that included freeze-all and SET to conventional IVF with fresh double embryo transfer in women <39 years old. The results indicated that the cumulative live birth rate in mini-IVF was 14% lower than that observed in conventional IVF; however, at the same time, mini-IVF completely eliminated OHSS, significantly reduced the risk of multiple pregnancy, and resulted in a 78% reduction in the total gonadotropin dose used per cycle.

Our study has several strengths. The design was rigorous and meticulous; only a small number of women withdrew after giving an informed consent, and only a small number of women were lost to follow up. The patient population included women of various ethnicities which made the results more generalizable. Furthermore, the conventional IVF arm resulted in pregnancy rates, OHSS, and multiple pregnancies rates that were comparable with the rates observed in US registries that strengthened our predefined power calculation.[15]

There are several limitations to our study. First and foremost, we compared 2 completely different strategies, which prevents the disentanglement of the effects of various components of mini-IVF such as SET, different stimulation protocols, and different strategy for embryo transfer. In other words, it is impossible to attribute the observed effects of mini-IVF on live birth rates, OHSS, multiple pregnancy rates, and gonadotropin use to the method of ovarian stimulation to the freeze-all concept or to the SET policy because these are all integral parts of mini-IVF. Future randomized controlled trials should focus on strictly

TABLE 2
Primary and secondary outcomes in the treatment groups

Pregnancy outcome	In vitro fertilization		Relative risk (95% confidence interval)	*P* value
	Mini	Conventional		
Randomly assigned patients, n[a]	285	279		
Clinical pregnancy, n (%)	161 (57)	211 (76)	0.67 (0.57-0.78)	
Live births, n (%)	140 (49)	176 (63)	0.78 (0.67-0.90)	
Multiple pregnancy per live births, n (%)	9 (6.4)	56 (32)	0.25 (0.14-0.46)	
Stimulation outcome[b]				
Total clomiphene dose, mg[a]	513 ± 101	—		
Total gonadotropin dose/cycle, IU[a]	459 ± 131	2079 ± 389		< .0001[c]
Days of stimulation, n[a]	10.7 ± 5.7	10.4 ± 5.7		.48[c]
Peak estradiol, pg/mL[a]	1657 ± 1067	3255 ± 2344		< .0001[c]
Moderate/severe ovarian hyperstimulation syndrome, n (%)	0	16 (5.7)		< .0001[d]

[a] Data are given as mean ± SD; [b] Among those who started ovarian stimulation (n = 548); [c] *T*-test; [d] Chi-square test.
Zhang et al. Mini-IVF vs conventional IVF. Am J Obstet Gynecol 2016.

evaluating these various components. Second, our study was a single-center study, which hampered generalizability.

Though mini-IVF resulted in significantly lower live birth rates, it is too early to state that it is inferior to conventional IVF. In our power calculation, we used a reduction of 10% as a clinically relevant reduction in live birth rates after mini-IVF. The absolute difference that was observed in our study was −14% with a 95% boundary of −22% to −6%. Thus, the prespecified acceptable 10% difference is still within the 95% CI of the observed difference. Furthermore, mini-IVF significantly reduced OHSS, multiple pregnancy rate, and gonadotropin use, thereby increasing the safety of IVF and controlling the cost of unwanted side-effects. It is unknown whether patients are willing to trade off these marginally lower live birth rates for increased safety and reduced costs. It is also unknown whether a lower cost of mini-IVF would motivate women to undergo >1 mini-IVF cycle for the same price as a single conventional IVF cycle. In this respect, it would be worthwhile to compare the cumulative pregnancy and live birth rates of 2 consecutive mini-IVF cycles with 1 conventional IVF cycle. Because mini-IVF is also likely to result in less treatment burden and stress, future trials should consider these additional relevant dimensions. The data that are provided in this study are the ingredients for shared decision-making to choose between mini-IVF and conventional IVF on a case by case basis.[22]

TABLE 3
Laboratory outcome data

Variable	In vitro fertilization		*P* value
	Mini	Conventional	
Randomly assigned patients, n	285	279	—
Oocyte retrievals, n (%)	275 (97)	253 (91)	.61[a]
Retrieved oocytes, n[b,c]	4.3 ± 3.2	12.8 ± 8	< .0001[d]
Inseminated oocytes (in vitro fertilization or intracytoplasmic sperm injection), n[b,c]	3.7 ± 2.8	10 ± 6.7	< .0001[d]
Fertilized 2 pronuclei oocytes, n[b,c]	3.1 ± 2.4	8.3 ± 5.8	< .0001[d]
Total blastocysts, n[b,e]	2.6 ± 1.9	5.9 ± 4.3	< .0001[d]
Cycles with blastocysts transferred/frozen, n (%)	234 (82)	235 (84)	.84[d]

[a] Chi-square test; [b] Data are given as mean ± SD; [c] Among those who had oocyte retrieval (n=528); [d] *T*-test; [e] Among those who reached blastocyst stage (n = 469).
Zhang et al. Mini-IVF vs conventional IVF. Am J Obstet Gynecol 2016.

Our mini-IVF protocol originally was developed at Kato Ladies Clinic in Japan and was adapted and modified successfully by our center.[20] In contrast to other treatment protocols in which CC was used for only a few days in the early follicular phase,[23] CC was administered in our protocol during the whole stimulation phase in conjunction with a low-dose of gonadotropins. This extended regimen not only favors the development of a mild ovarian response but also takes advantage of the ability of CC to prevent premature luteinizing hormone surge, thus reducing the risk of premature ovulation in addition to decreasing the amount of gonadotropins needed.[16] We also disengaged the embryo transfer from the stimulation phase, because it has been demonstrated that the CC-based minimal ovarian stimulation protocol was more efficient when embryos were vitrified electively

TABLE 4
Outcome of fresh and frozen-thawed embryo transfers in both arms

In vitro fertilization	Fresh embryo transfer	Frozen embryo transfer				
		First	Second	Third	Fourth	Fifth
Mini						
Total embryo transfers, n	—	228	80	26	6	—
Transferred embryos per cycle, n[a]	—	1 ± 0	1 ± 0	1 ± 0	1 ± 0	—
Clinical pregnancy, n (%)	—	106 (47)*	38 (48)	14 (54)	3 (50)	—
Implantation rate, n/N (%)	—	106/228 (47)*	38/80 (48)	14/26 (54)	3/6 (50)	—
Live birth, n (%)	—	90 (39)[b]	33 (41)[c]	14 (54)[d]	3 (50)[e]	—
Multiple pregnancy, n (%)	—	9 (9.3)	0	0	0	—
Conventional						
Total embryo transfers, n	120	111	67	25	9	2
Transferred embryos per cycle, n[a]	1.7 ± 0.5	1.7 ± 0.5	1.6 ± 0.5	1.5 ± 0.5	1.5 ± 0.5	1.6 ± 0.5
Double embryo transfer/total embryo transfers, n/N (%)	87/120 (72)	84/111 (75)	37/67 (55)	8/25 (32)	4/9 (44)	1/2
Clinical pregnancy, n (%)	89 (74)	76 (68)**	33 (49)	10 (40)	3 (33)	0
Implantation rate, n/N (%)	117/207 (56)	113/195 (58)**	42/104 (40)	10/33 (30)	5/13 (38)	0
Live birth, n (%)	74 (62)[f]	67 (60)[g]	24 (36)[h]	8 (32)[i]	3 (33)[j]	0
Multiple pregnancy, n (%)	27 (34)	31 (45)	6 (22)	0	2 (66)	0

[a]Data are given as mean ± SD; Chi-square test: b vs f, $P = .0001$, relative risk, 0.73 (95% CI, 0.62–0.86); b vs g, $P = .0003$, relative risk, 0.76 (95% CI, 0.65–0.88); c vs h, $P = .61$, relative risk, 1.11 (95% CI, 0.82–1.49); d vs i, $P = .16$, relative risk, 1.54 (95% CI, 0.89–2.63); e vs j, $P = .62$, relative risk, 1.50 (95% CI, 0.44–5.09); * vs **, $P < .05$.

Zhang et al. Mini-IVF vs conventional IVF. Am J Obstet Gynecol 2016.

(preferably at a blastocyst stage) and transferred at a later naturally or artificially prepared frozen embryo transfer cycle.[19]

Our trial is in line with recent evidence that suggests that the segmentation of IVF treatment could overcome the impaired endometrial receptivity that frequently occurs in fresh embryo transfer strategy.[24] In this respect, it is of note that the live birth rates per embryo transfer were stable in the mini-IVF arm (39% in the first frozen embryo transfer cycle then 41%, 54%, and 50% in subsequent cycles); the live birth rates in the conventional IVF arm dropped from 62% after fresh transfer to 30% in the fourth frozen embryo transfer cycle. Besides a potential effect on endometrial receptivity, this might indicate an increased embryo quality in the mini-IVF arm as compared with the conventional IVF arm. This hypothesis is yet to be determined.

In conclusion, mini-IVF with SET has a lower live birth rate, eliminates OHSS, reduces gonadotropin consumption, and reduces multiple pregnancy rates compared with conventional IVF with double embryo transfer. How these different dimensions are weighed by couples who are deciding between mini-IVF or conventional IVF and whether the lower live birth rate could be offset by a series of "lower cost" mini-IVF cycles should be the subject of future studies. ■

References

1. Macklon NS, Stouffer RL, Giudice LC, Fauser BC. The science behind 25 years of ovarian stimulation for in vitro fertilization. Endocrine reviews 2006;27:170-207.
2. Mocanu E, Redmond ML, Hennelly B, Collins C, Harrison R. Odds of ovarian hyperstimulation syndrome (OHSS) - time for reassessment. Human fertility 2007;10:175-81.
3. Walker MC, Murphy KE, Pan S, Yang Q, Wen SW. Adverse maternal outcomes in multifetal pregnancies. BJOG : an international journal of obstetrics and gynaecology 2004;111:1294-6.
4. Fauser BC, Devroey P, Macklon NS. Multiple birth resulting from ovarian stimulation for subfertility treatment. Lancet 2005;365:1807-16.
5. Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. Bmj 2004;328:261.
6. Alexander GR, Slay Wingate M, Salihu H, Kirby RS. Fetal and neonatal mortality risks of multiple births. Obstetrics and gynecology clinics of North America 2005;32:1-16. vii.
7. Martin JA, Hamilton BE, Ventura SJ, Menacker F, Park MM, Sutton PD. Births: final data for 2001. National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System 2002;51:1-102.
8. Pharoah PO. Risk of cerebral palsy in multiple pregnancies. Clinics in perinatology 2006;33:301-13.
9. Marlow N, Wolke D, Bracewell MA, Samara M, Group EPS. Neurologic and developmental disability at six years of age after extremely preterm birth. The New England journal of medicine 2005;352:9-19.
10. Ericson A, Kallen B. Congenital malformations in infants born after IVF: a population-based study. Human reproduction 2001;16:504-9.
11. van Heesch MM, Evers JL, Dumoulin JC, et al. A comparison of perinatal outcomes in singletons and multiples born after IVF or ICSI, stratified for neonatal risk criteria. Acta obstetricia et gynecologica Scandinavica 2014.

12. Gerris J, De Sutter P, De Neubourg D, et al. A real-life prospective health economic study of elective single embryo transfer versus two-embryo transfer in first IVF/ICSI cycles. Human reproduction 2004;19:917-23.
13. Pandian Z, Marjoribanks J, Ozturk O, Serour G, Bhattacharya S. Number of embryos for transfer following in vitro fertilisation or intracytoplasmic sperm injection. The Cochrane database of systematic reviews 2013;7:CD003416.
14. Coetsier T, Dhont M. Avoiding multiple pregnancies in in-vitro fertilization: who's afraid of single embryo transfer? Human reproduction 1998;13:2663-4.
15. Clinic Summary Report, SART CORS. Society for Assisted Reproductive Technology, 2014. (Accessed Aug 4, 2014, at https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?ClinicPKID=0.)
16. Teramoto S, Kato O. Minimal ovarian stimulation with clomiphene citrate: a large-scale retrospective study. Reproductive biomedicine online 2007;15:134-48.
17. Fauser BC, Van Heusden AM. Manipulation of human ovarian function: physiological concepts and clinical consequences. Endocrine reviews 1997;18:71-106.
18. Humaidan P, Polyzos NP. Human chorionic gonadotropin vs. gonadotropin-releasing hormone agonist trigger in assisted reproductive technology-"The king is dead, long live the king!". Fertility and sterility 2014;102:339-41.
19. Kato K, Takehara Y, Segawa T, et al. Minimal ovarian stimulation combined with elective single embryo transfer policy: age-specific results of a large, single-centre, Japanese cohort. Reproductive biology and endocrinology : RB&E 2012;10:35.
20. Zhang J, Chang L, Sone Y, Silber S. Minimal ovarian stimulation (mini-IVF) for IVF utilizing vitrification and cryopreserved embryo transfer. Reproductive biomedicine online 2010;21:485-95.
21. Kuwayama M. Highly efficient vitrification for cryopreservation of human oocytes and embryos: the Cryotop method. Theriogenology 2007;67:73-80.
22. Dancet EA, D'Hooghe TM, Spiessens C, et al. Quality indicators for all dimensions of infertility care quality: consensus between professionals and patients. Human reproduction 2013;28:1584-97.
23. Zarek SM, Muasher SJ. Mild/minimal stimulation for in vitro fertilization: an old idea that needs to be revisited. Fertility and sterility 2011;95:2449-55.
24. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders. Fertility and sterility 2011;96:344-8.

Author and article information

From the Department of Reproductive Endocrinology and Infertility, New Hope Fertility Center, New York, NY (Drs Zhang, Yang, Bodri, and Chavez-Badiola); the Department of Obstetrics and Gynecology, Division of Reproductive Biology, New York University School of Medicine, New York, NY (Dr Merhi); the Center for Reproductive Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands (Drs Repping and van Wely).

Received June 10, 2015; revised July 21, 2015; accepted Aug. 4, 2015.

Supported by an internal grant from New Hope Fertility Center.

The authors report no conflict of interest.

Corresponding author: John J. Zhang, MD, PhD. johnzhang98@yahoo.com