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Clinical outcomes from ART in predicted hyperresponders: *in-vitro* maturation of oocytes versus conventional ovarian stimulation for IVF/ICSI

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Running title: IVM versus conventional ovarian stimulation

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Abstract

Study question:

Do ongoing pregnancy rates (OPR) differ in predicted hyperresponders undergoing ART after in vitro maturation (IVM) of oocytes compared with conventional ovarian stimulation (OS) for IVF/ICSI?

Summary answer:

One cycle of IVM is non-inferior to one cycle of OS in women with serum anti-Müllerian Hormone (AMH) levels ≥10ng/mL.

What is known already:

Women with high antral follicle count (AFC) and elevated serum AMH levels, indicating an increased functional ovarian reserve, are prone to hyperresponse during ART treatment. To avoid iatrogenic complications of OS, IVM has been proposed as a mild-approach alternative treatment in predicted hyperresponders, including women with polycystic ovary syndrome (PCOS) who are eligible for ART. To date, inferior pregnancy rates from IVM compared to OS have hampered the uptake of IVM by ART clinics. However, it is unclear whether the efficiency gap between IVM and OS may differ depending on the extent of AMH elevation.

Study design, size, duration:

This study is a retrospective cohort analysis of clinical and laboratory data from the first completed highly purified human menopausal gonadotropin (HP-hMG) primed, non-hCG triggered IVM or OS (FSH or HP-hMG stimulation in a GnRH antagonist protocol) cycle with ICSI in predicted hyperresponders ≤36 years of age at a tertiary referral university hospital. A total of 1707 cycles were included between January 2016 and June 2022.

Participants/materials, setting, methods:

Predicted hyperresponse was defined as a serum AMH level ≥3.25ng/mL (Elecsys® AMH, Roche Diagnostics). The primary outcome was cumulative ongoing pregnancy rate (OPR) assessed 10-11 weeks after embryo transfer. The predefined non-inferiority limit was -10.0%. The analysis was adjusted for AMH strata. Time-to-pregnancy (TTP), defined as the number

of embryo transfer (ET) cycles until ongoing pregnancy was achieved, was a secondary outcome. Statistical analysis was performed using a multivariable regression model controlling for potential confounders.

Main results and the role of chance:

Data from 463 IVM cycles were compared with those from 1244 OS cycles. Women in the IVM group more often had a diagnosis of Rotterdam PCOS (434/463, 93.7%) compared to those undergoing OS (522/1193, 43.8%), were significantly younger (29.5 years versus 30.5 years, p≤0.001), had a higher BMI (25.7kg/m² versus 25.1kg/m², p≤0.01) and higher AMH (11.6ng/mL versus 5.3ng/mL, p≤0.001). Although IVM cycles yielded more cumulus oocyte complexes (COCs) (24.5 versus 15.0 COC, p≤0.001), both groups had similar numbers of mature oocytes (MII) (11.9 MII versus 10.6 MII, p=0.9).

In the entire cohort, non-adjusted cumulative OPR from IVM was significantly lower (198/463, 42.8%) compared to OS (794/1244, 63.8%), p≤0.001. When analysing OPR across different serum AMH strata, cumulative OPR in both groups converged with increasing serum AMH, and OPR from IVM was non-inferior compared to OS from serum AMH levels >10ng/mL onwards (113/221, 51.1% [IVM]; 29/48, 60.4% [OS]). The number of ETs needed to reach an ongoing pregnancy was comparable in both the IVM and the OS group (1.6 versus 1.5 ET's, p = 0.44). Multivariable regression analysis adjusting for ART type, age, BMI, oocyte number and PCOS phenotype showed that the number of COCs was the only parameter associated with OPR in predicted hyperresponders with a serum AMH >10ng/mL.

Limitations, reasons for caution:

These data should be interpreted with caution as the retrospective nature of the study holds the possibility of unmeasured confounding factors.

Wider implications of the findings:

Among subfertile women who are eligible for ART, IVM and OS resulted in comparable reproductive outcomes in a subset of women with a serum AMH ≥10ng/mL. These findings should be corroborated by an RCT comparing both treatments in selected patients with elevated AMH.

Study funding/competing interest(s):

There was no external funding for this study. All authors declared no conflict of interest pertaining to this study.

Trial registration number: N/A

KEYWORDS

Hyperresponder, PCOS, In Vitro Maturation, Ovarian Stimulation, ongoing pregnancy rate

Introduction

In assisted reproductive technology (ART) cycles, women with an increased functional ovarian reserve often exhibit ovarian hyperresponse to gonadotropins. Hyperresponse may lead to iatrogenic complications such as ovarian hyperstimulation syndrome (OHSS) or ovarian torsion (Vesztergom et al., 2021). To avoid these complications, mitigation strategies have been developed; these include the use of a gonadotropin-releasing hormone (GnRH) agonist rather than the conventional human Chorionic Gonadotropin (hCG) trigger for final oocyte maturation (Bodri et al., 2010), a "freeze-all" approach (Devroey et al., 2011), and the administration of GnRH antagonists and/or cabergoline after oocyte retrieval to accelerate luteolysis (Dahan et al., 2018). Although the increasing use of these interventions has almost eradicated the incidence of the severe form of OHSS, several hyperresponders will continue to suffer abdominal pain and bloating as the manifestations of a mild or moderate form of OHSS (Shrem et al., 2019). IVM of immature cumulus-oocyte complexes (COCs) collected from antral follicles has been proposed as an alternative treatment in predicted hyperresponders (Trounson et al., 1994). This approach has been advocated as more 'patient-friendly' compared to a conventional ovarian stimulation (OS) for IVF/ICSI because of the reduced hormonal burden and cost for the patient (Braam et al., 2021), a lower need for cycle monitoring (Gilchrist et al., 2023), and the absence of OHSS risk (Vuong et al., 2023). Although the first pregnancy after IVM in a hyperresponder patient has been reported nearly 30 years ago, IVM has only recently been declared non-experimental by the American Society for Reproductive Medicine (ASRM) (ASRM, 2021). Oocyte maturation rates after IVM and the developmental potential of IVM-derived embryos are lower compared to those after OS, mainly because currently available registered IVM culture systems struggle to meet the metabolic and developmental needs of in-vitro matured oocytes (Richani et al., 2021). Therefore, IVM has been mostly performed in women with increased functional ovarian reserve to compensate for the lower efficiency of IVM systems (Guzman et al., 2013; Walls et al., 2015). Women with Polycystic Ovary Syndrome (PCOS) have been considered suitable candidates for IVM, because of their higher risk of hyperresponse to gonadotropins due to an increased antral follicle count and/or elevated serum anti-Müllerian Hormone (AMH). PCOS is the most common endocrine disorder affecting 8-13% of all women of reproductive age and is typically diagnosed based on the Rotterdam criteria (Rotterdam ESHRE/ASRM-

Sponsored PCOS Consensus Workshop Group, 2004); a combination of two out of three following characteristics confers a diagnosis of PCOS: (1) polycystic ovarian morphology (PCOM), with PCOM defined by ≥20 antral follicles per ovary using high-resolution ultrasound, (2) clinical or biochemical hyperandrogenism and (3) oligo-/amenorrhea (Teede et al., 2018).

The uptake of IVM by ART clinics has been hampered by relatively modest pregnancy rates from IVM compared to OS (De Vos, 2021; Vuong et al., 2023), although live birth rates after IVM have improved over time and have reached ≈40% per started IVM cycle in centers of expertise (Mackens et al., 2020, Vuong et al., 2023). Other impediments to a more widespread use of IVM are related to the inconsistency of laboratory protocols and different clinical approaches in IVM clinics to date. According to the original IVM protocol, immature, cumulus-enclosed GV-stage oocytes are matured in-vitro in one step to MII stage oocytes (Edwards, 1965). Despite the clear definition of IVM, there has been a persistent interest among ART practitioners to "rescue" denuded immature oocytes that have failed to reach the MII stage following OS and an ovulation trigger in standard ART cycles. This practice, often referred to as rescue IVM, has been used in women with low oocyte maturation rates after OS, and continues to be conflated with the IVM protocol described in the present study, although the efficiency of rescue IVM is low (Practice Committees of the American Society for Reproductive Medicine, the Society of Reproductive Biologists and Technologists, and the Society for Assisted Reproductive Technology, 2021; Shani et al., 2023; Norman, 2023). Further hurdles include the requirement of specific laboratory skills, the lack of long-term follow-up data of IVM offspring (Norman, 2023), and the concern that IVM may result in higher rates of early pregnancy loss (EPL) (Söderström-Anttila et al., 2005; Suikkari, 2008; Buckett et al., 2008; Lim et al., 2009). We previously reported a higher risk of EPL after IVM compared to OS, but this increased risk was confined to pregnancies obtained after fresh ET (Mackens et al., 2020).

It is unclear whether the difference in efficiency between IVM and OS may vary depending on the extent of the functional ovarian reserve. Hyperresponders represent a heterogenous group of patients, ranging from women with only slightly elevated AMH levels and PCOM, to women with a more severe PCOS phenotype. Therefore, we set out to analyse the efficacy of IVM in predicted hyperreponders depending on different serum AMH cut-off levels, compared to OS followed by in- IVF or ICSI.

Materials and methods

Study design and study groups

This study is a single-centre retrospective analysis of clinical and laboratory data from non-hCG triggered IVM cycles compared to cycles using OS with gonadotropins in a gonadotropin releasing hormone (GnRH) antagonist protocol in predicted hyperresponder patients between January 2016 and June 2022 who were treated at a tertiary referral university hospital. Only the patient's first IVM or OS cycle was considered for the analysis. Patients were considered predicted hyperresponders when they had a serum AMH concentration >3.25ng/mL as a substitute for PCO-like morphology (PCOM), based on the recommendation that serum AMH could be used for assessing antral follicle excess in adults (Teede et al., 2023). In patients with a serum AMH concentration >3.25ng/mL who had hyperandrogenism (H) and/or oligo-anovulation (O), a diagnosis of PCOS was assigned ~~withheld~~ in accordance with the Rotterdam criteria, and the PCOS phenotype was assigned (phenotype A: HOP, with "P" designating PCOM; phenotype B: HO; phenotype C: HP; phenotype D: OP) (Rotterdam EA-SPCWG, 2004). Patients with phenotype B were not included in this study because these patients do not exhibit PCOM. Clinical hyperandrogenism was defined as the presence of hirsutism and/or acne; biochemical hyperandrogenism was based on elevated calculated free testosterone >0.64ng/dL corresponding to the mean + 2SD value in our standard population. If free testosterone was not elevated, then androstenedione (mean + 2SD value: 2130ng/L) and dehydroepiandrosterone sulfate (DHEAS) (mean + 2SD value: 3.40mg/L) were used as secondary parameters to determine hyperandrogenism. Analysis of androgens was performed using validated automated immunoassay methods (Elecsys electrochemiluminescence immunoassays on Cobas 6000, Roche Diagnostics). Serum AMH was analysed using the Elecsys AMH plus assay (Elecsys® AMH, Roche Diagnostics), and an AMH level of 3.25 ng/mL was used as the cut-off for PCOM. This cut-off is almost identical to the cut-off of 3.2 ng/mL for PCOM that was generated based on a comparison of AMH levels analysed by the Elecsys AMH plus assay between 455 women with PCOS and 500 controls (Dietz de Loos et al., 2021).

All patients included in this study were between 18 and 36 years old. Patients requesting preimplantation genetic testing (PGT) or fertility preservation and patients whose partner's sperm was extracted using testicular sperm extraction (TESE) were excluded from the study. All included patients were eligible for ART either because they had previously failed to become pregnant after ovulation induction and/or because of male factor or tubal factor infertility. Patients consented to undergo either IVM or OS after counselling. The option of IVM was more frequently discussed with patients exhibiting strongly elevated serum AMH levels indicative of a more severe PCOS phenotype (Guzman et al., 2013). Patients who underwent IVM were asked to donate a variable proportion of their COCs for IVM laboratory research if they had 30 or more antral follicles on pelvic ultrasound scan before oocyte retrieval, although the majority of COCs were allocated to the standard IVM protocol as part of patient's fertility treatment (previously described by Sanchez et al., 2017).

ART protocols

Ovarian stimulation protocol and oocyte retrieval

In the IVM group, highly purified hMG (HP-hMG) was started on day 3 of the menstrual cycle or on day 5 after discontinuing a short course (14–21 days) of combined oral contraceptive pill (OCP) pretreatment, which was prescribed to control IVM cycle programming. Ovarian stimulation was performed for three consecutive days, with a daily dose of 150 IU or 225 IU HP-hMG based on BMI. No hCG was administered before oocyte retrieval (OR). Ultrasound-guided retrieval of COCs from small antral follicles for IVM was scheduled 42 h after the last HP-hMG injection.

In the control group, OS was performed using recombinant follicle stimulating hormone (rFSH) or HP-hMG in a GnRH antagonist protocol. The gonadotropin starting dose was selected at the physician's discretion. Final oocyte maturation was induced by injection of 5,000 to 10,000 IU uhCG, 250 µg rhCG, or injection of 0.2 mg triptorelin, as soon as two to three leading follicles were 17–20 mm in size as observed on ultrasound scan. Oocyte retrieval was performed 36 h after ovulation trigger. All OR procedures in this study were performed using a 17-gauge single lumen needle (Cook Medical, K-OPS-1230-VUB, Limerick, Ireland).

IVM laboratory procedure

Follicles were aspirated using Human Tubal Fluid (HTF) (IVF BasicsVR HTF HEPES, Gynotec B.V. Malden, the Netherlands) supplemented with heparin (5000 IU/mL, Heparin Leo, Leo Pharma, Belgium; final heparin concentration 20 IU/mL) or Flushing medium (Medicult, Origio) and follicular aspirates were filtered through a cell strainer (FalconVR , 70 µm mesh size, BD Biosciences, CA, USA). After collection, COC were washed and transferred to a four-well dish (Nunc; Thermo Fisher Scientific; MA, USA) containing IVM medium (IVM System, Medicult, Origio) supplemented with 75 mIU/mL HP-hMG (Menopur, Ferring, Saint-Prex, Switzerland), 100 mIU/mL hCG (Pregnyl, MSD, Oss, the Netherlands) and 10 mg/mL human serum albumin (Vitrolife, Göteborg, Sweden). COCs were cultured for 28–40 h in groups of 10 COC per well in 500 µL IVM medium with oil overlay (Ovoil, Vitrolife) at 37 °C under atmospheric oxygen.

Embryo culture and transfer

Oocytes that matured to the metaphase II stage after IVM were inseminated using ICSI with partner sperm as described by Van Landuyt et al. (2005). In the OS group, oocytes were inseminated using IVF of ICSI at the discretion of the physician, except in cases with poor sperm quality (sperm concentration below 15 x 10^6/ml), where all oocytes were denuded and mature oocytes were inseminated using ICSI. Fertilization was assessed 16–18 h post-insemination by the presence of two pronuclei.

Embryo culture after IVM or OS was done as previously described (Mackens et al., 2020). Briefly, embryos were cultured in individual droplets of 25 µl of sequential media formulations (Quinn's AdvantageTM Fertilization, Cleavage and Blastocyst medium, SAGE or FertTM, CleavTM, BlastTM medium, Origio) with oil overlay (Ovoil, Vitrolife) until Day 3 or until Day 5 (or Day 6) after ICSI, depending on the number of embryos available on Day 3, as previously described by Mackens et al., 2020. On day 3, the embryos were evaluated for the number and symmetry of blastomeres, percentage of fragmentation, vacuolization, granulation, and multinucleation. On day 5, the blastocysts were scored according to the grading system by Gardner and Schoolcraft (1999). Based on all these parameters, an embryo quality score (EQ) was assigned to each embryo based on a predefined algorithm, defining four categories: excellent (EQ A), good (EQ B), moderate (EQ C), or poor (EQ D) as previously

described (De Munck et al., 2015). Embryo grading was performed in the same way for embryos derived from in-vitro and in-vivo matured oocytes, by a team of ten highly trained embryologists for evaluations whose performance is audited using internal and external quality control compliant with ISO 15189:2016, to avoid bias in embryo assessment. Embryos were selected for transfer or vitrification according to the morphological criteria described in Belva et al. (2016). Vitrification was performed using closed CBS-VIT high-security straws (CryoBioSystem, L'Aigle, France) in combination with DMSO, ethylene glycol and sucrose as cryoprotectants (Irvine ScientificVR Freeze kit, Newtownmountkennedy, Ireland) according to the method previously described by Van Landuyt et al. (2011). Fresh embryo transfer (ET) was performed on Day 3 or 5 after ICSI, with vitrification of surplus embryos. In cycles with no fresh embryo transfer ("freeze-all"), all embryos of good morphological quality were vitrified on Day 3 or on Day 5/6 after ICSI. Vitrified-warmed embryo transfer was performed in an artificial endometrium priming cycle using oral estradiol valerate (Progynova®, Bayer) or transdermal estradiol (Oestrogel®, Besins Healthcare) and vaginal micronised progesterone (Utrogestan®, Besins Healthcare, or Amelgen®, Gedeon Richter), as previously described (Mackens et al., 2020). Transfer of a Day 3 vitrified embryo was performed 1 day after warming, whereas vitrified blastocysts were transferred on the day of warming.

Ethical approval

The study was approved by the Ethical Committee of Universitair Ziekenhuis Brussel (BUN: 1432023000018). Since this was a retrospective analysis, informed consent was not obtained.

Outcome measures

The primary outcome parameter was cumulative ongoing pregnancy rate (COPR) defined as a clinical pregnancy with the presence of a heartbeat at 10 weeks of gestation (Kolte et al. 2015). Other outcome parameters were cumulative live birth rate (CLBR), time-to-pregnancy (TTP) and OHSS rate. Time-to-pregnancy was expressed as the number of ET cycles until ongoing pregnancy was achieved. Cumulative live birth rate was the percentage of deliveries with at least one live birth resulting from an initiated ART cycle, including all cycles in which fresh or frozen embryos were transferred, until one delivery of a live birth occurred or until all embryos were used.

The embryo utilisation rate was defined as the total number of embryos transferred and cryopreserved per 2PN oocyte per cycle.

Statistical analysis

Descriptive statistical analysis was performed on patient and ART characteristics. Continuous data are presented as the mean ± SD and categorical data are described as the number of cases accompanied by the corresponding percentages. Categorical data and continuous data that did not show normal distribution were analysed by Pearson's X^2 test / Fisher exact test or Mann Whitney test as appropriate. Multivariable regression analysis was performed to further assess the association between COPR and treatment strategy (IVM versus COS) after adjusting for confounders. The following confounders were considered for the analysis: age, AMH, BMI, number of COC retrieved, free testosterone, sperm concentration, and PCOS phenotype.

The likelihood of COPR was described as an odds ratio (OR) and 95% CI. A two-tailed alpha of 0.05 was applied in all statistical analyses, which were performed using STATA 13.0 (Stata Statistical 312 Software: Release 13; StataCorp., College Station, TX, USA).

Results

Patient characteristics

In total, 1707 patients were included. Data from 463 IVM cycles were compared with those from 1244 OS cycles. An overview of the baseline patient characteristics is shown in Table I. Several patient characteristics were significantly different among women in the IVM group compared to those in the OS group; patients who had IVM were younger (29.5 ± 3.4 years versus 30.5 ± 3.4 years, $p<0.001$), had significantly higher circulating AMH-levels (11.6 ± 7.7 ng/mL versus 5.3 ± 2.1 ng/mL, $p<0.001$), and higher circulating levels of total and free testosterone. The distribution of PCOS phenotypes among women in the IVM group was significantly different ($p<0.001$) compared to the OS group: 229/463 (49.5%) of women in the IVM group had Phenotype A, as compared to only 127/1244 (10.6%) in the OS group. Women who had IVM exhibited less frequently PCOM without associated features (29/463, 6.3%), whereas 671/1244 (56.2%) women in the OS group had PCOM without a diagnosis of PCOS.

Women in the IVM group had a higher BMI compared to women in the OS group (25.8 ± 5.4 kg/m² versus 25.0 ± 4.8 kg/m², p<0.01). Sperm quality was significantly better in the IVM group, with sperm concentration below 15 x 10^6/mL in 18.7% of IVM cases compared to 36.8% in the OS group (p<0.001).

Cycle characteristics

Treatment cycle characteristics are presented in Table 2. In the IVM group, 56/463 (12.1%) women donated on average 9.4 ± 5.5 COC for basic scientific research while the remaining COCs were allocated to their own fertility treatment. When compared to the OS group, and after subtraction of oocytes that were donated for research, IVM cycles yielded significantly more COCs (24.5 ± 19.8 oocytes versus 15.0 ± 8.3 oocytes, p=0.001). The number of metaphase II (MII) oocytes was comparable in both groups (11.9 ± 11.2 versus 10.6 ± 7.1, p=0.9). The embryo utilization rate (3.1 ±3.0 versus. 4.0 ±3.0; p <0.001) was significantly lower in the IVM group compared to the OS group.

Reproductive outcomes

In the entire cohort, when considering all ETs performed after OR, OS cycles more often resulted in an ongoing pregnancy compared to IVM cycles (COPR 63.8% [794/1244] versus. 42.8% [198/463], p<0.001). When analyzing COPR in different categories of hyperresponders based on serum AMH cut-off levels, COPR after IVM and OS converged with increasing serum AMH levels, as shown in Figure 1. More specifically, a tendency towards a higher COPR was observed with increasing serum AMH levels in women who underwent IVM, while COPR remained stable up to a serum AMH level of 12 ng/mL in women who had OS. The efficiency gap between IVM and OS was less than 10% in women with serum AMH levels ≥10ng/mL; in this subgroup, a COPR after IVM of 51.1% (113/221) was observed, compared to a COPR after OS of 60.4% (29/48).

When considering only those cycles that ultimately resulted in an ongoing pregnancy after consecutive transfer of embryos, patients in the IVM group more frequently had a transfer of a cleavage-stage embryo (64.6% versus. 17.1%), when compared to patients in the OS group (p<0.001). In both groups, ongoing pregnancy was most achieved following vitrified-warmed

ET rather than fresh ET (95.5% for IVM and 62.1% for OS). Time-to-pregnancy as expressed by the number of embryo transfers needed to achieve ongoing pregnancy was comparable in both groups (1.6 ± 1.3 versus. 1.5 ± 1.0 embryo transfers, p=0.44) (Table 3). There were no events of OHSS in the IVM group, compared to 12 cases (1.5%) of moderate or severe OHSS in the OS group, p= 0.005, according to the criteria proposed by Golan and Weissman (2009). Overall, cumulative live birth rate (CLBR) was significantly lower in the IVM group (175/463 (37.8%)) compared to the OS group (712/1244 (57.2%), p=<0.0001). When considering the outcome in a subgroup of women with serum AMH levels of ≥10ng/mL, a smaller difference in CLBR was observed (99/212 (46.7%) after IVM versus 28/47 (59.6%) after OS, p= 0.110) (table 3).

To assess which variables predicted COPR adjusted for measured confounding, we performed multivariable regression analysis. The type of ART, age, free testosterone, and number of COCs significantly affected COPR, with adjusted Odds Ratios (aOR) of 3.73 (95% CI: 2.64–5.26, p<0.001), 0.94 (95% CI: 0.91–0.98, p=0.001), 0.93 (95% CI: 0.88–0.97, p=0.002), and 1.04 (95% CI: 1.03–1.05, p<0.001). Based on the observation that the efficiency gap between IVM and OS in terms of COPR was less than 10% in women with serum AMH levels ≥10ng/mL, a multivariable regression analysis was performed in this selected subset of patients. The multivariable regression model adjusted for ART type, age, BMI, free testosterone, number of COCs, PCOS phenotype, and sperm concentration showed that the number of COCs (OR 1.03; 95%CI 1.01 – 1.05, p=0.007) and free testosterone (OR 0.88; 95%CI 0.81 – 0.97, p=0.006) were the only parameters predicting COPR in predicted hyperresponders with a serum AMH ≥10ng/mL (Table 5).

Discussion

The objective of our study was to evaluate the size of the efficiency gap between IVM and OS followed by in-vitro fertilization in predicted hyperresponders, across a range of serum AMH cut-off levels. According to our data, cumulative ongoing pregnancy rate (COPR) per started ART cycle was lower in hyperresponders after IVM compared to OS in general, but there was a trend towards higher COPR after IVM with increasing serum AMH levels of the patient. In contrast, this correlation between serum AMH levels and cumulative pregnancy rates was not

observed in hyperresponders who had OS, and COPR after IVM and OS converged as AMH increased. To the best of our knowledge, this is the first study to correlate the extent of excess functional ovarian reserve with clinical outcomes after standard ART and IVM, and to identify the patient population who may achieve the highest pregnancy rates when they embark on IVM treatment. According to the results of this study, patients with AMH levels above 10ng/mL may represent the most suitable target population for IVM; these patients may opt for IVM as a more patient-friendly method of ART, without sacrificing success rates. We must admit that the 1.5% risk of OHSS after OS in our study is rather high and this may not reflect the actual risk of moderate to severe OHSS when a "freeze-all" approach is used. Indeed, a substantial proportion of patients in our study had a fresh ET after OS rather than a freeze-all approach. According to recent data, the risk of OHSS in hyperresponders who have no fresh ET is less than 1%; in a recent RCT comparing IVM and OS in Vietnam the incidence of moderate to severe OHSS after OS and a "freeze-all" strategy was only 0.7% (Vuong et al., 2020). In view of this, patient preference and the reduced hormonal burden of IVM have replaced the avoidance of OHSS as the main indications for IVM in hyperresponders (De Vos et al., 2021).

Our data corroborate previous findings showing that cumulative outcomes correlate with the number of oocytes collected, in conventional ART (Fanton et al., 2023) as well as in IVM cycles. Indeed, several studies in the field of IVM have explored the ability of circulating levels of AMH, alongside AFC, to identify women suitable for IVM treatment based on the number of retrieved oocytes (Fadini et al., 2011; Guzman et al., 2013; Seok et al., 2016; Sonigo et al., 2016). In a retrospective cohort study in South Korea encompassing 186 patients with PCOS who had hCG-primed IVM, the authors identified a serum AMH cut-off level of 8.5ng/mL to discriminate patients who had a live birth after IVM from those who were not pregnant (Seok et al., 2016). Pregnancy outcomes after the first embryo transfer in 107 IVM cycles and 177 OS cycles in PCOS patients with serum AMH levels ≥8.5 ng/mL were similar, although AMH analysis in that study had been performed using a manual ELISA method which results in higher values compared to the fully automated AMH electrochemiluminescence assay used in our study (Anckaert et al., 2016). Nevertheless, data from that study as well as ours emphasise the importance of proper patient selection for IVM treatment and may explain

why OS has consistently outperformed IVM in previous comparative studies when unselected hyperresponders were recruited.

Although we observed a higher likelihood of COPR after IVM in women with higher AMH compared to women with lower AMH, the higher COPR in these patients is not caused by higher AMH *per se*, but by the potential of these women to yield high numbers of COC, as shown by the multivariable regression analysis. We speculate that, although AMH and number of COCs are intricately correlated with each other based on the number of antral follicles, not all women with elevated AMH will have a high number of COCs at egg retrieval when they undergo IVM. This can be due to technical problems during egg retrieval for IVM; indeed, some women with high AMH levels may have extremely high numbers of antral follicles, to the extent that the egg retrieval procedure must be prematurely ended when the procedure takes too long, and the procedure becomes too painful for the patient. On the other hand, when women with very high AMH levels undergo conventional ovarian stimulation (OS), ovarian response may be suboptimal if the dose of FSH is underneath the threshold for optimal ovarian response. These women with very high AMH have an increased risk of having a rather low follicular output rate and an accordingly suboptimal oocyte yield.

The observation that increased AMH levels confer improved success rates after IVM does not only confirm earlier studies by our group (Guzman et al., 2013), but provides an opportunity for validation in a prospective trial in patients with an excessive functional ovarian reserve. The risk of iatrogenic complications and side effects of conventional ART has become very small, even in this subgroup of women at the more severe end of the spectrum of hyperresponders when an adapted OS protocol with GnRH agonist trigger and a freeze-all strategy is prescribed. However, a proportion of these patients may prefer a treatment with lower burden, minimal need for monitoring and a lower cost of medication. According to a survey among hyperresponders in the Netherlands, a significant proportion of women were willing to trade off the chance of a pregnancy for a lower risk of OHSS (Braam et al., 2020), although the willingness to accept lower pregnancy rates may depend on financial coverage of ART. Indeed, in countries with a high out-of-pocket cost for the patient, the uptake of IVM as a mild approach ART will likely be low unless IVM becomes more efficient compared to OS.

When introducing IVM in the fertility clinic, physicians and laboratory staff may be subjected to a learning curve, and there may be a relation between a clinic's volume of IVM cycles and their success rates. In view of this, the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome advocated that IVM should be offered to selected women with PCOS in units with sufficient expertise; according to this updated guideline, the use of IVM should be restricted to services with sufficient expertise, and advocacy is needed for regional or national centres of expertise (Balen, 2023).

Overall, the results of our study are in line with published data in other large IVM clinics; in a retrospective study encompassing 121 women with polycystic ovaries in Australia, CLBR after IVM and single blastocyst transfer was 41.3% compared to 55.1% after OS (Walls et al., 2015) (ref.). With a live birth rate of only 22.3% at six months after OR, outcomes after IVM with single blastocyst transfer in a large RCT in China were considerably lower (Zheng X. et al., 2021). According to data from the largest published RCT comparing IVM and OS in a single centre in Vietnam, where embryos were vitrified at the cleavage stage, CLBR at 12 months after randomization was 44.0% in the IVM group and 62.6% in the OS group (Odds ratio 0.7, 95% CI 0.6 - 0.83) (Vuong et al., 2020). Nevertheless, previous studies have considered the group of patients who had IVM treatment as a homogenous group of patients with a hyperresponder profile and/or PCOS. However, we have previously reported that outcomes after IVM may differ significantly between women with different PCOS subtypes, and that women with a combination of PCOM, hyperandrogenism and oligo-anovulation have the best cumulative outcomes after IVM (Mackens et al., 2020). The present study suggests a valuable role for serum AMH as a tool to select patients who are most suitable for IVM treatment.

Our study has several limitations, which mostly stem from the retrospective design. First, a subset of patients in the IVM group consented to donate a proportion of their COCs for scientific research aimed at the development of new IVM culture media, as previously described (Sanchez et al., 2017). When doing so, patients could benefit from a discount if they had to undergo a second IVM cycle. In this study 58 of the 463 patients (12.1%) donated on average 9.4 ± 5.5 COCs for research in their first IVM cycle, which may have mitigated their chances of pregnancy from that cycle. Despite that, COPR after up to two cycles of IVM was similar to one cycle of OS in women with serum AMH-levels $\geq$7ng/mL. The concept of

ascertaining cumulative outcomes after multiple cycles of IVM versus one cycle of OS is not new and has previously been suggested by others (Wessel et al., 2023).

Second, several patients in both groups had travelled from abroad for fertility treatment in our clinic and went back to their country of origin once they achieved an ongoing pregnancy. Although CLBR is a more clinically relevant parameter of success in ART, loss to follow-up of those patients resulted in a substantial amount of missing data regarding live birth.

Third, patients with a severe PCOS phenotype and very high levels of serum AMH are relatively underrepresented in the OS group, because they more frequently embarked on IVM treatment after discussion with the physician. As a result of this selection bias, the results are less robust in the upper range of the serum AMH spectrum.

In conclusion, the data from our study confirm the findings of previous observational studies as well as RCTs: currently available IVM systems cannot achieve cumulative outcomes that are comparable to those after OS, except in selected women with an excessive functional ovarian reserve. According to our data, only a proportion of predicted hyperresponders, more specifically those with a serum AMH of 10ng/mL or more, may expect cumulative ongoing pregnancy rates similar to those after OS, but with fewer hormonal side effects and a lower risk of OHSS. Whether these findings should lead us to suggest that IVM may only benefit a small subgroup of women with PCOS is uncertain: time to pregnancy appeared to be similar in both groups of our study, and patients may balance efficiency expressed as cumulative pregnancy rates against the overall treatment burden and their willingness to accept side effects related to hyperresponse depending on local ART coverage policies. Meanwhile, novel IVM culture systems using biphasic culture systems or based on supplementation of oocyte-secreted factors or other molecules are being engineered – the culture systems should result in improved oocyte competence and narrow down the efficiency gap between IVM and standard ART (Gilchrist et al., 2016; Sanchez et al., 2017). Finally, more robust answers on the role of IVM in hyperresponders should be delivered by a prospective RCT comparing the most efficient IVM system with standard ART in properly selected patients, more specifically in women with a severe PCOS phenotype.

Data availability statement:

The data underlying this article will be shared on reasonable request to the corresponding author.

Authors' roles:

L.M. and M.D.V. were responsible for the concept and study design. L.M. and E.G. performed the data collection. P.D. performed the statistical analyses. L.M. and M.D.V. drafted the manuscript. All authors contributed to the interpretation, discussion and editing of the manuscript. All authors approved the last version.

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Figure 1 Unadjusted analysis of cumulative ongoing pregnancy rate (COPR) per started cycle according to incremental thresholds of serum anti-Müllerian Hormone (AMH)

OS: ovarian stimulation for IVF/ICSI

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Table 1: Baseline patient characteristics

	IVM (N=463)	Ovarian Stimulation (N=1244)	*P value*
Age (years)	29.5 (±3.4)	30.5 (±3.4)	<0.001
BMI (kg/m²)	25.8 (±5.4)	25.0 (±4.8)	<0.01[a]
AMH (ng/mL)	11.6 (±7.7)	5.3 (±2.1)	<0.001[b]
Testosterone (ng/dl)	48.2 (±24.0)	32.5 (±16.6)	<0.001[c]
Calculated free testosterone (ng/dl)	0.60 (±0.41)	0.40 (±0.33)	<0.001[d]
Sperm concentration (10^6/mL)	56.2 (±46.2)	40.8 (±46.5)	<0.001
% Sperm with progressive motility (WHO grades A, B)	49.6 (21.1)	45.2 (22.2)	<0.001
Male factor[e] (*N*, %)	87 (18.7%)	458 (36.8%)	<0.001
PCOS type A HOP[g] (*N*, %)	229 (49.5)	127 (10.6)	<0.001[f]
PCOS type C HP[g] (*N*, %)	35 (7.6)	125 (10.5)	
PCOS type D OP[g] (*N*, %)	170 (36.7)	270 (22.6)	
Polycystic ovary morphology (*N*, %)	29 (6.3)	671 (56.2)	

Baseline characteristics are presented as mean (± SD) unless stated otherwise.
AMH = Antimüllerian hormone PCOS=polycystic ovary syndrome

[a]N=1241 in the OS group due to missing data
[b]N=1238 in OS group due to missing data
[c]N=393 in IVM group; N=1019 in OS group due to missing data
[d]N=381 in IVM group; N=946 in OS group due to missing data
[e]male factor = sperm concentration below the 5th percentile (15 * 10^6/ml) according to WHO guidelines
[f]N=1193 in the OS group due to missing data
[g]Patients exhibiting H, hyperandrogenism; O, oligo-anovulation; P, polycystic ovary morphology

777 **Table 2**: ART treatment cycle characteristics
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	IVM (N=463)	**Ovarian Stimulation (N=1244)**	*P value*
Number of Cumulus Oocyte Complexes. Mean (±SD)	24.5 (±19.8)	15.0 (±8.3)	<0.001
Metaphase II oocytes Mean (±SD)	11.9 (±11.2)	10.6 (±7.1)	0.9
Insemination method			<0.001
ICSI	100%	91.3%	
IVF	0%	8.7%	
Fertilized oocytes Mean (±SD)	7.6 (±8.3)	8.9 (±5.6)	<0.001
Fertilization rate	64.6	76.5	<0.001
Utilized embryos Mean (±SD)	3.1 (±3.0)	4.0 (±3.0)	<0.001
Embryo quality[a]			<0.001
A (Excellent)	34.7	52.1	
B (Good)	24.0	23.7	
C (Moderate)	23.9	16.2	
D (Poor))	17.4	8.0	
Cycles with D3 embryos utilized (fresh/frozen ET) (*N*, %)	293 (63.3%)	295 (23.7%)	<0.001
Cycles with D5 embryos utilized (fresh/frozen ET) (*N*, %)	107 (23.1%)	881 (70.8%)	
Cycles with no embryos available (*N*, %)	63 (13.6%)	68 (5.5%)	<0.001
OHSS[b] (*N*, %)			0.005
None	463 (100%)	782 (98.5%)	
Mild	0 (0%)	8 (1.0%)	
Moderate	0 (0%)	3 (0.4%)	
Severe	0 (0%)	1 (0.1%)	

779 Data are presented as % unless stated otherwise

780 [a]Embryo grading system after De Munck et al., (2015)
781 [b]OHSS grading according to the criteria proposed by Golan and Weissman (2009)
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Table 3: Reproductive outcomes from cycles with ongoing pregnancy

	IVM (N=198)	Ovarian Stimulation (N=794)	*P value*
Number of embryo transfers to reach ongoing pregnancy (mean, SD)	1.6 (±1.3)	1.5 (±1.0)	0.440
Embryo transfer procedure to reach ongoing pregnancy (*N*, %):			
Day 3 transfer	128 (64.6%)	136 (17.1%)	<0.001
Day 5 transfer	70 (35.4%)	658 (82.9%)	
Fresh ET	9 (4.5%)	301 (37.9%)	<0.001
Frozen ET	189 (95.5%)	493 (62.1)	
Single ET	182 (91.9%)	758 (95.5%)	0.045
Double ET	16 (8.1%)	36 (4.5%)	
CLBR* (*N*, %)	175 (38.8%)	712 (59.9%)	<0.001
CLBR AMH ≥10ng/mL** (*N*, %)	99 (46.7%)	28 (59.6%)	0.110

CLBR= cumulative live birth rate was calculated as live birth rate on a per-retrieval basis and was defined as at least one live birth from all linked embryo transfers (i.e., accounting only for the first live birth associated with a retrieval).

Treatment characteristics are presented as mean ± SD for continuous data. Categorical data are presented as percentages (%).

* N= 451 for IVM and N=1187 for OS due to loss-to-follow-up

** N= 212 for IVM and N=47 for OS due to loss-to-follow-up

809 **Table 4:** Multivariable regression analysis for cumulative ongoing pregnancy rate in hyperresponder
810 patients

	Odds Ratio	95% CI	*P value*
ART type (IVM/Ovarian Stimulation)	3.73	2.64 – 5.26	<0.001
Age	0.94	0.91 – 0.98	0.001
BMI	0.98	0.96 – 1.01	0.238
COC	1.04	1.03 – 1.05	<0.001
AMH	1.01	0.98 – 1.05	0.449
Free testosterone	0.93	0.88 – 0.97	0.002
Sperm concentration	1.00	1.00 – 1.00	0.153
Phenotype[a]:			
A (HOP)	1	-	
C (HP)	0.74	0.47 – 1.16	0.194
D (OP)	0.78	0.52 – 1.16	0.220
Polycystic ovary morphology	0.73	0.49 – 1.11	0.141

811 [a]Patients exhibiting H, hyperandrogenism; O, oligo-anovulation; P, polycystic ovary morphology.

Table 5: Multivariable regression analysis for ongoing pregnancy rate in hyperresponder patients with an anti-Müllerian Hormone (AMH) concentration ≥10ng/mL

	Odds Ratio	95% CI	*P value*
ART type (IVM/Ovarian Stimulation)	1.70	0.76 – 3.79	0.195
Age	0.93	0.85 – 1.02	0.110
BMI	1.03	0.96 – 1.10	0.370
COC	1.03	1.01 – 1.05	0.007
Free testosterone	0.88	0.81 – 0.97	0.006
Sperm concentration	1.00	1.00 – 1.00	0.249
Phenotype[a]:			
A (HOP)	1	-	
C (HP)	1.05	0.38 – 2.88	0.923
D (OP)	0.65	0.31 – 1.40	0.272
Polycystic ovary morphology	0.55	0.14 – 2.27	0.411

aPatients exhibiting H, hyperandrogenism; O, oligo-anovulation; P, polycystic ovary morphology.