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ORIGINAL ARTICLE *Infertility*

In-vitro maturation of oocytes versus conventional IVF in women with infertility and a high antral follicle count: a randomized non-inferiority controlled trial

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STUDY QUESTION: Is one cycle of IVM non-inferior to one cycle of conventional in IVF with respect to live birth rates in women with high antral follicle counts (AFCs)?

SUMMARY ANSWER: We could not demonstrate non-inferiority of IVM compared with IVF.

WHAT IS KNOWN ALREADY: IVF with ovarian hyperstimulation has limitations in some subgroups of women at high risk of ovarian stimulation, such as those with polycystic ovary syndrome. IVM is an alternative ART for these women. IVM may be a feasible alternative to IVF in women with a high AFC, but there is a lack of data from randomized clinical trials comparing IVM with IVF in women at high risk of ovarian hyperstimulation syndrome.

STUDY DESIGN, SIZE, DURATION: This single-center, randomized, controlled non-inferiority trial was conducted at an academic infertility center in Vietnam from January 2018 to April 2019.

PARTICIPANTS/MATERIALS, SETTING, METHODS: In total, 546 women with an indication for ART and a high AFC (≥24 follicles in both ovaries) were randomized to the IVM (n = 273) group or the IVF (n = 273) group; each underwent one cycle of IVM with a prematuration step versus one cycle of IVF using a standard gonadotropin-releasing hormone antagonist protocol with gonadotropin-releasing hormone agonist triggering. The primary endpoint was live birth rate after the first embryo transfer. The non-inferiority margin for IVM versus IVF was −10%.

MAIN RESULTS AND THE ROLE OF CHANCE: Live birth after the first embryo transfer occurred in 96 women (35.2%) in the IVM group and 118 women (43.2%) in the IVF group (absolute risk difference –8.1%; 95% confidence interval (CI) −16.6%, 0.5%). Cumulative ongoing pregnancy rates at 12 months after randomization were 44.0% in the IVM group and 62.6% in the IVF group (absolute risk difference −18.7%; 95% CI –27.3%, −10.1%). Ovarian hyperstimulation syndrome did not occur in the IVM group, versus two cases in the IVF group. There were no statistically significant differences between the IVM and IVF groups with respect to the occurrence of pregnancy complications, obstetric and perinatal complications, preterm delivery, birth weight and neonatal complications.

LIMITATIONS, REASONS FOR CAUTION: The main limitation of the study was its open-label design. In addition, the findings are only applicable to IVM conducted using the prematuration step protocol used in this study. Finally, the single ethnicity population limits the external generalizability of the findings.

WIDER IMPLICATIONS OF THE FINDINGS: Our randomized clinical trial compares live birth rates after IVM and IVF. Although IVM is a viable and safe alternative to IVF that may be suitable for some women seeking a mild ART approach, the current study findings approach inferiority for IVM compared with IVF when cumulative outcomes are considered. Future research should incorporate multiple cycles of IVM in the study design to estimate cumulative fertility outcomes and better inform clinical decision-making.

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Introduction

Conventional IVF with ovarian hyperstimulation is an appropriate option used for many couples with fertility issues. However, ovarian hyperstimulation has limitations in some subgroups of women at high risk of ovarian hyperstimulation syndrome (OHSS), such as those with polycystic ovary syndrome. This includes the possibility of high cycle cancelation rates and potentially serious adverse events due to the occurrence of OHSS (Qiao and Feng, 2011).

IVM is an alternative assisted reproductive technology for these women. The original understanding of IVM involves retrieval of small follicles of 2–10 mm in diameter without prior hCG administration that is then matured *in vitro* (Edwards, 1965; Edwards *et al.*, 1969). This process has several advantages over IVF, including the absence of (or minimal) controlled ovarian stimulation, improved convenience and a lower monitoring burden (Vuong *et al.*, 2019). IVM is a successful and widely practiced assisted reproductive technology for advanced domestic animal breeding (Lonergan and Fair, 2016). IVM involves retrieval of immature germinal vesicle stage oocytes and culture of intact cumulus-oocyte complexes (COCs) *in vitro* until the metaphase II stage (De Vos *et al.*, 2016); thereafter conventional IVF or intracytoplasmic sperm injection are performed (Cha and Chian, 1998). IVM was first used to achieve successful pregnancy and delivery of a live infant in 1991 (Cha *et al.*, 1991). Since then, several variants of IVM have been used successfully as an alternative to IVF in different patient groups, with variable success rates, but it has not gained widespread acceptance (Child *et al.*, 2001; Soderstrom-Anttila *et al.*, 2005; Grynberg *et al.*, 2013; Walls *et al.*, 2015).

In women with a high antral follicle count (AFC), we showed that IVM is a feasible alternative to conventional IVF (Ho *et al.*, 2019). Nevertheless, systematic reviews have highlighted a lack of high-quality evidence in the field (Siristatidis *et al.*, 2013, 2015), and the international evidence-based guideline for polycystic ovary syndrome has strongly recommended further research on this question (Teede *et al.*, 2018). There are no data from randomized controlled trials to inform the clinical management of women with high AFC undergoing IVM. Due to this evidence gap, we performed a randomized controlled trial to determine whether one cycle of IVM is non-inferior to one cycle of conventional IVF in terms of live birth in women with a high AFC.

Materials and methods

Study design

This single-center, randomized, controlled, non-inferiority trial was conducted at IVFMD, My Duc Hospital in Ho Chi Minh City, Vietnam (NCT03405701). The study was approved by the hospital ethics committee and conducted according to Good Clinical Practice and Declaration of Helsinki 2002 principles, including oversight by an independent data and safety monitoring committee. All participants provided written informed consent. The study protocol is available online in a protocol paper (Vuong *et al.*, 2018).

Study population

Women with an indication for assisted reproductive technology and a high AFC (24 or more follicles in both ovaries, as defined previously (Broekmans *et al.*, 2010)) who had undergone $\leq$2 previous IVM or IVF attempts were eligible. Couples had to agree to have all Day 3

embryos frozen and not more than two embryos replaced per transfer. Oocyte donation and preimplantation genetic diagnosis cycles were excluded. AFC was measured using a transvaginal transducer (frequency bandwidth 8 MHz; Toshiba, Japan). The total number of follicles per ovary measuring 2–9 mm was counted, and the absence of corpora lutea, cysts or dominant follicles was confirmed.

Randomization

After providing written informed consent, women were randomized (1:1) to one cycle of IVM or one cycle of IVF on Day 2 of the menstrual cycle using block randomization by an independent study coordinator via telephone, using a computer-generated random list (block size 2, 4 or 8). Block randomization was used to ensure that the size of the study groups remained similar at all times during the study. Blinding was not used in the trial.

Treatments

Preparation for oocyte retrieval in the IVM group was based on whether cycle length was normal or irregular, as described previously (Vuong *et al.*, 2018). Oocyte pick-up took place 42 h after the last injection of highly purified human menopausal gonadotropins (Menopur®, Ferring), which were given for 2 days to improve follicular growth and oocyte health and reduce the variability in response between patients. The oocyte pick-up procedure was performed using a double-needle system, with a 17G external needle and a 19G internal needle (Kitazato, Japan). The pressure used for collection was 100–120 mm Hg. After aspiration, follicular fluid was transferred to the lab where immature oocytes were identified under a stereomicroscope using the sliding technique; subsequently, all fluid was poured into a strainer for a final check for any missed oocytes.

All COCs were placed in a meiotic arresting prematuration medium (Medicult IVM medium (Origio, Denmark); supplemented with recombinant follicle-stimulating hormone (rFSH) 1 mIU/ml (Puregon MSD, Australia), insulin 5 ng/ml (Sigma, Schnelldorf, Germany), estradiol 10 nmol/l (Sigma, Schnelldorf, Germany), human serum albumin 10 mg/ml (SAGE, Denmark) and C-type natriuretic peptide 25 nM (Tocris Bioscience, Abingdon, UK) for 24 h at 37°C, 6% carbon dioxide in air under oil. After 24 h, COCs were washed and transferred into IVM medium (Origio, Denmark; containing insulin 5 ng/ml, estradiol 10 nmol/l, human recombinant amphiregulin 100 ng/ml and rFSH 100 mIU/ml) and incubated under oil for a further 30 h at 37°C in 6% carbon dioxide in air. This procedure is collectively termed capacitation IVM, as described previously (Sanchez *et al.*, 2019; Vuong *et al.*, 2020).

Women in the IVF group underwent ovarian hyperstimulation using a highly purified human menopausal gonadotropin/gonadotropin-releasing hormone antagonist protocol. Follicular development was monitored using serum estradiol and progesterone concentrations, plus ultrasound scanning. Gonadotropin-releasing hormone agonist trigger (triptorelin; Diphereline, Ipsen Beaufour) was given when at least two leading follicles reached 17 mm in diameter, with oocyte retrieval 36 h later.

In both groups, fertilization of mature oocytes at 3–4 h after oocyte retrieval (IVF group) or maturation check (IVM group) was performed using intracytoplasmic sperm injection. Embryo evaluation was performed at 68 ± 1 h after fertilization based on the Istanbul consensus (ALPHA Scientists in Reproductive Medicine and ESHRE Special Interest Group Embryology, 2011). Day 3 embryos were vitrified for transfer in a subsequent cycle (maximum two embryos per transfer). The same endometrial preparation procedure was used in both groups (oral estradiol valerate (Valiera, Laboratorios Recalcine) 2 mg four times daily from Day 2 of the menstrual cycle; after treatment with estradiol valerate for ≥10 days and when endometrial thickness was ≥8 mm, progesterone (Cyclogest, Actavis) 200 mg was administered intravaginally four times daily); see the study protocol paper for full details (Vuong *et al.*, 2018). Embryo transfer was scheduled 3 days after starting progesterone.

Outcomes

The primary outcome was live birth after the first embryo transfer of the started cycle. Live birth was defined as the birth of at least one newborn after 24 weeks' gestation that exhibited any sign of life (twins were a single count). Predefined secondary outcomes included cumulative ongoing pregnancy rate (pregnancy with detectable heart rate at ≥12 weeks' gestation at 6 and 12 months after randomization), maternal safety (OHSS), pregnancy complications (ectopic pregnancy, miscarriage, multiple pregnancy, multiple delivery), obstetric and perinatal complications (gestational diabetes, hypertensive disorders of pregnancy, antepartum hemorrhage, preterm delivery, spontaneous preterm birth, iatrogenic preterm birth, low/very low birth weight, high/very high birth weight, large/small for gestational age) and neonatal complications (congenital anomaly, admission to the neonatal intensive care unit) (Vuong *et al.*, 2018).

Statistical analyses

The trial had a non-inferiority design. Details and assumptions for the sample size calculation have been detailed elsewhere (Vuong *et al.*, 2018). Briefly, it was calculated that 546 participants (273 per group) would be needed to demonstrate the non-inferiority of IVM compared with IVF with a non-inferiority margin of −10%. An interim analysis was performed by an independent statistician after enrollment of the first 273 participants using a two-sided significance test with the Haybittle–Peto spending function and a type I error rate of 5% with stopping criteria of $P < 0.001$ (Z alpha = 3.29). Researchers were not informed of the results of the interim analysis.

Both intention-to-treat and per-protocol analyses were performed according to the statistical analysis plan. The live birth rate between groups was compared by calculating a risk difference and the associated 95% confidence interval (CI). Time to ongoing pregnancy was assessed in a Cox proportional hazard analysis and hazard ratios were estimated. In addition, a Kaplan–Meier curve was presented with a log-rank test. Between-group differences in secondary endpoints were analyzed using parametric methods (normally distributed data), non-parametric methods (skewed data) or Fisher's exact test (categorical variables) and were reported as relative risk and 95% CI. There was no adjustment of 95% CI values for multiplicity. Full details of statistical methodology have been reported previously (Vuong *et al.*, 2018).

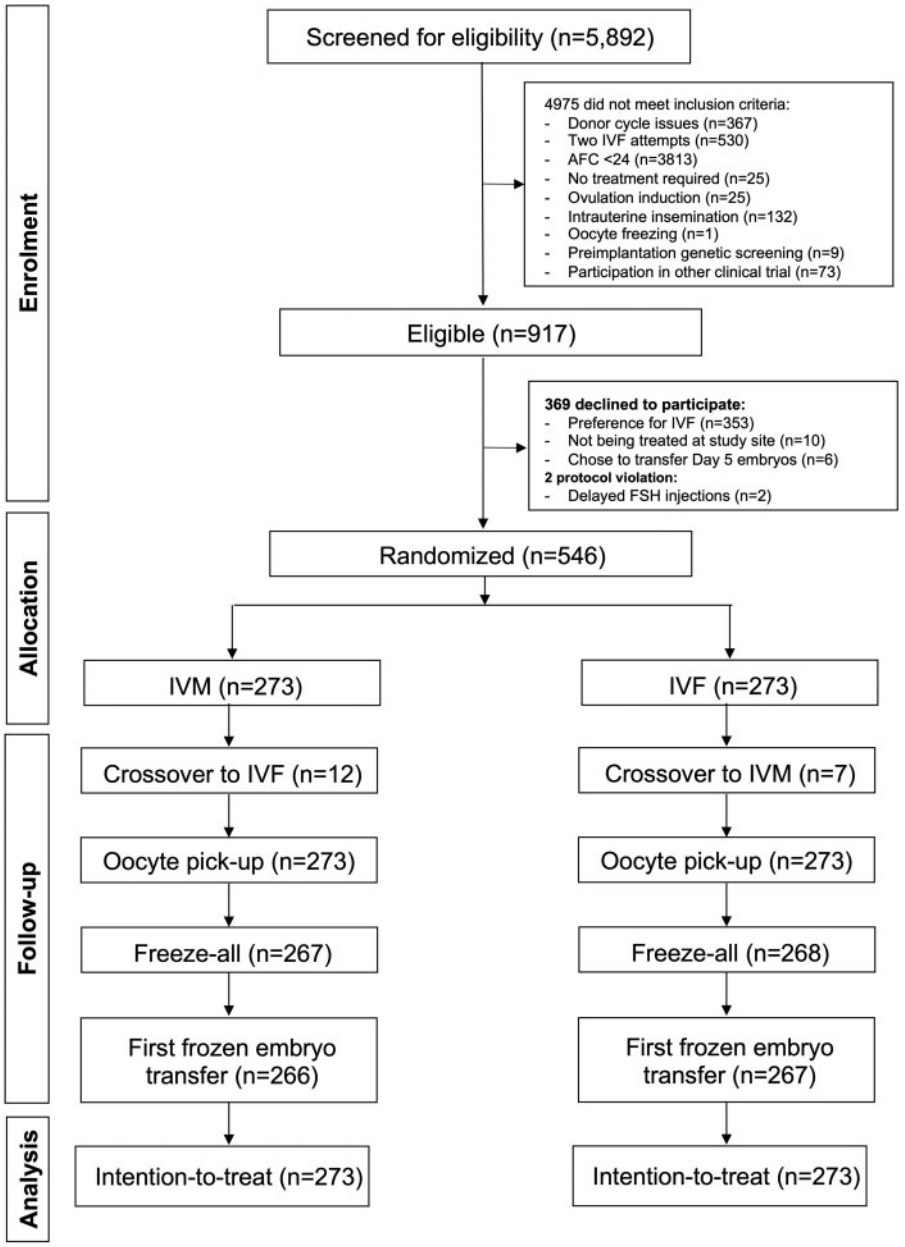

Figure 1. Patient enrollment. AFC, antral follicle count.

Results

Study population

From January 2018 to April 2019, a total of 5892 women scheduled for IVF were screened, of whom 917 were potential hyper-responders and therefore met the eligibility criteria, and 546 provided informed consent (59.5% of eligible patients). Participants were randomly assigned to the IVM (n = 273) or IVF (n = 273) group (Fig. 1). Baseline characteristics in the two study groups were comparable (Table I). Women in the IVM group had a shorter duration of stimulation (2.3 ± 1.3 vs. 8.8 ± 1.7 days), a lower total dose of highly purified human menopausal gonadotropins (373.4 ± 355.1 vs. 2060.7 ± 655.6 IU), and achieved lower levels of estradiol (350.9 ± 1473.8 vs. 10 706.9 ± 9473.1 pg/ml) and progesterone (0.3 ± 0.7 vs. 1.0 ± 1.2 ng/ml), as assessed on the last day of follicle-stimulating hormone injection, compared with the IVF group.

Laboratory outcomes

Numbers of oocytes retrieved, metaphase II oocytes, fertilized oocytes and freezable embryos, and the maturation rate were all significantly lower in the IVM group compared with the IVF group (Table II). The number of top-quality embryos was significantly lower in the IVM

Table I Demographic and clinical characteristics at baseline.

Characteristic	IVM (n = 273)	IVF (n = 273)
Age (years)	29.9 ± 3.4	29.6 ± 3.6
BMI, kg/m^2	22.2 ± 3.0	22.1 ± 3.5
Polycystic ovary syndrome, n (%)	196 (71.8)	192 (70.3)
Anti-Müllerian hormone, ng/ml	8.5 ± 4.0	8.1 ± 3.4
Total antral follicle count, n	45.3 ± 20.0	43.9 ± 19.2
Dehydroepiandrosterone sulfate, µg/ml	2.15 ± 0.85	2.04 ± 0.77
Free testosterone index	3.15 ± 3.01	3.26 ± 3.20
Estradiol level on Day 3, pg/ml	45.21 ± 47.72	49.18 ± 45.90
Duration of infertility, years	3 [2–5]	3 [2–6]
Number of previous IVF attempts, n (%)		
None	243 (89.0)	247 (90.5)
One	30 (11.0)	26 (9.5)
Indication for IVF, n (%)		
Male factor	25 (9.2)	28 (10.3)
Tubal factor	18 (6.6)	20 (7.3)
Ovulation induction failure	230 (84.2)	225 (82.4)

Values are mean ± standard deviation, median [interquartile range] or number of participants (%).

versus IVF group (3.2 ± 2.7 vs. 7.9 ± 5.1; difference –4.7, 95% CI –5.4, –4) (Table II). Results were similar in the per-protocol analysis (Table II).

Fertility outcomes

The live birth rate after the first embryo transfer was 35.2% (96/273) in the IVM group and 43.2% (118/273) in the IVF group (absolute risk difference –8.1%; 95% CI –16.6%, 0.5%), meaning that there were 8.1 fewer live births per 100 women treated with IVM versus IVF (Table III). The lower 95% CI value for the difference in live birth rate between the IVM and IVF groups (primary endpoint; –16.6%) failed to exceed the predefined non-inferiority margin of –10%. The live birth rate per single transfer did not differ significantly between the IVM and IVF groups (CI values included zero). Per-protocol analysis of the primary outcome showed similar findings (Table IV). There was no statistically significant difference in live birth rate between the IVM and IVF groups in patient subgroups with (35.7% vs. 41.1%; $P = 0.27$) and without (33.8% vs. 48.1%; $P = 0.07$) polycystic ovary syndrome.

Rates of positive pregnancy test, implantation, clinical pregnancy and ongoing pregnancy were not significantly different between the IVM and IVF groups in the intention-to-treat (Table III) and per-protocol (Table IV) analyses. Cumulative ongoing pregnancy rates at 6 months (35.2% vs. 48.7%; –13.5%, 95% CI –22.1, –5.0; $P = 0.001$) and 1 year (44.0% vs. 62.6%; –18.7, 95% CI –27.3, –10.1; $P < 0.001$) were both significantly lower in the IVM versus IVF group (Fig. 2). This is attributable to the lower number of embryo transfer cycles performed in the

Table II Laboratory outcomes.

Outcome	IVM	IVF	Between-group difference (95% CI)
Intention-to-treat analysis	**(n = 273)**	**(n = 273)**	
Oocytes retrieved	14.1 ± 8.0	19.7 ± 8.6	–5.5 (–6.9, –4.1)*
MII oocytes	8.9 ± 5.4	15.6 ± 7.4	–6.7 (–7.8, –5.6)*
Maturation rate (MII), %	64.3 ± 17.4	79.3 ± 16.2	–15.1 (–17.9, –12.2)*
Fertilized oocytes (2PN)	7.3 ± 4.6	13.6 ± 6.6	–6.3 (–7.3, –5.4)*
Cleavage embryos	4.8 ± 3.4	10.8 ± 5.7	–6 (–6.8, –5.2)*
Number of top-quality embryos	3.2 ± 2.7	7.9 ± 5.1	–4.7 (–5.4, –4)*
Number of freezable embryos	4.0 ± 2.6	7.9 ± 5.1	–3.9 (–4.5, –3.1)*
Patients with no oocyte retrieved, n (%)	1 (0.4)	3 (1.1)	–0.7 (–2.5, 1.1)
Patients with no mature oocytes, n (%)	1 (0.4)	3 (1.1)	–0.7 (–2.5, 1.1)
Patients with no embryo, n (%)	5 (1.8)	2 (0.7)	1.1 (–1.2, 3.4)
Per-protocol analysis	**(n = 268)**	**(n = 278)**	
Oocytes retrieved	14.2 ± 8.2	19.6 ± 8.4	–5.5 (–6.9, –4.1)
MII oocytes	8.8 ± 5.4	15.7 ± 7.3	–6.9 (–8.0, –5.9)
Maturation rate (MII), %	63.3 ± 17.3	80.0 ± 15.6	–16.7 (–19.4, –13.9)
Fertilized oocytes (2PN)	7.1 ± 4.5	13.7 ± 6.5	–6.6 (–7.5, –5.7)
Cleavage embryos	4.6 ± 3.1	11.0 ± 5.6	–6.4 (–7.1, –5.6)
Number of top-quality embryos	3.0 ± 2.5	7.9 ± 5.1	–4.9 (–5.6, –4.2)
Number of freezable embryos	4.0 ± 2.4	7.9 ± 5.1	–4 (–4.6, –3.3)
Patients with no oocyte retrieved, n (%)	1 (0.4)	3 (1.1)	–0.7 (–2.4, 1.1)
Patients with no embryo, n (%)	7 (2.6)	0 (0.0)	2.6 (0.3, 4.9)

Values are mean ± standard deviation or number of participants (%).
*Statistically significant between-group difference.
2PN, 2 pronuclear; MII, metaphase II.

Table III Fertility outcomes and complications after the first embryo transfer (intention-to-treat analysis).

	IVM (n = 273)	IVF (n = 273)	Between-group difference, % (95% CI)	Rate ratio for IVM vs. IVF (95% CI)
Live birth, n (%)	96 (35.2)	118 (43.2)	–8.1 (–16.6, 0.5)	0.81 (0.66, 1)
Number of embryos transferred	1.9 ± 0.3	2.0 ± 0.2	–	–
1 embryo transferred, n (%)	23 (8.6)	6 (2.2)	–	–
2 embryos transferred, n (%)	243 (91.4)	261 (97.8)	–	–
Total embryos transferred	509	528	–	–
Fertility outcomes, n (%)				
Positive pregnancy test	151 (55.3)	168 (61.5)	–6.2 (–14.8, 2.4)	0.9 (0.78, 1.04)
Clinical pregnancy	138 (50.5)	154 (56.4)	–5.9 (–14.6, 2.9)	0.9 (0.77, 1.05)
Implantation	177/509 (34.8)	206/528 (39.0)	–4.2 (–10.3, 1.8)	–
Ongoing pregnancy	104 (38.1)	126 (46.2)	–8.1 (–16.7, 0.6)	0.83 (0.68, 1.01)
Cumulative ongoing pregnancy at 6 months	96 (35.2)	133 (48.7)	–13.5 (–22.1, –5.0)	0.72 (0.59, 0.88)
Median time to ongoing pregnancy after 6 months follow-up, days	137 [123, 149]	125 [119, 146]	–*	–
Cumulative ongoing pregnancy at 12 month	120 (44.0)	171 (62.6)	–18.7 (–27.3, –10.1)	0.7 (0.6, 0.83)
Median time to ongoing pregnancy after 12 months follow-up, days	144 [126, 167]	127 [119, 172]	–**	–
Maternal safety, n (%)				
Moderate/severe OHSS	0 (0.0)	2 (0.7)	–	–
Pregnancy complications, n (%)				
Ectopic pregnancy	5 (1.8)	2 (0.7)	1.1 (–1.2, 3.4)	2.5 (0.49, 12.78)
Miscarriage <12 weeks	30 (11.0)	27 (9.9)	1.1 (–4.4, 6.6)	1.11 (0.68, 1.82)
Multiple pregnancy	39 (14.3)	52 (19.0)	–4.8 (–11.4, 1.8)	0.75 (0.51, 1.1)
Multiple delivery	26 (9.5)	37 (13.6)	–4.0 (–9.7, 1.7)	0.7 (0.44, 1.13)
Obstetric and perinatal complications, n (%)				
Gestational diabetes mellitus	25 (9.2)	29 (10.6)	–1.5 (–6.8, 3.9)	0.86 (0.52, 1.43)
Hypertensive disorders of pregnancy	6 (2.2)	13 (4.8)	–2.6 (–6, 0.9)	0.46 (0.18, 1.2)
Antepartum hemorrhage	0 (0)	0 (0)	–	–
Preterm delivery				
Delivery at <24 weeks' gestation	8 (2.9)	8 (2.9)	0 (–2.8, 2.8)	1 (0.38, 2.63)
Delivery at <28 weeks' gestation	9 (3.3)	10 (3.7)	–0.4 (–3.8, 3.1)	0.9 (0.37, 2.18)
Delivery at <32 weeks' gestation	11 (4.0)	10 (3.7)	0.4 (–3.2, 4)	1.1 (0.47, 2.55)
Delivery at <37 weeks' gestation	33 (12.1)	36 (13.2)	–1.1 (–7, 4.8)	0.92 (0.59, 1.43)
Spontaneous preterm birth				
Delivery at <24 weeks' gestation	8 (2.9)	8 (2.9)	0 (–2.8, 2.8)	1 (0.38, 2.63)
Delivery at <28 weeks' gestation	9 (3.3)	10 (3.7)	–0.4 (–3.8, 3.1)	0.9 (0.37, 2.18)
Delivery at <32 weeks' gestation	11 (4.0)	10 (3.7)	0.4 (–3.2, 4)	1.1 (0.47, 2.55)
Delivery at <37 weeks' gestation	20 (7.3)	24 (8.8)	–1.5 (–6.4, 3.5)	0.83 (0.47, 1.47)
Iatrogenic preterm birth				
Delivery at <24 weeks' gestation	0 (0)	0 (0)	–	–
Delivery at <28 weeks' gestation	0 (0)	0 (0)	–	–
Delivery at <32 weeks' gestation	0 (0)	0 (0)	–	–
Delivery at <37 weeks' gestation	13 (4.8)	12 (4.4)	0.4 (–3.5, 4.2)	1.08 (0.5, 2.33)
Birth weight, grams				
Singleton	3240.0 ± 413.0	3167.7 ± 502.6	72.3 (74.9, –219.6)	–
Twins	2446.0 ± 583.2	2360.5 ± 476.7	85.5 (109.2, –280.0)	–
Low birth weight, n (%)	1 (0.4)	5 (1.8)	–1.5 (–3.6, 0.6)	0.2 (0.02, 1.7)
Very low birth weight, n (%)	0 (0.0)	1 (0.4)	–	–
High birth weight, n (%)	2 (0.7)	2 (0.7)	0 (–1.4, 1.4)	1 (0.14, 7.05)

(continued)

Table III Continued

	IVM (n = 273)	IVF (n = 273)	Between-group difference, % (95% CI)	Rate ratio for IVM vs. IVF (95% CI)
Very high birth weight, n (%)	0 (0)	0 (0)	–	–
Large for gestational age, n (%)	28 (10.3)	22 (8.1)	2.2 (–3, 7.4)	1.27 (0.75, 2.17)
Small for gestational age, n (%)	3 (1.1)	3 (1.1)	0 (–1.7, 1.7)	1 (0.2, 4.91)
Neonatal complications, n (%)				
Congenital anomaly	0 (0)	0 (0)	–	–
Admission to NICU	5 (1.8)	7 (2.6)	–0.7 (–3.6, 2.1)	0.71 (0.23, 2.22)

Values are mean ± standard deviation, median [interquartile range], or number of participants (%).
*Hazard ratio 0.61, 95% CI 0.48, 0.81; log-rank $P < 0.001$.
**Hazard ratio 0.58, 95% CI 0.46, 0.73; log-rank $P < 0.001$.
NICU, neonatal intensive care unit.

IVM group compared to the IVF group, due to there being significantly fewer frozen embryos available for subsequent transfer in the IVM group (at 6 months the proportion of patients having had two embryo transfer cycles was 6% in the IVM group versus 14% in the IVF group ($P = 0.003$); at 12 months the proportion of patients having had two or three embryo transfer cycles was 18% or 3% with IVM vs. 29% or 7% with IVF ($P = 0.002$ or $P = 0.06$, respectively)).

Complications

OHSS was not observed in the IVM group but occurred in two women (0.7%) with early moderate/severe grade in the IVF group ($P = 0.48$ for between-group difference) (Table III). There were no statistically significant differences between the two groups with respect to the occurrence of pregnancy complications, obstetric and perinatal complications, preterm delivery, birth weight and neonatal complications (Table III).

Discussion

In women with high AFC, we could not demonstrate non-inferiority or inferiority of one cycle of IVM versus one cycle of IVF in terms of live birth after the first embryo transfer, because the lower bound of the 95% CI exceeded the predefined non-inferiority margin (–10%) and the upper bound of the 95% CI crossed zero in both the intention-to-treat and per-protocol analyses. However, cumulative ongoing pregnancy rates at 6 and 12 months were lower in the IVM group compared with the IVF group. Evidence regarding differences in fertility outcomes between IVM and IVF was also limited, but point estimates for all fertility outcomes favored IVF. Safety outcomes, including OHSS, and obstetric, perinatal and neonatal complications did not differ between groups. There were no cases of OHSS with IVM.

This is the first randomized clinical trial comparing live birth rates after IVM with IVF. As such, these data fill a previous knowledge gap in the field. The main limitation of the study was its open-label design. However, blinding in infertility trials is very difficult and the study had an objective primary outcome (i.e. live birth). We used the primary endpoint of live birth after first embryo transfer, but using cumulative live birth rate might provide a more holistic comparison of IVM and IVF, and would be more clinically relevant. In addition, some features of the study limit the generalizability of the findings. The laboratory IVM protocol used in this study is relatively new, and there are a wide variety of IVM protocols that have been used to date (De Vos *et al.*, 2016; Vuong *et al.*, 2019). Therefore, the IVM outcomes reported in the current study are only applicable when the same *in-vitro* capacitation and clinical IVM protocols are used. It is possible that the new culture system used in our study might have contributed to the rates of live birth seen in the IVM group and this may not be the case with different approaches to IVM. In addition, the single ethnicity study population limits the external generalizability of our findings. Furthermore, the findings are only generalizable to women with similar characteristics to those enrolled in the trial (i.e. women with a potential hyperresponse to ovarian stimulation). Another factor is that the laboratory IVM protocol studied needs to be used with the specific clinical protocol used in the current study. Future research into different IVM protocols and technology might further improve the applicability and accessibility of this approach to assisted reproductive technologies for women with high AFC. Finally, our center has extensive experience with IVM, having performed more than 4000 IVM cycles since 2006 (~300 cycles per year). This experience might have been another contributing factor to the performance achieved with IVM in the current study.

At the time this study was designed, there were no published data on which to base the sample size calculation. However, the live birth rate in the IVM group was overestimated in our assumptions. This would impact on the power of the study to confirm or refute non-inferiority. Data from a recent pilot study at our center in women with polycystic ovary syndrome reported a live birth rate of 47.5% (19/40) in the capacitation IVM group (compared with 32.5% (13/40) in the standard IVM group) (Vuong *et al.*, 2020). The higher live birth rate in the capacitation IVM group in that study compared with the current trial may be due, at least in part, to the smaller sample size in that pilot trial (40 women per treatment group vs. 273 per group in the current study), or due to differences in patient characteristics and prognostic factors between study populations.

This study employed a freeze-all strategy in both the IVM and IVF groups. Day 3 embryos were frozen as per our routine protocol. Use of Day 3 versus Day 5 embryos remains a controversial topic and, based on current evidence (Coskun *et al.*, 2000; Blake *et al.*, 2004; Papanikolaou *et al.*, 2005, 2006; Zech *et al.*, 2007), the timing of

Table IV Fertility outcomes and complications after the first embryo transfer (per-protocol analysis).

Variables	IVM (N = 268)	IVF (N = 278)	Between-group difference, % (95% CI)	Rate ratio for IVM vs. IVF (95% CI)
Live birth, n (%)	95 (35.4)	119 (42.8)	–7.4 (–15.9, 1.2)	0.83 (0.67, 1.02)
Number of embryos transferred	1.9 ± 0.3	2.0 ± 0.2	–	–
1 embryo transferred, n (%)	23 (8.6)	6 (2.2)	–	–
2 embryos transferred, n (%)	236 (88.1)	268 (96.4)	–	–
Total embryos transferred	495	542	–	–
Fertility outcomes, n (%)				
Positive pregnancy test	148 (55.2)	171 (61.5)	–6.3 (–14.9, 2.3)	0.9 (0.78, 1.04)
Clinical pregnancy	136 (50.7)	156 (56.1)	–5.4 (–14.1, 3.4)	0.9 (0.77, 1.06)
Implantation	34.8 ± 37.2	38.7 ± 38.3	–3.9 (–10.4, 2.5)	–
Ongoing pregnancy	104 (38.8)	126 (45.3)	–6.5 (–15.1, 2.1)	0.86 (0.7, 1.04)
Maternal safety, n (%)				
Moderate/severe OHSS	0 (0.0)	2 (0.7)	–	–
Pregnancy complications, n (%)				
Ectopic pregnancy	4 (1.5)	3 (1.1)	0.4 (–1.8, 2.7)	1.38 (0.31, 6.12)
Miscarriage <12 weeks	29 (10.8)	28 (10.1)	0.7 (–4.8, 6.2)	1.07 (0.66, 1.76)
Multiple pregnancy	38 (14.2)	53 (19.1)	–4.9 (–11.5, 1.7)	0.74 (0.51, 1.09)
Multiple delivery	25 (9.4)	38 (13.7)	–4.3 (–10, 1.4)	0.68 (0.43, 1.1)
Obstetric and perinatal complications, n (%)				
Gestational diabetes mellitus	25 (9.3)	29 (10.4)	0.4 (–1.8, 2.7)	1.38 (0.31, 6.12)
Hypertensive disorders of pregnancy	6 (2.2)	13 (4.7)	0.7 (–4.8, 6.2)	1.07 (0.66, 1.76)
Antepartum hemorrhage	0 (0)	0 (0)	–	–
Preterm delivery				
Delivery at <24 weeks' gestation	9 (3.4)	7 (2.5)	0.8 (–2.4, 4)	1.33 (0.5, 3.53)
Delivery at <28 weeks' gestation	10 (3.7)	9 (3.2)	0.5 (–3, 3.9)	1.15 (0.48, 2.79)
Delivery at <32 weeks' gestation	12 (4.5)	9 (3.2)	1.2 (–2.4, 4.8)	1.38 (0.59, 3.23)
Delivery at <37 weeks' gestation	34 (12.7)	35 (12.6)	0.1 (–5.6, 5.8)	1.01 (0.65, 1.57)
Spontaneous preterm birth				
Delivery at <24 weeks' gestation	9 (3.4)	7 (2.5)	0.8 (–2.4, 4)	1.33 (0.5, 3.53)
Delivery at <28 weeks' gestation	10 (3.7)	9 (3.2)	0.5 (–3, 3.9)	1.15 (0.48, 2.79)
Delivery at <32 weeks' gestation	12 (4.5)	9 (3.2)	1.2 (–2.4, 4.8)	1.38 (0.59, 3.23)
Delivery at <37 weeks' gestation	21 (7.8)	23 (8.3)	–0.4 (–5.4, 4.5)	0.95 (0.54, 1.67)
Iatrogenic preterm birth				
Delivery at <24 weeks' gestation	0 (0)	0 (0)	–	–
Delivery at <28 weeks' gestation	0 (0)	0 (0)	–	–
Delivery at <32 weeks' gestation	0 (0)	0 (0)	–	–
Delivery at <37 weeks' gestation	13 (4.9)	12 (4.3)	0.5 (–3.3, 4.4)	1.12 (0.52, 2.42)
Birth weight, grams				
Singleton	3240.0 ± 413.0	3167.7 ± 502.6	72.3 (–74.9, 219.6)	–
Twins	2446.0 ± 583.2	2360.5 ± 476.7	85.5 (–109.2, 280.0)	–
Low birth weight, n (%)	2 (0.7)	4 (1.4)	–0.7 (–2.8, 1.4)	0.52 (0.1, 2.81)
Very low birth weight, n (%)	0 (0.0)	1 (0.4)	–	–
High birth weight, n (%)	2 (0.7)	2 (0.7)	0 (–1.4, 1.5)	1.04 (0.15, 7.31)
Very high birth weight, n (%)	0 (0)	0 (0)	–	–
Large for gestational age, n (%)	27 (10.1)	23 (8.3)	1.8 (–3.4, 7)	1.22 (0.72, 2.07)
Small for gestational age, n (%)	2 (0.7)	4 (1.4)	–0.7 (–2.8, 1.4)	0.52 (0.1, 2.81)
Neonatal complications, n (%)				
Congenital anomaly	0 (0)	0 (0)	–	–
Admission to NICU	2 (0.7)	4 (1.4)	–0.7 (–3.5, 2.2)	0.74 (0.24, 2.31)

Values are mean ± standard deviation or number of patients (%).
NICU, neonatal intensive care unit.

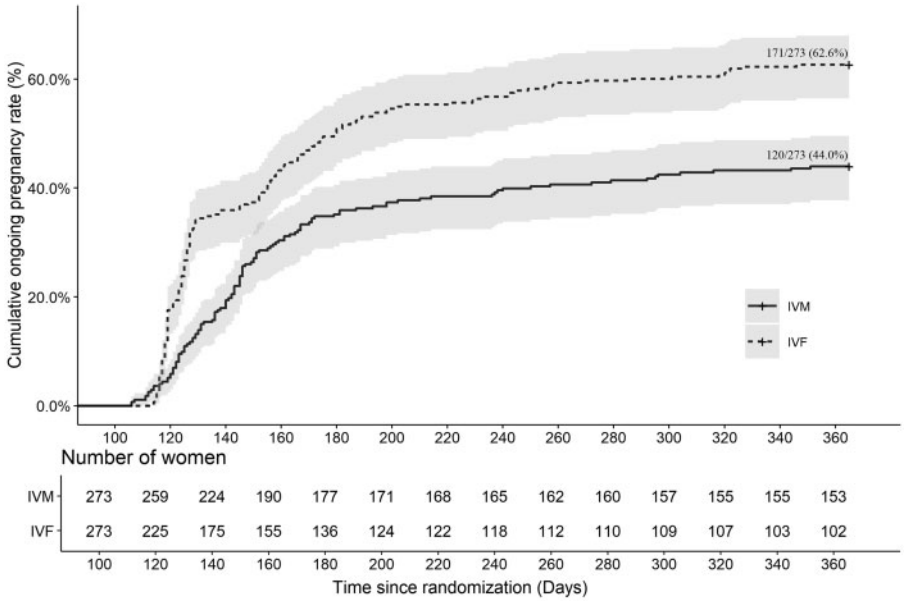

Figure 2. Kaplan–Meier curve of cumulative ongoing pregnancy rate at 12 months after randomization in the first started cycle.

embryo transfer is unlikely to have materially influenced our findings. Data from a retrospective cohort study by Cohen *et al.* (2018) showed that fertilization, clinical pregnancy and live birth rates in women with polycystic ovary syndrome were significantly lower in vitrified versus fresh oocytes from IVM cycles. However, live birth rates in both the vitrified (8.9%) and fresh embryo (25.9%) groups in that study were substantially lower than the live birth rate achieved in the IVM group in the current trial (35.2%), perhaps due to the different IVM protocols used in the two studies. This reflects ongoing research efforts to develop and identify the best protocol for IVM. In a retrospective case-control study, rates of biochemical pregnancy, clinical pregnancy and live birth did not differ between women with polycystic ovarian morphology who underwent IVF versus IVM after transfer of frozen embryos, but were significantly lower with IVM compared with IVF after fresh embryo transfer (Walls *et al.*, 2015). Taken together, these retrospective data suggest the potential for IVM to be more successful when combined with a freeze-only approach, but this needs to be evaluated in prospective clinical trials before any conclusions can be drawn.

The notable significant differences between the IVM and IVF groups in duration of stimulation, total dose of follicle-stimulating hormone used, and hormone levels, reflect the minimal stimulation used in the IVM protocol. Specifically, the amount of follicle-stimulating hormone administered to patients was 5.5-fold lower in the IVM versus IVF group and there were fewer days of injections in the IVM versus IVF group (2.3 vs. 8.8 days). This mild approach is well suited to women with polycystic ovary syndrome, polycystic ovarian morphology and/or high AFC, who are at higher risk of developing potentially life-threatening complications, such as OHSS (MacDougall *et al.*, 1992; Brinsden *et al.*, 1995). There were no cases of OHSS in the IVM group in this study, consistent with all previous IVM publications (Siristatidis *et al.*, 2013; Vuong *et al.*, 2019). As was recently reported in a multicenter discrete choice experiment in the Netherlands, higher risk women with polycystic ovary syndrome are willing to trade off cancelation rate, number of hormone injections, the chance of pregnancy and costs, for lower risk of OHSS (Braam *et al.*, 2020).

As expected, laboratory outcomes were better with IVF, although the number of oocytes retrieved in the IVM group was acceptable. Significantly more good-quality embryos were obtained in the IVF group (7.9 ± 5.1 vs. 3.2 ± 2.7 in IVM) and this is likely to account for the better cumulative outcome in the IVF group. As a result, when calculating the cumulative outcome of a complete cycle, more women in the IVM group did not have embryos to transfer at a later stage in this trial. Therefore, given the above-mentioned women's preference, it is important to compare multiple cycles of IVM versus IVF within a certain period of time in future trials to guarantee that participants in both groups receive interventions throughout the trial. Another potential implication of our study findings is that the outcomes achieved with IVM could provide further impetus to use this approach in fertility preservation, whereby women diagnosed with cancer can have oocyte collection for IVM at short notice with minimal or no gonadotropin stimulation (Smitz *et al.*, 2011), and/or *ex vivo*-IVM can be applied to oocytes collected during processing of ovarian tissue for preservation (Segers *et al.*, 2015).

Conclusion

In women with high AFC undergoing infertility treatment, this study produced statistically inconclusive findings regarding the non-inferiority of the IVM technique used compared with IVF. However, other outcomes such as cumulative pregnancy rate and the number of top-quality embryos indicate that IVM is currently less effective than IVF. Although the results from the current study suggest that

IVM is a viable and safe alternative to IVF that may be suitable for some women seeking a mild ART approach, the current study findings approach inferiority for IVM compared with IVF. Further development of IVM protocols is needed to identify approaches that achieve fertility outcomes equivalent to those achieved with current IVF, to avoid or minimize ovarian hyperstimulation in subgroups for whom this would be beneficial, such as those with polycystic ovary syndrome and high AFC.

Authors' roles

L.N.V., V.N.A.H., T.M.H., V.Q.D., T.H.P., N.G.H., A.H.L., T.D.P., R.W., J.S., R.B.G., R.J.N. and B.W.M. designed the study and monitored data collection. The statistical analysis plan was written by T.D.P. and L.N.V. Data analysis was conducted by T.D.P., acts as guarantor of the data and the analysis. Planning for the first draft of the manuscript was undertaken by L.N.V., V.N.A.H., T.D.P. and B.W.M. The first draft of the paper was written by L.N.V. and B.W.M. All authors were involved in the decision to publish the paper and in critical revisions of the manuscript. L.N.V. acts as overall guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data and controlled the decision to publish.

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Conflict of interest

L.N.V. has received speaker and conference fees from Merck, grant, speaker and conference fees from Merck Sharpe and Dohme, and speaker, conference and scientific board fees from Ferring; T.M.H. has received speaker fees from Merck, Merck Sharp and Dohme, and Ferring; R.J.N. has received conference and scientific board fees from Ferring, is a minor shareholder in an IVF company and receives grant funding from the National Health and Medical Research Council (NHMRC) of Australia; B.W.M. has acted as a paid consultant to Merck, ObsEva and Guerbet, and is the recipient of grant money from an NHMRC Investigator Grant; R.B.G. reports grants and fellowships from the NHMRC of Australia; J.S. reports lecture fees from Ferring Pharmaceuticals, Biomérieux, Besins Female Healthcare and Merck, grants from Fund for Research Flanders (FWO), and is co-inventor on granted patents on CAPA-IVM methodology in the USA (US10392601B2) and Europe (EP3234112B1); T.D.P., V.Q.D., V.N.A.H., N.H.G., A.H.L., T.H.P. and R.W. have no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work.

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