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ORIGINAL ARTICLE *Infertility*

A prediction model to select PCOS patients suitable for IVM treatment based on anti-Müllerian hormone and antral follicle count

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STUDY QUESTION: Which baseline patient characteristics can help assisted reproductive technology practitioners to identify patients who are suitable for *in-vitro* maturation (IVM) treatment?

SUMMARY ANSWER: In patients with polycystic ovary syndrome (PCOS) who undergo oocyte IVM in a non-hCG-triggered system, circulating anti-Müllerian hormone (AMH), antral follicle count (AFC) and total testosterone are independently related to the number of immature oocytes and hold promise as outcome predictors to guide the patient selection process for IVM.

WHAT IS ALREADY KNOWN: Patient selection criteria for IVM treatment have been described in normo-ovulatory patients, although patients with PCOS constitute the major target population for IVM. With this study, we assessed the independent predictive value of clinical and endocrine parameters that are related to oocyte yield in patients with PCOS undergoing IVM.

STUDY DESIGN, SIZE, DURATION: Cohort study involving 124 consecutive patients with PCOS undergoing IVM whose data were prospectively collected. Enrolment took place between January 2010 and January 2012. Only data relating to the first IVM cycle of each patient were included.

PARTICIPANTS/MATERIALS, SETTING, METHOD: Patients with PCOS underwent oocyte retrieval for IVM after minimal gonadotrophin stimulation and no hCG trigger. Correlation coefficients were calculated to investigate which parameters are related to immature oocyte yield (patient's age, BMI, baseline hormonal profile and AMH, AFC). The independence of predictive parameters was tested using multivariate linear regression analysis. Finally, multivariate receiver operating characteristic (ROC) analyses for cumulus oocyte complexes (COC) yield were performed to assess the efficiency of the prediction model to select suitable candidates for IVM.

MAIN RESULTS AND THE ROLE OF CHANCE: Using multivariate regression analysis, circulating baseline AMH, AFC and baseline total testosterone serum concentration were incorporated into a model to predict the number of COC retrieved in an IVM cycle, with unstandardized coefficients [95% confidence interval (CI)] of 0.03 (0.02–0.03) ($P < 0.001$), 0.012 (0.008–0.017) ($P < 0.001$) and 0.37 (0.18–0.57) ($P < 0.001$), respectively. Logistic regression analysis shows that a prediction model based on AMH and AFC, with unstandardized coefficients (95% CI) of 0.148 (0.03–0.25) ($P < 0.001$) and 0.034 (−0.003–0.07) ($P = 0.025$), respectively, is a useful patient selection tool to predict the probability to yield at least eight COCs for IVM in patients with PCOS. In this population, patients with at least eight COC available for IVM have a statistically higher number of embryos of good morphological quality (2.9 ± 2.3; 0.9 ± 0.9; $P < 0.001$) and cumulative ongoing pregnancy rate [30.4% (24 out of 79); 11% (5 out of 45); $P = 0.01$] when compared with patients with less than eight COC. ROC curve analysis showed that this prediction model has an area under the curve of 0.7864 (95% CI = 0.6997–0.8732) for the prediction of oocyte yield in IVM.

LIMITATIONS, REASONS FOR CAUTION: The proposed model has been constructed based on a genuine IVM system, i.e. no hCG trigger was given and none of the oocytes matured *in vivo*. However, other variables, such as needle type, aspiration technique and whether or not hCG-triggering is used, should be considered as confounding factors. The results of this study have to be confirmed using a second independent validation sample.

WIDER IMPLICATIONS OF THE FINDINGS: The proposed model could be applied to patients with PCOS after confirmation through a further validation study.

STUDY FUNDING/COMPETING INTEREST(S): This study was supported by a research grant by the Institute for the Promotion of Innovation by Science and Technology in Flanders, Project number IWT 070719.

Introduction

In-vitro maturation (IVM) of oocytes has the potential to become an alternative mild-approach assisted reproductive technology (ART), more specifically in patients with polycystic ovary syndrome (PCOS) (Tan and Child, 2002), who have an increased risk of developing ovarian hyperstimulation syndrome (OHSS). Although novel approaches including GnRH agonist triggering (Humaidan *et al*., 2010) and treatment segmentation (Devroey *et al*., 2011) can reduce OHSS incidence significantly, IVM is currently the only ART with no reported cases of OHSS. However, inferior pregnancy rates when compared with conventional hormone-driven ART (Smitz *et al*., 2011) and concerns with regard to safety of *in-vitro* culture (Harper *et al*., 2012) are major current impediments to a more widespread implementation of this technique. Nevertheless, the development of this ART could be further enhanced by the establishment of criteria to guide the selection of patients who would benefit most from IVM.

Parameters that reflect the ovarian follicular pool in patients undergoing ART have gained considerable interest in recent years. There is now accumulating evidence that anti-Müllerian hormone (AMH) levels, significantly increased in women with PCOS (Cook *et al*., 2002; Laven *et al*., 2004), and antral follicle counts (AFCs) are correlated with ovarian response to gonadotrophin stimulation (Broer *et al*., 2009). Because previous trials have shown that age, BMI, baseline estradiol (E2), inhibin A, FSH and other parameters may be determinants of oocyte yield in IVM cycles (Mikkelsen *et al*., 2000; Mikkelsen *et al*., 2001; Child *et al*., 2002b; Fadini *et al*., 2011), we set out to examine whether a prediction model incorporating markers of ovarian follicular reserve and other endocrine parameters that correlate with oocyte yield in IVM cycles could be established to improve patient selection and increase efficiency of IVM in patients with PCOS.

Materials and Methods

Patients

Between January 2010 and January 2012, 124 consecutive patients with PCOS were recruited for IVM treatment. Institutional ethical committee approval was granted and informed consent was obtained from all patients. The diagnosis of PCOS was established according to the Revised ESHRE/ASRM (European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine) criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

IVM cycle characteristics

The clinical approach and cycle monitoring have previously been described (De Vos *et al*., 2011). Regularly cycling patients had a baseline hormone analysis and ultrasound scan of the ovaries on cycle day 2 to assess the AFC. In oligo/anovulatory patients, withdrawal bleeding was induced using oral dydrogesterone (10 mg daily for 5 days). Patients were mildly stimulated with 150 IU highly purified human menopausal gonadotrophins (HP-hMG) (Menopur®, Ferring Pharmaceuticals A/S, Copenhagen, Denmark), starting on day 3 after menstrual periods or progesterone-induced withdrawal bleeding, for three consecutive days. A second ultrasound scan was performed on day 6 of the IVM treatment cycle. All patients received transdermal 17β-estradiol gel (Oestrogel®, Besins Healthcare, Paris, France) for endometrial preparation from cycle day 6 onwards, at a dose of 4 mg or 7.5 mg daily, depending on endometrium thickness. Oocyte retrieval was scheduled on day 7 or later, depending on endometrial thickness (>5 mm), but before the largest follicle reached a diameter of 10 mm. The procedure was performed by 1 out of 2 skilled operators using a 17-gauge single lumen needle (Cook Medical, K-OPS-1230-VUB, Limerick, Ireland). The aspiration pressure was 70 mmHg. No hCG trigger was administered because this trigger induces *in vivo* meiotic resumption in a proportion of oocytes that results in a heterogeneous population of oocytes at the time of collection and hence requires divergent handling and ICSI timings in the laboratory. Furthermore, hCG leads to gap junction closure within the cumulus oocyte complexes (COC) that may disrupt the important interaction of signals between the oocyte and the somatic cells in the follicle during the *in vitro* maturation phase. It has been suggested that impaired bidirectional communication within the follicle could compromise subsequent oocyte and embryonic developmental potential (Albertini and Barrett, 2003; Albuz *et al*., 2010).

Single or dual embryo transfer (ET) occurred on day 3 after ICSI, unless endometrial thickness was less than 6 mm on the day of transfer, in which case ET was cancelled, and all morphologically good quality embryos were vitrified ('freeze all policy'). Vitrified-warmed ET was performed in an ulterior artificial endometrial priming cycle with transdermal estradiol gel (Oestrogel®) and micronized vaginal progesterone (Utrogestan®, Besins).

Data analysis

Data relating to patient characteristics and endocrine parameters were prospectively collected. Only data from the first IVM cycle in the patient cohort were included. Among the parameters analysed to evaluate their contribution to oocyte yield, we included age, BMI, AFC, baseline (cycle day 3) serum AMH, FSH, estradiol (E_2), LH, progesterone and total testosterone concentration. Serum AMH levels were analysed with the Immunotech AMH enzyme immunoassay (Beckman Coulter, Marseilles, France).

Statistical analysis

For categorical variables, Fisher's exact test was used. Continuous variables did not show a normal distribution, and, therefore, Mann–Whitney *U*-test was performed.

The correlation between the aforementioned patient characteristics and endocrine parameters and the number of COC retrieved was assessed.

To establish a prediction model for oocyte yield in this study, we selected a cut-off at eight COC retrieved because this number of COC represents the average number of COC required to obtain at least one good quality embryo, based on the embryological data of this cohort (Table I) and based on previous studies (De Vos *et al*., 2011; Guzman *et al*., 2012).

Initially, Spearman's rank correlation coefficients and corresponding *P*-values were calculated for the candidate predictive variables and oocyte yield as the outcome parameter. Subsequently, a stepwise regression analysis was performed to identify which subset of variables offered the best prediction of oocyte yield. *P*-values for addition or deletion of a variable in the model were used in the forward and backward step with threshold values of 0.05 and 0.1, respectively. Generalized linear regression was used, whereby oocyte yield was modelled as a Poisson distributed variable, and a log link was applied. The frequency of oocyte retrievals with at least eight COC was modelled as a binomial variable and a logit link was applied. Finally, the model incorporating these variables was compared with a model incorporating only one of the explanatory variables by means of a likelihood ratio test.

All tests were performed using a two-sided *P*-value of 0.05 for statistical significance. All analyses were performed using pROC library from R 2.14.1 for Windows.

Results

Overall, data from 124 patients were included in the analysis. Forty-four patients had oligomenorrhoea and 80 patients had amenorrhoea. The median age of the participants was 28.3 ± 3.7 years. mean BMI was 25.7 ± 5.8 kg/m^2 and 12 patients had a history of smoking. The injected total dose of gonadotrophins was 408.8 ± 200.4 UI/ml, with an average duration of stimulation of 3.5 ± 2.1 days. Baseline patient characteristics and endocrine data are summarized in Table 2. The mean number of COC retrieved per cycle was 18.2 ± 13.8. Table 3 summarizes the comparative embryological data in the group with less than eight COC and at least eight COC available for IVM culture. Finally, to compare clinical outcomes between both groups, cumulative pregnancy rates after fresh ET and/or frozen ET were calculated. These results showed an ongoing pregnancy rate of 30.4% (24 out of 79) in the group with at least 8 COC available for IVM culture, compared with 11% (5 out of 45) in the group with less than 8 COC ($P = 0.01$, Table I).

The correlation between baseline parameters and oocyte yield was assessed using Spearman's rank correlation analysis; this analysis showed that BMI, baseline AMH, FSH, E_2, testosterone and AFC were significantly correlated with this outcome parameter (Table 4).

Independence of the variables correlating with oocyte yield was assessed using multivariate linear regression analysis according to a stepwise regression model. Unstandardized coefficients (95% CI) were 0.03 (0.02–0.03) ($P < 0.001$), 0.012 (0.008–0.017) ($P < 0.001$) and 0.37 (0.18–0.57) ($P < 0.001$) for AMH, AFC and testosterone, respectively. Maximum likelihood analysis revealed that the model to

Table I Cumulative clinical outcome per initiated cycle.

	Overall	Less than eight COC	At least eight COC	*P*-value
Patients	124	45	79	
Ongoing pregnancy rate after fresh ET	10% (8 out of 83)	11% (3 out of 27)	9% (5 out of 56)	0.711
Cumulative ongoing pregnancy rate (after fresh ET + FET)	23.4% (29 out of 124)	11% (5 out of 45)	30.4% (24 out of 79)	0.01
Mean number of embryos transferred (fresh ET)	1.17 ± 0.37	1.11 ± 0.32	1.20 ± 0.40	0.334
Mean number of embryos transferred (FET)	1.48 ± 0.46	1.50 ± 0.58	1.48 ± 0.45	0.952

ET, embryo transfer; FET, frozen embryo transfer.

Table II Baseline patient characteristics and serum hormone concentration at the start of the IVM cycle.

Variable	All patients Mean (SD)	Less than eight COC Mean (SD)	At least eight COC Mean (SD)	*P*-value
Patients	124	29	95	
Age (years)	28.3 (3.7)	29.4 (2.9)	28.0 (3.8)	0.051
BMI (kg/m^2)	25.7 (5.8)	24.1 (4.9)	26.2 (5.9)	0.109
Duration of infertility (years)	2.1 (1.9)	2.6 (2.3)	1.9 (1.8)	0.175
FSH (IU/l)	5.6 (1.6)	5.6 (1.9)	5.6 (1.5)	0.899
E_2 (ng/l)	46.7 (19.8)	43 (20)	48 (20)	0.102
LH (IU/l)	9.1 (5.3)	7.5 (5.0)	9.6 (5.4)	0.082
Progesterone (μg/l)	0.6 (0.3)	0.6 (0.2)	0.6 (0.3)	0.451
AMH (μg/l)	13.2 (9.5)	8.2 (3.7)	14.8 (10.1)	<0.001
Testosterone (mg/dl)	0.44 (0.22)	0.36 (0.15)	0.46 (0.23)	0.057
AFC	36.2 (16.3)	28.6 (15.0)	38.6 (16.1)	0.001

BMI, body mass index; FSH, follicle stimulating hormone; E_2, estradiol; LH, luteinizing hormone; AMH, anti-Müllerian hormone; AFC, antral follicle count. All serum hormonal values were baseline values (cycle day 2).

Table III Embryology development and clinical outcome per initiated cycle.

Variable	All patients	Less than eight COC	At least eight COC	*P*-value
Patients	124	29	95	
Mean number of COC retrieved per cycle	18.2 ± 13.8	5.0 ± 1.4	22.2 ± 13.3	<0.001[a]
Number of patients after COC donation[b]	124	45	79	
Mean number of COC available for IVM per cycle[b,c]	13.4 ± 9.9	4.8 ± 1.7	18.4 ± 9.2	<0.001[a]
Mean number of matured oocytes per cycle[b,c]	7.2 ± 5.4	3.0 ± 1.7	9.6 ± 5.3	<0.001[a]
Mean number of fertilized 2PN oocytes per cycle[b,c]	4.85 ± 4.1	2.2 ± 1.5	6.4 ± 4.3	<0.001[a]
Mean number of GQE per cycle[b,c]	2.19 ± 2.1	0.9 ± 0.9	2.9 ± 2.3	<0.001[a]
GQE rate per cycle	45% (271 out of 601)	43% (42 out of 98)	46% (229 out of 503)	0.658[d]
Cancellation rate	23 out of 124 (18.5%)	15 out of 45 (33.3%)	8 out of 79 (10%)[b]	<0.001[a]

IVM; *in vitro* maturation; COC, oocyte-cumulus complexes; PN, pronuclei; ET, embryo transfer; GQE, good quality embryo (embryo of good morphological quality); GQE rate, ratio of the number of good quality embryos over the number of matured oocytes; Cancellation rate = proportion of cycles with no good quality embryos available either for fresh ET or vitrification.
[a]Mann–Whitney *U*-test.
[b]A number of patients enrolled into this study donated a proportion of COC for translational IVM research (IWT-TBN 070719). In this study, 16 patients who had at least 8 COC after oocyte retrieval were transferred to the group of less than 8 COC because the number of COC available for IVM culture after subtraction of the COC donated for research was <8 COC.
[c]COC were donated for research.
[d]Fisher's exact test.

Table IV Intercorrelations using Spearman's rank correlation analysis of predictive variables with oocyte yield and predictive parameters.

Predicting parameters	Rho	*P*-value
Age (year)	−0.152	0.093
BMI (kg/m^2)	0.211	0.022
AMH (μg/l)	0.491	<0.001
FSH (IU/l)	−0.191	0.035
E2 (ng/l)	0.216	0.020
LH (IU/l)	0.152	0.095
Progesterone (μg/l)	0.064	0.484
Testosterone (mg/dl)	0.296	0.002
AFC	0.472	<0.001

BMI, body mass index; AMH, anti-Müllerian hormone; FSH, follicle stimulating hormone; E_2, estradiol; LH, luteinizing hormone; AFC, antral follicle count. All serum hormonal values included in the analysis were baseline values (cycle day 2).

Table V Multivariate linear regression analysis using stepwise regression model to predict COC yield or the probability to retrieve at least eight COC.

Model 1	Ln (COC yield) = 1.795 + 0.027 (AMH) + 0.013 (AFC) + 0.374 (testosterone)
Model 2	Logit (*P*) = −1.486 + 0.148 (AMH) + 0.034 (AFC)

AMH, anti-Müllerian hormone; AFC, antral follicle count. Model 1 = multivariate logistic regression model to predict COC yield in an IVM cycle. Model 2 = logistic regression model to predict the probability to have at least eight COC in a IVM cycle. Logit(*P*) log[*P*/(1−*P*)]; log = the natural logarithm; *P* = probability to obtain at least eight COC after oocyte retrieval, *P* is expressed on a scale of 0 −1.

predict oocyte yield based on baseline AMH, AFC and total serum testosterone was superior to a prediction based on AFC ($P = 0.015$) alone and baseline total testosterone ($P = 0.0071$) alone; however, this model was not significantly superior to baseline circulating AMH as a sole predictor ($P = 0.085$).

We went on to perform logistic regression analysis to demonstrate that a prediction model based on AMH and AFC, with unstandardized coefficients (95% CI) of 0.148 (0.03–0.25) ($P < 0.001$) and 0.034 (−0.003–0.07) ($P = 0.025$), respectively, can be used as a patient selection tool to predict the probability to obtain at least eight COC in a non-hCG-triggered IVM cycle in patients with PCOS (Table 5). To predict the capability of these predictive variables to discriminate between candidates for IVM who would have a COC yield of less than eight or at least eight COC, a receiver operating characteristic (ROC) curve analysis was performed for each of the parameters that had been found to be significantly correlated with oocyte yield in the logistic regression model (Fig. 1). The ROC curve for baseline AMH as a sole predicting parameter of oocyte yield resulted in an area under the curve (AUC) of 0.7448 (95% CI = 0.655–0.835), and the ROC curve for AFC resulted in an AUC of 0.7139 (95% CI = 0.6021–0.826). The combined ROC curve analysis for these two predictive variables resulted in an AUC of 0.7864 (95% CI = 0.6997–0.8732).

Discussion

This study is, to our knowledge, the first trial that investigates the combined predictive potential of markers of ovarian follicular reserve and other parameters with regard to immature oocyte yield for IVM in patients with PCOS. Previous reports have shown that in IVM cycles, the number of available oocytes is strongly correlated

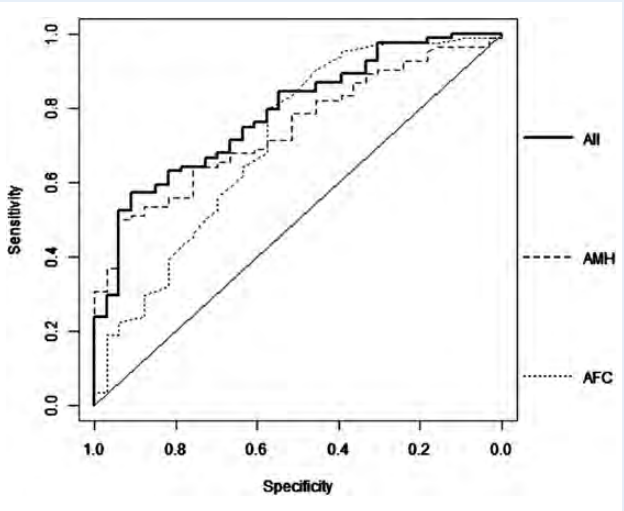

Figure 1 ROC curve analysis for total number of COC collected per oocyte retrieval. AUC, area under the curve. Model 2 AUC = 0.7864; AMH-AUC = 0.7448; AFC-AUC = 0.7139.

with treatment outcome (Child *et al*., 2001; Mikkelsen *et al*., 2001; Tan and Child, 2002; Child *et al*., 2002a; Child *et al*., 2002b; Fadini *et al*., 2009). Although there is a substantial body of published literature about potential predictors of successful IVM outcome, including baseline serum FSH, E_2, inhibin A levels, AFC, BMI and circulating AMH (Mikkelsen *et al*., 2000; Child *et al*., 2001; Mikkelsen *et al*., 2001; Tan and Child, 2002; Child *et al*., 2002b; Fadini *et al*., 2009; Shalom-Paz *et al*., 2011), no study has evaluated the predictive ability of a model that incorporates these variables in patients with PCOS.

In a retrospective study including 87 oocyte retrievals with normal regular cycles, Mikkelsen *et al*. reported higher pregnancy rates in cycles with a low serum estradiol level of < 200 pmol/l and low inhibin A serum levels of < 10 pg/ml (Mikkelsen *et al*., 2000), although no such correlation was found in a study by Child *et al*., who used 100 pmol/l as a threshold for estradiol (Child *et al*., 2002b). In the latter study, multiple regression analysis was performed to identify basal serum FSH concentration as a significant independent prediction parameter for the number of immature oocytes collected, although no conclusions could be drawn with regard to pregnancy rate. In another retrospective study encompassing 116 hCG-triggered IVM cycles in patients with PCOS, no correlation was found between BMI and the number of oocytes collected, or with pregnancy rate (Shalom-Paz *et al*., 2011). Our data demonstrate a positive correlation between BMI and oocyte yield, although when incorporated into a multivariate linear regression model, BMI appears not to be a predictor of oocyte yield.

The study by Fadini *et al*. demonstrated that circulating AMH levels are predictive of the number of oocytes obtained in regularly cycling women without PCO/PCOS (Fadini *et al*., 2011). The data from our study consolidate the role of AMH as a predictive parameter of oocyte yield in patients with PCOS, who constitute the main target population for IVM. However, our study demonstrates that a superior prediction model is obtained when AFC is added as a predictive parameter that may seem to contradict common knowledge that AFC and AMH are highly correlated factors and often used alternatively. It is generally accepted that AMH and AFC provide similar information as predictors of ovarian response to gonadotrophin stimulation, also in patients with PCOS (Nardo *et al*., 2009). However, in the setting of IVM cycles, where ovarian stimulation is minimal and, hence, 'ovarian response' to gonadotrophins is limited, it may not be unreasonable to assume that AMH and AFC could behave differently as predictors of immature oocyte yield in minimally stimulated IVM cycles, although this hypothesis merits further scrutiny.

Embryological data in our study are consistent with a significantly higher number of embryos of good morphological quality in the group with at least eight COC available for IVM culture and with a lower risk of cycle cancellation due to absence of an embryo suitable for ET. Nevertheless, maturation rate and fertilization rate (data not shown) and number of good quality embryos per zygote were similar in both groups (Table 3), which suggests that the proportion of developing embryos of good quality was similar in both groups and also implies that a higher absolute number of COC available for IVM culture results in significantly more embryos of good morphological quality (2.9 ± 2.3 versus 0.9 ± 0.9, $P = 0.001$). As a result, the major advantage of having at least eight COC available for IVM culture, as reflected by a statistically higher cumulative pregnancy rate in that group (shown in Table 1), is based on the additional transfer of supernumerary embryos.

The prediction model described here has a limitation, in that oocyte yield in a IVM system does not only depend on patient parameters. After appropriate patient selection, oocyte retrieval may also depend on parameters related to the specific IVM system used such as aspiration pressure, needle type, aspiration technique, on the operator's learning curve and on whether or not hCG-triggering is used. Optimization of the oocyte retrieval procedure could certainly enhance oocyte recovery rates, which is crucial to fully exploit the potential oocyte yield, predicted by our model. With current IVM techniques, implantation rates are still low when compared with ART after controlled ovarian gonadotrophin stimulation (Son and Tan, 2010). Since the introduction of IVM in human ART, researchers have been working towards an improvement of the clinical and laboratory aspects of IVM; this has resulted in divergent IVM systems, ranging from genuine IVM without hormonal priming, to several modalities of gonadotrophin-primed IVM, including hCG triggering. The lack of a standardized IVM system and the heterogeneity of the patient population to whom IVM is offered have been major impediments to the evidence-based validation of IVM. Nevertheless, the selection of patients suitable for IVM is key to the further development of the technology, irrespective of the IVM culture system itself. Therefore, the role of parameters that can predict IVM outcome merits considerable attention. With the current study, we have established for the first time that in patients with PCOS, a model based on AMH and AFC, parameters reflecting antral follicular abundance, facilitates the selection of patients who have an increased probability to achieve ET and pregnancy after non-hCG-triggered IVM treatment.

In conclusion, according to our results, it appears that AMH and AFC are the only independent predictive parameters of COC yield for IVM treatment in patients with PCOS. When combined in a multivariate model, these parameters have a strong predictive potential (AUC = 0.7864) for COC yield and could be used to guide the patient selection process for IVM.

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Authors' roles

L.G. drafted the manuscript, participated in the study design, performed data analysis and executed the IVM culture procedure; C.O.H. undertook patient recruitment and management and provided data interpretation; N.P.P. participated in the study design, performed data analysis and corrected the manuscript; E.A. supervised the hormonal assays and corrected the manuscript; W.C. performed statistical data analysis; H.T. revised the final version of the manuscript; P.D. supervised the clinical activities and revised the final version of the manuscript; G.V. supervised the laboratory activities; J.S. supervised the laboratory activities, reviewed and edited the manuscript and is the principal investigator of the oocyte maturation project; M.D.V. performed patient recruitment and management, supervised the clinical activities and revised the manuscript.

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Conflict of interest

None declared.

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