Original Article

Prediction of Reproductive Outcomes of Intracytoplasmic Sperm Injection Cycles Using a Multivariate Scoring System

Ahmed Abuelsoud Abden, Momen Ahmed Kamel, Ahmed Nabil Fetih, Ali Haroun Yousef

Department of Obstetrics and Gynecology, Faculty of Medicine, Assiut University, Asyut, Egypt

Abstract

Background: Prediction of *in vitro* fertilisation (IVF)/intracytoplasmic sperm injection (ICSI) success is crucial in counselling patients about their real chance of getting a live birth before commencing treatment. A multivariate scoring system proposed by Younis *et al*., 2010, was amongst the predictive models used to evaluate IVF/ICSI success. The score entitles basal endocrine, clinical and sonographic parameters. **Aims:** The objective of this study is to assess the predictability of the Younis multivariate score for pregnancy outcomes in ICSI cycles. **Settings and Design:** This prospective observational cohort study (NCT03846388) included patients who pursued IVF or ICSI in a tertiary infertility unit between February 2019 and December 2021. **Materials and Methods:** The score variables were age, body mass index, antral follicle count, basal follicle-stimulating hormone (FSH), basal FSH/luteinising hormone ratio, infertility duration, number of previous cancellations and mean ovarian volume. For each woman included in the study, Younis multivariate score was calculated. Then, we correlate the different reproductive outcomes with score levels to validate the score predictability. A score of ≤14 was defined as a low score based on the previous study's results. **Statistical Analysis Used:** The student's *t*-test and Mann–Whitney test were used to compare numerical variables, whereas categorical variables were analysed using the Chi-square test. A receiver operating curve (ROC) and a multivariate logistic regression model were used to investigate the predictability of the Younis scoring model for cycle outcomes. **Results:** Two hundred ninety-two ICSI-ET cycles were analysed. Of the total cohort, 143 (48.97%) women included showed a low score (≤14), whereas 149 (51.03%) women showed a high score (>14). Women with low scores had significantly higher pregnancy and live birth rates compared to women with high scores (60.1% vs. 7.4%, respectively, $P < 0.001$; 44.7% vs. 6.7%, respectively, $P < 0.001$). The area under the curve (AUC) in the ROC curve analysis showed a higher predictability for the scoring system for live birth rate with an AUC of 0.796, with a sensitivity of 86.5% and specificity of 63.8% when using a cut-off level of ≤14. For pregnancy prediction, the AUC was 0.829, with a sensitivity of 88.66% and a specificity of 70.77% when using the same cut-off. Women who have a low score have a high chance of having frozen embryos. Likewise, women who have a high score have a very high chance of cycle cancellation. **Conclusions:** The Younis multivariate score can be used for the prediction of ICSI cycle outcomes and to calculate the chance of cycle cancellation, pregnancy and take-home baby before ICSI.

Keywords: *Cycle cancellation, intracytoplasmic sperm injection, live birth, Younis multivariate score*

Received: 07-01-2024 **Revised:** 03-03-2024
Accepted: 03-03-2024 **Published:** 28-03-2024

Access this article online

Quick Response Code:

Website: www.jhrsonline.org

DOI: 10.4103/jhrs.jhrs_4_24

Address for correspondence: Dr. Ahmed Abuelsoud Abden, Department of Obstetrics and Gynecology, Faculty of Medicine, Assiut University, Asyut, Egypt.
E-mail: dr_ahmedabo22@yahoo.com

How to cite this article: Abden AA, Kamel MA, Fetih AN, Yosef AH. Prediction of reproductive outcomes of intracytoplasmic sperm injection cycles using a multivariate scoring system. J Hum Reprod Sci 2024;17:33-41.

Introduction

Because assisted reproductive technology is costly and time-consuming, finding a method to predict the success of assisted reproductive technology (ART) is crucial in counselling the patients about their real chance of getting a live birth before they start ART cycles.[1,2] Many predictors have been evaluated by many authors in the past few years.[3] Sperm parameters, oocyte quality and endometrial receptivity were the most frequently studied predictors of ART success. Oocyte quality is directly related to the woman's age and ovarian reserve.[4]

Hormonal and ultrasound ovarian reserve tests are available in most ART centres. They are inexpensive and can be easily performed before starting ART therapy.[5] The woman's age, antral follicle count (AFC) and laboratory tests (serum anti-Mullerian hormone [AMH], basal follicle-stimulating hormone [FSH], estradiol and inhibin levels) were amongst the frequently investigated cycle parameters in predicting ovarian response and cycle outcomes.[5,6] Serum AMH was found to have more predictability than FSH in assessing ovarian reserve amongst all age groups.[7] Combining the aforementioned markers with other patients' demographics and treatment response, information was elaborated on some prediction models to provide a more prognostic guide for infertility providers and endorse patient counselling.

In recent years, many scores have been tested for predicting *in vitro* fertilisation (IVF)/intracytoplasmic sperm injection (ICSI) success for each specific couple according to certain parameters that create what is called a 'multivariate score'. One of these proposed scores was the multivariate score of Younis *et al*.,[8] which involves basal endocrine, clinical characteristics and some sonographic parameters. This score showed good predictability for low ovarian reserve, implantation and pregnancy outcomes in IVF cycles.[8] The authors concluded that a cumulative score >14 was more accurate in predicting low ovarian reserve than age, AFC or day-3 FSH level separately. We conducted this prospective study to further evaluate this multivariate score prediction for the IVF reproductive outcomes.

Materials and Methods

Study design

We conducted this prospective cohort study in a tertiary infertility unit according to the Helsinki Declaration. The study was approved by the Assiut University Medical Ethical Committee, and consent was obtained from all participants before recruitment. The study was registered at ClinicalTrials.gov under the NCT number (NCT03846388) and received a local IRB approval under number 17200297 on June 28 (2019). The study included patients who pursued IVF/ICSI from February 2019 to December 2021.

Study objectives

The objective of this study is to assess the predictability of the Younis multivariate score for different reproductive outcomes in ICSI cycles.

Study subjects

The present study enrolled patients who were 20–40 years old and had a body mass index (BMI) of 18–35 kg/m^2. Patients should have normal thyroid-stimulating hormone and prolactin levels before commencing IVF stimulation. Cases with abnormal uterine cavity evident by hysterosalpingography (HSG) or hysteroscopy were excluded. The study did not include cycles with surgically retrieved sperms.

Sample size calculation

For sample size calculation, we used data from the Younis *et al.* study to compare the pregnancy rate in women with high scores and those with low scores (A score of ≤14 was defined as a low score based on the previous study's results). We assumed that the difference in pregnancy rate between the group of low-score and high-score group was 27% (38% vs. 11%), respectively. Using the OpenEpi program (version 3.01) (www.OpenEpi.com), the sample size was calculated to be 60 cases for the first group and 60 cases for the second group with an adjusting alpha error at 0.05 and the power at 90%. We assumed that there may be different baseline demographic and clinical characteristics in our study and that one of Younis *et al*. Therefore, we thought to increase the power of the study and sample size to account for this point that may affect the study results. The sample involved eligible women in our centre from February 2019 to December 2021.

Table 1: The Younis multivariate score

	1	2	3	4	5
BMI (kg/m^2)	<30	>30			
Number of previous cancellations	1	2			
Infertility duration (years)	<2	2–10	>10		
Mean ovarian volume (cm^3)	>10	5–10	<5		
Basal FSH/LH ratio	<2	2–4	>4		
Basal FSH (IU/L)	<6	6–8	8–12	12–15	>15
AFC	>12	10–12	7–9	4–6	<3
Age (years)	<25	26–30	31–35	36–40	>41

BMI=Body mass index, FSH=Follicle-stimulating hormone, LH=Luteinising hormone, AFC=Antral follicle count

The study protocol

The Younis multivariate score [Table 1] includes baseline clinical characteristics such as age, BMI, duration of infertility and number of previous cycle cancellation due to poor ovarian response. Similarly, assessment of basal FSH, FSH/luteinising hormone (LH) ratio and ovarian reserve parameters such as AFC, total and mean ovarian volume.[8] For each woman included in the study, Younis multivariate score was calculated.

The determination of the starting gonadotropin dose was based on ovarian reserve markers, age, BMI and data of previous IVF stimulation in patients who have previous trials. At our centre, we usually use either conventional long GnRH-agonist or flexible GnRH-antagonist protocols. Ovulation triggering was performed with either 10,000 IU human chorionic gonadotropin (HCG) (Choriomon, IBSA, Switzerland) or two injections of 250 µg recombinant HCG (Ovitrelle; EMD Serono, Canada) when ≥3 follicles achieved a mean diameter of ≥17 mm. In cases with a risk of ovarian hyperstimulation syndrome (OHSS), GnRHa triggering was used with the administration of three ampoules of GnRHa (Triptofem 0.1 mg, Ferring, Switzerland). Thereafter, ICSI was done for the retrieved eggs using husband's sperms only. Regarding laboratory details, we used Thermo Forma Series 2 triple gas for incubation with the following settings temperature 37, O2 5% and CO2 6%. Single-step culture media (Global total) was used. Luteal phase support was performed with combining intramuscular and vaginal progesterone (Prontogest 100 mg IM, IBSA, Switzerland; 400 mg vaginal supp., IBSA, Switzerland) for 14 days till the pregnancy test was done. Cases received GnRHa trigger in which oestrogen was added to progesterone for luteal support. Transfer of a maximum of three best-quality embryos on day 3, day 4 or day 5 according to the number and quality of the available embryos. Good-quality embryos were defined according to Volpes *et al*.[9] as those achieving eight cell stages on day 3 with <20% fragmentation. Similarly, good-quality day 4 embryos were either embryos with early blastulation or compacted morula.[10] On the other hand, the modified Gardner score was the selected model for day 5 embryo grading.[11] Then, we correlate the different reproductive outcomes (pregnancy rate, live birth rate, cycle cancellation possibility and chance of having frozen embryos) with score levels to validate the score predictability.

Study outcomes

The main study's outcome was the live birth that was defined as the number of patients with a living neonate delivered at ≥20 weeks of gestation per 100 initiated cycles.[12] The secondary outcomes included clinical pregnancy rates, implantation and cycle cancellation rates. Clinical pregnancy was defined as the number of patients with positive foetal heart pulsations detected by transvaginal ultrasound 4 weeks after embryo transfer divided by the number of initiated cycles per 100.[12] Implantation rate was estimated as the number of gestational sacs observed, divided by the total number of transferred embryos,[12] whereas cycle cancellation rate was the percentage of patients who did not pursue ET.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS Statistics for Windows, version 21.0; SPSS Inc., Chicago, IL, USA) The Student's *t*-test was used to compare numerical variables that were expressed as mean standard deviation. On the other hand, categorical variables were presented in numbers (percentages) and analysed using the Chi-square test. We used the Kolmogorov–Smirnov test to detect the variable's distribution normality. The normally distributed variables were compared by the Student's *t*-test, whereas the skewed ones were analysed using the Mann-Whitney test. We utilised the receiver operating curve (ROC) to investigate the predictability of the Younis score model for cycle outcomes. A multivariable logistic regression model was developed to account for the impact of other confounding cycle factors (AMH level and gonadotropin dose) on the probability of live birth. We did the multivariate regression model including AMH level, gonadotropin dose and the Younis score which has been created from the other cycle parameters such as (age, FSH, infertility duration and ovarian volume). To investigate the predictive value of the Younis score according to the ovarian reserve profile, we had classified the patients according to their anticipated ovarian response based on AMH level using AMH level of 1.2 ng/ml according to Bologna criteria[13] as the cut-off level to discriminate poor reserve (<1.2 ng/ml) and good ovarian reserve (≥1.2 ng/ml). Binary logistic regression for the Younis score and negative cycle outcomes in both ovarian reserve groups was performed. Moreover, we have combined AMH to the Younis score and created a modified score. First, we classified AMH to five percentile categories; 0–25th, 25–50th, 50–75th, 75–90th and >90th percentiles. The pregnancy outcomes were examined in each category and give scores to each category based on its rank on pregnancy rate [Table 2]. Thus, the group with the highest pregnancy rate was scored as 1 and the group with the lowest pregnancy rate was scored as 5 and assigned it as the modified multivariate score [Table 3].

Results

Our study involved the analysis of 292 ICSI cycles. The baseline demographics and clinical characteristics are shown in Table 4. Antagonist protocol was performed in 87.3%, and 12.7% of cycles were stimulated with the long GnRH-agonist protocol. Ovulation triggering was performed by HCG trigger in all cases except in 23 (7.9%), who pursued triggering by GnRHa due to the risk of OHSS. Twenty-nine cycles (9.9%) did not receive triggering due to poor response, in which the expected number of eggs was <2 according to our centre's policy. The cycles were not completed, and embryo transfer was abandoned in 39 women (13.4%), and the causes of this cancellation are expressed in Table 5.

Of the total cohort, 143 (48.97%) women included showed a low score (≤14), whereas 149 (51.03%) women showed a high score (>14). The cause of infertility and stimulation protocol was comparable amongst both groups. However, the triggering type was different with the HCG trigger almost exclusively used in the high score group (99.2%) compared to 84.6% in the low score group, $P < 0.001$. This can be explained by the fact that it was rare to use GnRHa trigger in the high score group due to the scarce incidence of OHSS risk. Women with a low score received a significantly lower total gonadotropin dose and had a significantly higher number of pre-ovulatory follicles, mature oocytes, good-quality embryos and a higher chance of having additional embryos for freezing. Similarly, women with low scores had significantly higher pregnancy and live birth rates compared to women with high scores (60.1% vs. 7.4%, $P < 0.001$; 44.7% vs. 6.7%, $P < 0.001$) [Table 6].

The area under the curve (AUC) in the ROC curve analysis showed a higher predictability for the scoring system for live birth rate with an AUC of 0.796, with a sensitivity of 86.5% and specificity of 63.8% when using a cut-off level of 14 [Figure 1]. For pregnancy prediction, the AUC was 0.829, with a sensitivity of 88.66% and a specificity of 70.77% when using the same cut-off [Figure 2]. Similarly, women who have a high score have a very high chance of cycle cancellation, with a sensitivity of 89% and a specificity of 86% when using a cut-off level of 17 [Figure 3]. Women who have a high score have a high chance of having frozen embryos, with a sensitivity of 76% and specificity of

Table 2: Anti-Mullerian hormone percentile categories and pregnancy rate

AMH level	Pregnancy rate, *n* (%)	Mark in the modified score
<1.2 (0–25th percentile)	13/66 (19)	5
1.2–2.09 (25th–50th percentile)	22/75 (29)	4
2.1–3.69 (50th–75th percentile)	34/75 (45)	1
3.7–6.6 (75th–90th percentile)	21/55 (38)	2
≥6.6 (≥90th percentile)	7/21 (33)	3

AMH=Anti-Mullerian hormone

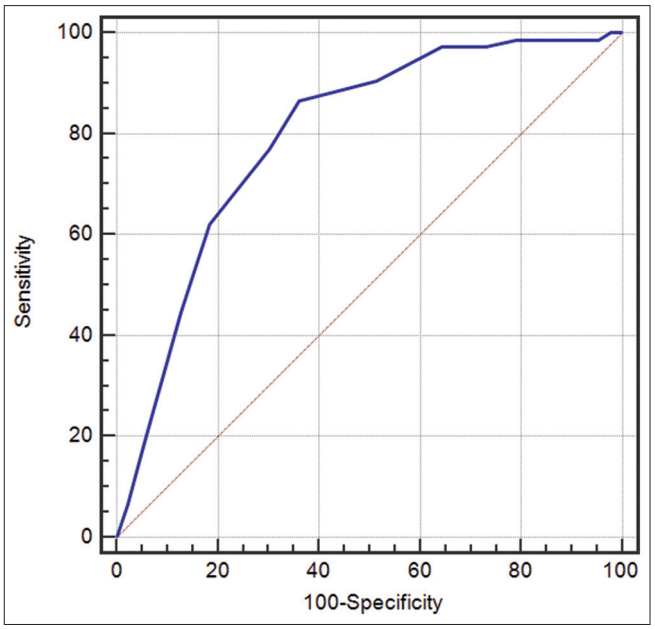


Figure 1: Receiver operating curve for Younis score in live birth predictability

Table 3: The modified multivariate score

	1	2	3	4	5
BMI (kg/m^2)	≤30	>30			
Number of previous cancellations	1	2			
Infertility duration (years)	≤2	2–10	>10		
Mean ovarian volume (cm^3)	>10	5–10	≤5		
Basal FSH/LH ratio	≤2	2–4	>4		
Basal FSH	≤6	6–8	8–12	12–15	>15
AFC	>12	10–12	7–9	4–6	≤3
Age (years)	≤25	26–30	31–35	36–40	>41
AMH (ng/mL)	2.1–3.69	3.7–6.59	≥6.6	1.2–2.09	<1.2

BMI=Body mass index, FSH=Follicle-stimulating hormone, LH=Luteinising hormone, AMH=Anti-Mullerian hormone, AFC=Antral follicle count

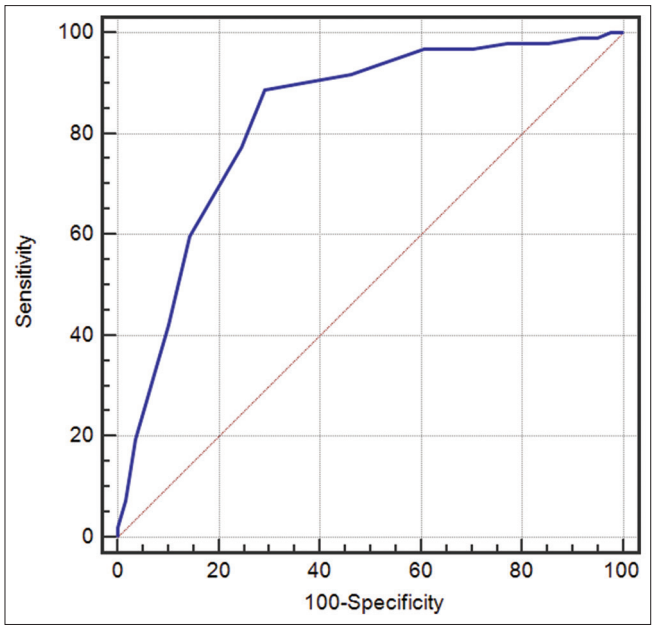


Figure 2: Receiver operating curve for Younis score in pregnancy predictability

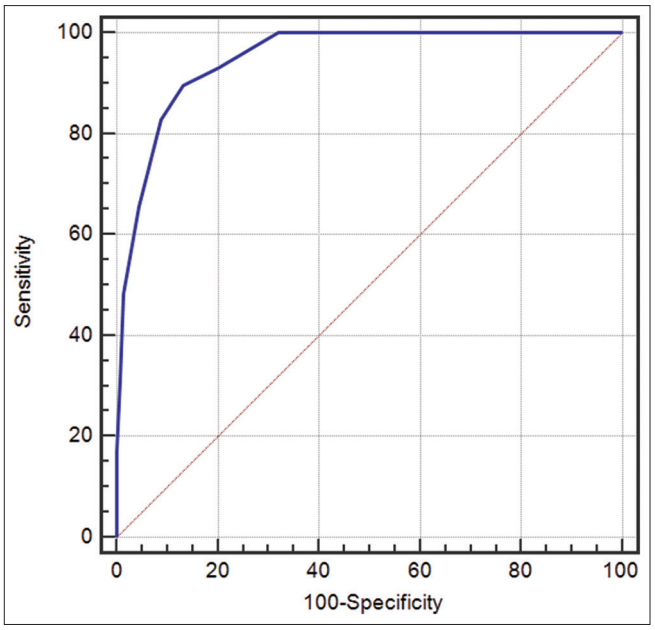


Figure 3: Receiver operating curve for Younis score in cycle cancellation predictability

Table 4: Baseline clinical characteristics

Cycle variables	Mean±SD/*n* (%)
Age (years)	31.29±4.98
BMI (kg/m^2)	31.03±3.93
Infertility duration (years)	7.51±3.97
FSH (IU/L)	6.36±3.60
LH (IU/L)	3.98±2.85
FSH/LH ratio	1.95±1.16
AMH (ng/mL)	2.71±2.16
Basal AFC	11.03±5.21
Basal mean ovarian volume (cm^3)	5.71±2.25
Cause of infertility	
Male	95 (32.5)
Unexplained	86 (29.5)
Ovarian	62 (21.2)
Tubo-peritoneal	29 (9.9)
Combined	20 (6.9)
Type of infertility	
Primary	255 (87.3)
Secondary	37 (12.7)

BMI=Body mass index, FSH=Follicle-stimulating hormone, LH=Luteinising hormone, AMH=Anti-Mullerian hormone, AFC=Antral follicle count, SD=Standard deviation

84% when using a cut-off level of 13 [Figure 4 and Table 7].

The Younis score model's predictability of live birth rates was still strong despite being adjusted to AMH level and gonadotropin dose, as shown by the multivariate logistic regression analysis model (odds ratio 95% confidence interval; 1.885 [1.599–2.222], $P < 0.001$) [Table 8]. The results of Younis score prediction for cycle outcomes according to ovarian response categories are illustrated in Tables 9 and 10. The score was shown to have a good predictive value in both ovarian response categories.

Regarding the modified score, the ROC analysis for the predictive value of the new score to pregnancy outcome showed a comparable predictability to the old Younis score as shown in Table 11. The AUC in the ROC curve analysis showed a high predictability for the new scoring system for pregnancy with an AUC of 0.789, with a sensitivity of 83.5% and specificity of 61.5% when using a cut-off level of 17.

Our data clearly show that age, basal AFC and mean ovarian volume are the most significant independent variables that predict the pregnancy rate of infertile women in ICSI cycles. The ROC AUC for the three variables was comparable, corresponding to 0.67, 0.73 and 0.76, respectively [Supplementary Table 1 and Supplementary Figures 1-3]. Other less significant independent variables were also found to predict pregnancy rates. These include BMI, infertility duration, FSH, FSH/LH ratio and AMH with ROC AUCs, corresponding to 0.59, 0.65, 0.61, 0.62 and 0.60, respectively [Supplementary Table 1 and Supplementary Figures 4-8].

Discussion

The Younis score variables were age, BMI, AFC, basal FSH, basal FSH/LH ratio, infertility duration, number of previous cancellations and mean ovarian volume. The Younis multivariate score was shown to have a

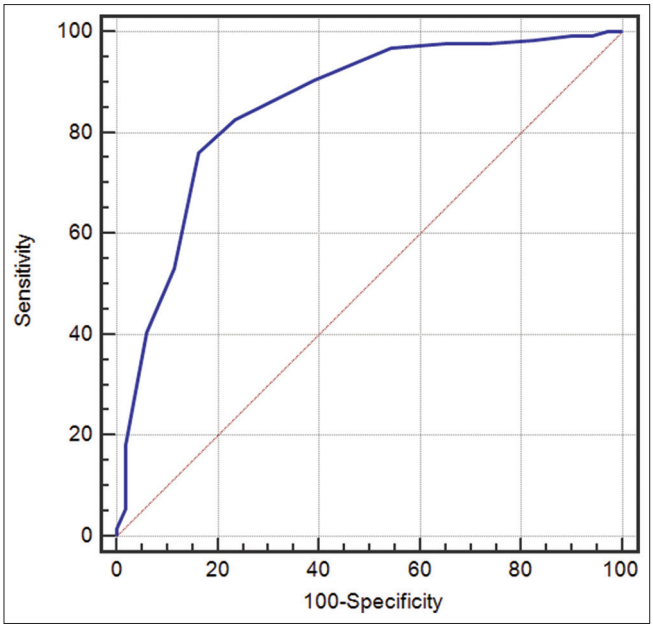


Figure 4: Receiver operating curve for Younis score in chance of having frozen embryos predictability

high predictability for reproductive outcomes in infertile women undergoing ART. It can be used in the prediction of cycle cancellation possibility, chance of having frozen embryos, pregnancy and take-home baby in couples undergoing ICSI.

The prediction of IVF outcomes is of utmost importance in patients' counselling about their anticipated success rate. Infertile women may also interested to know before starting the first IVF/ICSI treatment cycle whether they have a high or low chance of having a live birth using ART. Younis' study included 168 women, but in our study, prospectively, we included 292 women undergoing ICSI. Our study differed from Younis' study in that we examined the score as a predictor of taking home a baby, the possibility of having frozen embryos and the possibility of cycle cancellation. The ROC curve revealed that the Younis multivariate score at a cut-off value of 14 showed high predictability for pregnancy and take-home baby in women who underwent IVF/ICSI with an AUC of 0.829 and 0.796, respectively.

Several reports combined sonographic and hormonal ovarian reserve parameters for pregnancy prediction and assessment of ovarian reserve.[14-16] A prospective study conducted by Bancsi *et al*.,[14] which included 120 women who pursued their first-ranked IVF cycle, concluded that AFC is more accurate than age and hormonal parameters in predicting poor response during controlled ovarian stimulation (COS). The study evaluated the ovarian reserve using basal total ovarian volume, AFC, FSH, E2 and inhibin-B. It is noteworthy to mention that the separate or combined use of AFC, inhibin B and FSH did not show

Table 5: Intracytoplasmic sperm injection cycle outcomes

	n (%)
Stimulation protocol	
GnRH-antagonist	255 (87.3)
Long GnRH-agonist	37 (12.7)
Type of trigger	
HCG	240 (82.2)
Agonist trigger	23 (7.9)
No trigger (poor ovarian response)	29 (9.9)
Completed cycles (embryo transfer done)	253 (86.6)
Cancelled cycles (no embryo transfer done)	39 (13.4)
Poor ovarian response (<2 follicles)	29 (9.9)
Severe OHSS	2 (0.68)
Empty follicle syndrome	2 (0.68)
Fertilization failure	4 (1.37)
Poor quality embryos	2 (0.68)
Embryo cryopreservation	126 (43.1)
Implantation rate	14.5
Pregnancy rate	
Per initiated cycle (*n*=292)	97 (33.2)
Per embryo transfer (*n*=253)	97 (38.3)
Live birth rate	74 (25.3)
Type of pregnancy (*n*=97)	
Singleton	76
Twins	19
Triplet	2

GnRH=Gonadotropin releasing hormone, HCG=Human chorionic gonadotropin, OHSS=Ovarian hyperstimulation syndrome

a reliable prediction for pregnancy.[14] In the present study, from the ROC curve analysis of our results, it is apparent that AFC, ovarian volume mean and FSH show a reliable prediction for pregnancy [Supplementary Table 1 and Supplementary Figures 2, 3 and 6]. Delta inhibin level was not measured in the current study.

Another report by Erdem *et al*.[15] investigated the use of AFC, inhibin-B, basal FSH, the clomiphene citrate challenge test and mean ovarian volume in a small sample (56 patients). Ovarian volume was the best single predictor for ovarian reserve, with an AUC of 0.82 in the ROC analysis. Compared to ultrasound and endocrine reserve markers, the age was the only independent predictor of pregnancy.[15] The present study clearly showed that age, AFC and mean ovarian volume are the most significant independent variables that predict pregnancy in ICSI cycles [Supplementary Table 1].

Similarly, a retrospective study by Muttukrishna *et al*.[16] on 81 women assessed using AFC, FSH, AMH and inhibin-B. They defined low ovarian reserve as ≤4 retrieved oocytes. Delta inhibin-B was calculated as the level of inhibin-B on day 4 minus day 3. Delta inhibin was found to be the most accurate predictor for

Table 6: Clinical characteristics and cycle outcomes in groups with low ≤14 and high (>14)

	Low score (*n*=143)	High score (*n*=149)	*P*
Age (years)	28.69±4.49	33.79±4.06	**<0.001**
BMI (kg/m^2)	30.06±4.31	31.96±3.28	**<0.001**
Infertility duration (years)	5.80±2.99	9.15±4.11	**<0.001**
FSH (IU/L)	5.16±2.03	7.52±4.34	**<0.001**
LH (IU/L)	4.02±2.57	3.95±3.09	**0.251**
FSH/LH ratio	1.51±0.72	2.36±1.33	**<0.001**
AMH (ng/mL)	3.74±2.31	1.72±1.41	**<0.001**
Basal AFC	14.73±4.24	7.47±3.17	**<0.001**
Basal mean ovarian volume (cm^3)	7.30±1.78	4.18±1.46	**<0.001**
Endometrial thickness (mm) (at day of trigger)	9.77±1.81	8.25±1.67	**<0.001**
Dose of gonadotropins (units)	2960.31±868.56	3956.61±1231.82	**<0.001**
Stimulation days	11.41±1.37	10.98±2.18	**0.044**
Preovulatory follicles	15.11±5.67	8.13±3.73	**<0.001**
Retrieved oocytes	14.86±6.37	7.54±3.88	**<0.001**
Mature oocytes	12.13±5.63	5.92±3.28	**<0.001**
Fertilization rate (%)	72±14	63±22	**0.006**
Good-quality embryos	6.99±3.60	2.92±2.15	**<0.001**
Embryo cryopreservation	104 (72.7)	22 (14.8)	**<0.001**
Pregnancy rate	86 (60.1)	11 (7.4)	**<0.001**
Live birth rate	64 (44.7)	10 (6.7)	**<0.001**
Cause of infertility			
Unexplained	48 (33.6)	38 (25.5)	0.277
Male	42 (29.4)	53 (35.6)	
Ovulatory	29 (20.3)	33 (22.1)	
Tubo-peritoneal	12 (8.4)	17 (11.4)	
Combined	12 (8.4)	8 (5.4)	
Protocol			
GnRH-antagonist	126 (88.1)	129 (86.6)	0.694
LongGnRH-agonist	17 (11.9)	20 (13.4)	
Trigger			
HCG	121 (84.6)	119 (99.2)	**<0.001**
Agonist	22 (15.4)	1 (0.8)	

Significant *P* value is presented as bold. Numerical data are presented as mean±SD and compared with Student's *t*-test. Categorical data are presented in *n* (%) and analysed by the Chi-square test. BMI=Body mass index, FSH=Follicle-stimulating hormone, LH=Luteinising hormone, AMH=Anti-Mullerian hormone, AFC=Antral follicle count, HCG=Human chorionic gonadotropin, SD=Standard deviation

Table 7: Predictability of score model for cycle reproductive outcomes

	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC
Pregnancy prediction	≤14	88.66	70.77	60.1	92.6	0.829
Live birth prediction	≤14	86.49	63.76	44.8	93.3	0.796
Cycle cancellation possibility	>17	89.66	86.69	42.6	98.7	0.949
Chance of having frozen embryos	≤13	76.19	83.73	78.0	82.2	0.853

PPV=Positive predictive value, NPV=Negative predictive value, AUC=Area under the curve

Table 8: Multivariate binary logistic regression analysis model

	95% CI	*P*
AMH	1.267 (1.056–1.519)	**0.011**
Score (≤15)	1.885 (1.599–2.222)	**<0.001**
Dose of gonadotropin	1.000 (0.999–1.000)	0.142
Constant	0.000	**0.001**

Significant *P* value is presented as bold. AMH=Anti-Mullerian hormone, CI=Confidence interval

oocytes retrieved, followed by basal AMH and AFC. A cumulative score involving patient's age, basal AMH, basal FSH, AFC, delta E2 and delta inhibin was the best predictor for poor ovarian response with a ROC AUC of 0.9, 87% sensitivity and 80% specificity. However, these parameters did not show a reliable prediction of pregnancy.[16] The present study clearly showed that age, basal AMH, basal FSH, AFC and mean ovarian volume

Table 9: Binary logistic regression for the Younis score and negative cycle outcomes in poor ovarian reserve group (<1.2)

	OR 95% CI	*P*
Negative live birth	1.590 (1.186–2.133)	0.002
Negative pregnancy	1.520 (1.169–1.978)	0.002
Negative embryo freezing	1.502 (1.137–1.983)	0.004

CI=Confidence interval, OR=Odds ratio

Table 10: Binary logistic regression for the Younis score and negative cycle outcomes in average and high ovarian reserve group (≥1.2)

	OR 95% CI	*P*
Negative live birth	1.580 (1.355–1.843)	<0.001
Negative pregnancy	1.762 (1.500–2.069)	<0.001
Negative embryo freezing	1.723 (1.486–1.999)	<0.001

CI=Confidence interval, OR=Odds ratio

Table 11: The modified score prediction for pregnancy outcome

	Cut-off	Sensitivity	Specificity	+PV	−PV	AUC
Score	≤17	83.51	61.54	51.9	88.2	0.789

PPV=Positive predictive value, NPV=Negative predictive value, AUC=Area under the curve

show a reliable prediction of pregnancy [Supplementary Table 1]. Delta inhibin level was not measured in the current study.

The relatively small number of women included was a common limitation of the previously mentioned three studies.[14-16] In addition, two studies[15,16] included a dynamic test, and only one study[15] included age as a part of the multivariate model. All indices included in the three studies[14-16] were not reliable predictors of pregnancy.

The Younis score does not include measuring delta inhibin-B. Therefore, we could not assess the value of this parameter in predicting cycle outcomes. The advantage of the investigated Younis score is its simplicity and feasibility. It does not include expensive ovarian reserve studies such as inhibin-B and even AMH which are not available on a regular basis in every ART unit. This score is closely related to pregnancy and live birth rates in an IVF setting.

Interestingly, female height was reported for the first as an independent predictor for live birth in IVF/ICSI cycles by Vaegter *et al*.[17] The authors proposed a prediction model for live birth which included age, infertility cause, treatment history, embryo score, ovarian sensitivity and endometrial thickness as independent predictors.[17] Our study demonstrated a good predictability for age, BMI and endometrial thickness to pregnancy rates [Supplementary Figures 1, 4 and 9].

Recently, Wen *et al*.[18] elucidated that female age has a strong predictability to live birth with a prominent drop in IVF success in women aged >37 years. Moreover, the study reported six independent predictors for IVF/ICSI success, which are age, BMI, cycle number, male factor, ovulatory disorders and endometrial thickness. Nevertheless, the study did not recommend using this prediction model to make decisions on freeze-all embryos, cycle cancellation or holding IVF cycle for further treatment. On the contrary, using the Younis score, women with high scores had significantly lower embryo-freezing, pregnancy and live birth rates and a higher risk of cycle cancellation.

Recent literature proposed that singleton live and term birth rate per initiated is the most significant outcome of all ART therapy compared to any other outcome even pregnancy rate.[19] The present study has some strength points due to its prospective design and involving live birth as the main study outcome. Moreover, this prediction model was found to be feasible and easily applicable most IVF/ICSI cycles.

Conclusions

This study supports the implementation of the Younis multivariate score in the prediction of pregnancy, take-home baby, chance of having frozen embryos and cycle cancellation possibility in couples undergoing ICSI in different ovarian response categories. Combining AMH with the old score gives a similar good predictability to cycle outcomes. A large multicentred study is recommended to further investigate the predictive value of this score.

Authors' contributions

AAA, conducting the study, recruiting participants' data collection and statistical analysis. MAK, conception and design of the work, analysis and interpretation of data, have drafted the work and substantively revised it. ANF, critical revision and design of the work, analysis and interpretation of data, have drafted the work and substantively revised it. AAY, design of the work, analysis, and interpretation of data, have drafted the work and substantively revised it.

Financial support and sponsorship

Nil.

Conflicts of interest

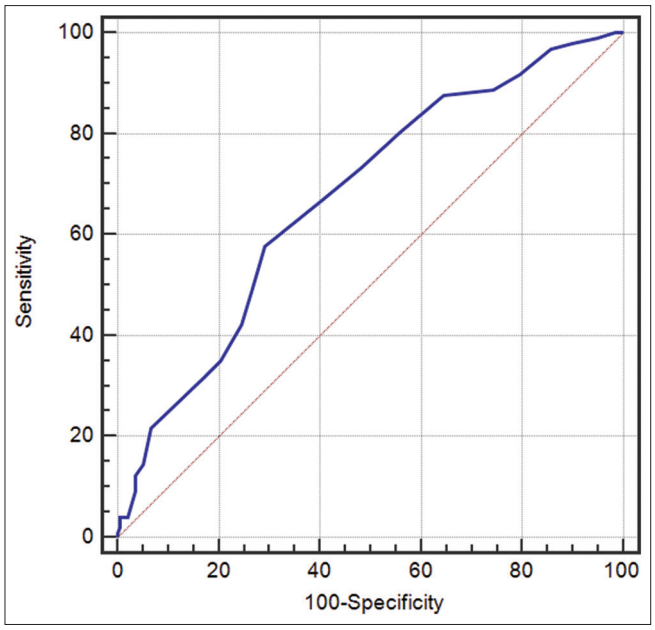
There are no conflicts of interest.

Data availability statement

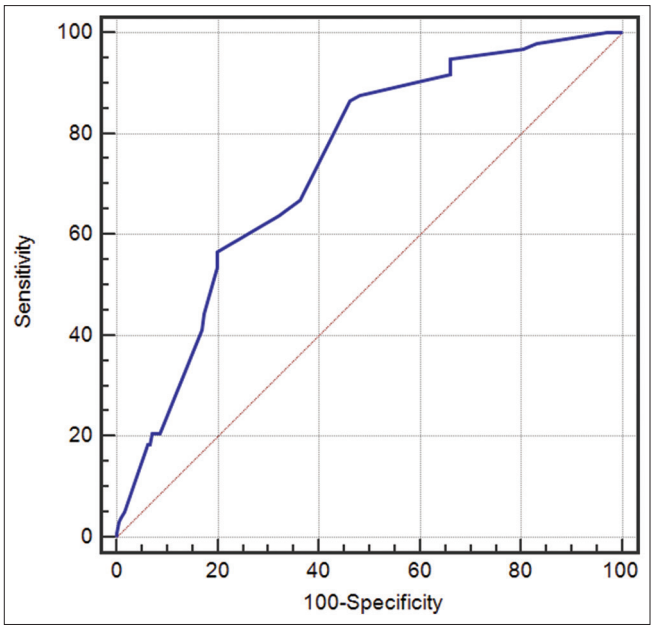
Raw data are available upon request.

References

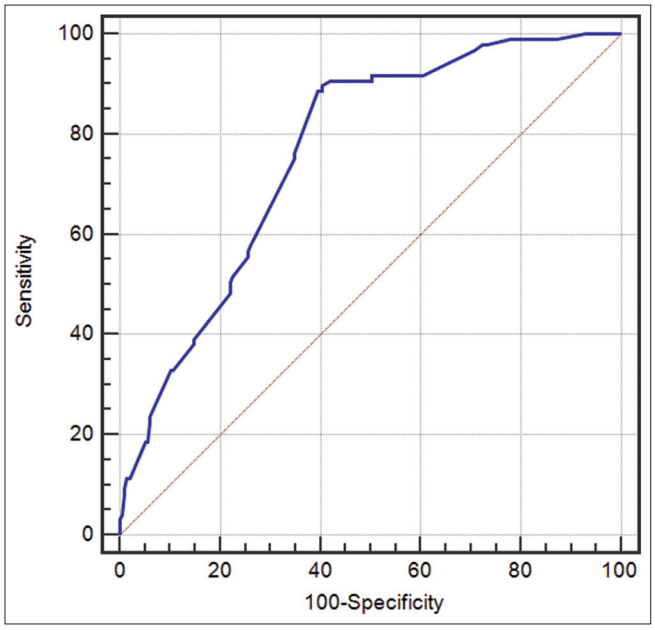
1. Zarinara A, Zeraati H, Kamali K, Mohammad K, Shahnazari P, Akhondi MM. Models predicting success of infertility treatment: A systematic review. J Reprod Infertil 2016;17:68-81.
2. Hamdine O, Eijkemans MJ, Lentjes EG, Torrance HL, Macklon NS, Fauser BC, *et al.* Antimüllerian hormone: Prediction of cumulative live birth in gonadotropin-releasing hormone antagonist treatment for *in vitro* fertilization. Fertil Steril 2015;104:891-8.e2.
3. Lukaszuk K, Liss J, Kunicki M, Jakiel G, Wasniewski T, Woclawek-Potocka I, *et al.* Anti-müllerian hormone (AMH) is a strong predictor of live birth in women undergoing assisted reproductive technology. Reprod Biol 2014;14:176-81.
4. Lemmen JG, Rodríguez NM, Andreasen LD, Loft A, Ziebe S. The total pregnancy potential per oocyte aspiration after assisted reproduction-in how many cycles are biologically competent oocytes available? J Assist Reprod Genet 2016;33:849-54.
5. Yao L, Zhang W, Li H, Lin W. The role of serum AMH and FF AMH in predicting pregnancy outcome in the fresh cycle of IVF/ICSI: A meta-analysis. Int J Clin Exp Med 2015;8:1755-67.
6. Revelli A, Biasoni V, Gennarelli G, Canosa S, Dalmasso P, Benedetto C. IVF results in patients with very low serum AMH are significantly affected by chronological age. J Assist Reprod Genet 2016;33:603-9.
7. Wang S, Zhang Y, Mensah V, Huber WJ 3rd, Huang YT, Alvero R. Discordant anti-müllerian hormone (AMH) and follicle stimulating hormone (FSH) among women undergoing *in vitro* fertilization (IVF): Which one is the better predictor for live birth? J Ovarian Res 2018;11:60.
8. Younis JS, Jadaon J, Izhaki I, Haddad S, Radin O, Bar-Ami S, *et al*. A simple multivariate score could predict ovarian reserve, as well as pregnancy rate, in infertile women. Fertil Steril 2010;94:655-61.
9. Volpes A, Sammartano F, Coffaro F, Mistretta V, Scaglione P, Allegra A. Number of good quality embryos on day 3 is predictive for both pregnancy and implantation rates in *in vitro* fertilization/intracytoplasmic sperm injection cycles. Fertil Steril 2004;82:1330-6.
10. Feil D, Henshaw RC, Lane M. Day 4 embryo selection is equal to Day 5 using a new embryo scoring system validated in single embryo transfers. Hum Reprod 2008;23:1505-10.
11. Balaban B, Gardner DK. Morphological assessment of blastocyst stage embryos: Types of grading systems and their reported outcomes. In: Human Gametes and Preimplantation Embryos: Assessment and Diagnosis. New York, NY: Springer New York; 2013. p. 31-43.
12. Zegers-Hochschild F, Mansour R, Ishihara O, Adamson GD, Dyer S, de Mouzon J, *et al*. International committee for monitoring assisted reproductive technologies world report: Assisted reproductive technology. Hum Reprod 2009;24:2683-7.
13. Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L, *et al.* ESHRE consensus on the definition of 'poor response' to ovarian stimulation for *in vitro* fertilization: The Bologna criteria. Hum Reprod 2011;26:1616-24.
14. Bancsi LF, Broekmans FJ, Eijkemans MJ, de Jong FH, Habbema JD, te Velde ER. Predictors of poor ovarian response in *in vitro* fertilization: A prospective study comparing basal markers of ovarian reserve. Fertil Steril 2002;77:328-36.
15. Erdem M, Erdem A, Gursoy R, Biberoglu K. Comparison of basal and clomiphene citrate induced FSH and inhibin B, ovarian volume and antral follicle counts as ovarian reserve tests and predictors of poor ovarian response in IVF. J Assist Reprod Genet 2004;21:37-45.
16. Muttukrishna S, McGarrigle H, Wakim R, Khadum I, Ranieri DM, Serhal P. Antral follicle count, anti-mullerian hormone and inhibin B: Predictors of ovarian response in assisted reproductive technology? BJOG 2005;112:1384-90.
17. Vaegter KK, Lakic TG, Olovsson M, Berglund L, Brodin T, Holte J. Which factors are most predictive for live birth after *in vitro* fertilization and intracytoplasmic sperm injection (IVF/ICSI) treatments? Analysis of 100 prospectively recorded variables in 8,400 IVF/ICSI single-embryo transfers. Fertil Steril 2017;107:641-8.e2.
18. Wen M, Wu F, Du J, Lv H, Lu Q, Hu Z, *et al.* Prediction of live birth probability after *in vitro* fertilization and intracytoplasmic sperm injection treatment: A multi-center retrospective study in Chinese population. J Obstet Gynaecol Res 2021;47:1126-33.
19. Bellver J, Albert C, Soares SR, Alvarez C, Pellicer A. The singleton, term gestation, and live birth rate per cycle initiated: A 1-year experience in *in vitro* fertilization cycles with native and donated oocytes. Fertil Steril 2005;83:1404-9.



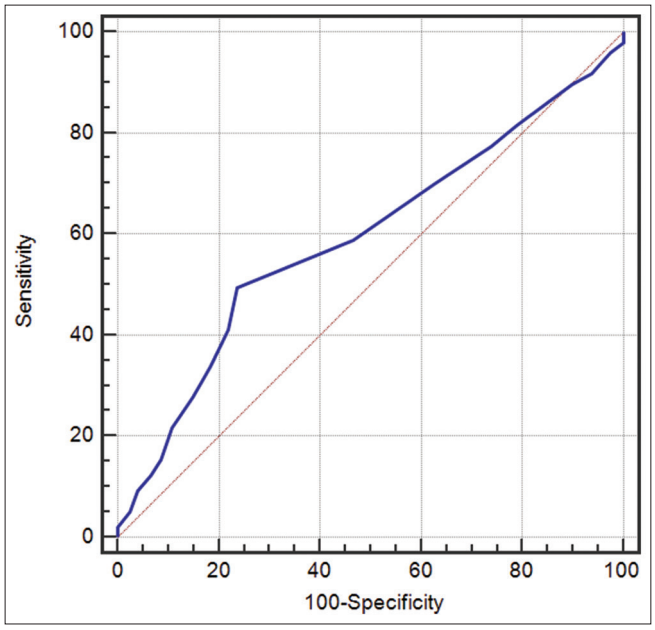
Supplementary Figure 1: Receiver operating curve for age in pregnancy predictability



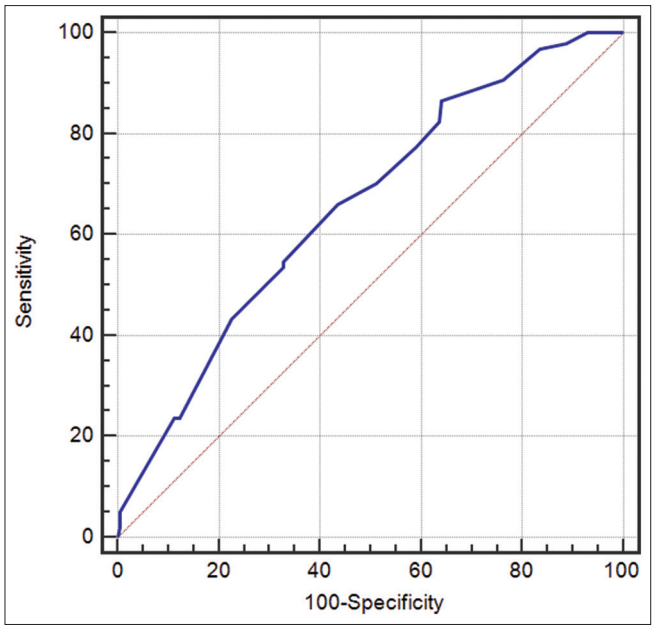
Supplementary Figure 2: Receiver operating curve for follicle-stimulating hormone in pregnancy predictability



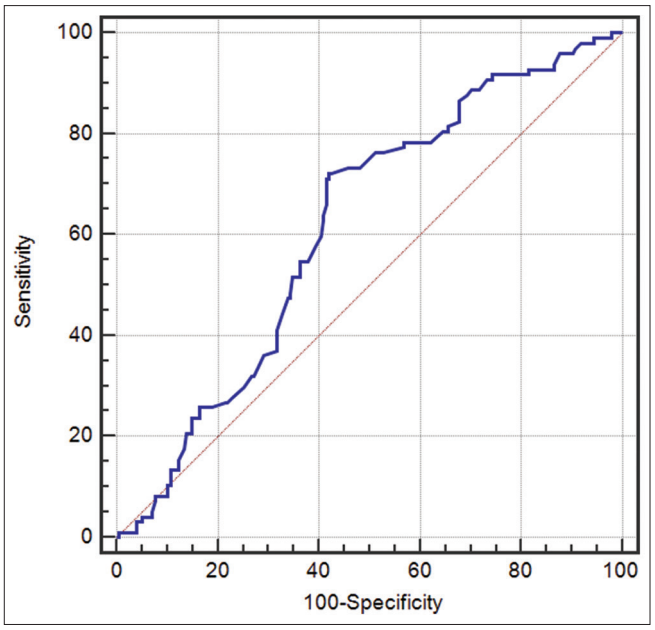
Supplementary Figure 3: Receiver operating curve for mean ovarian volume (cm^3) in pregnancy predictability



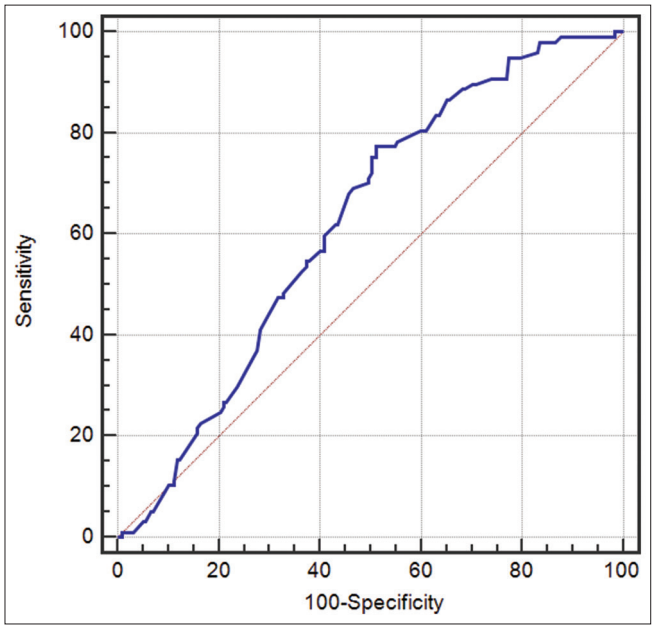
Supplementary Figure 4: Receiver operating curve for body mass index in pregnancy predictability



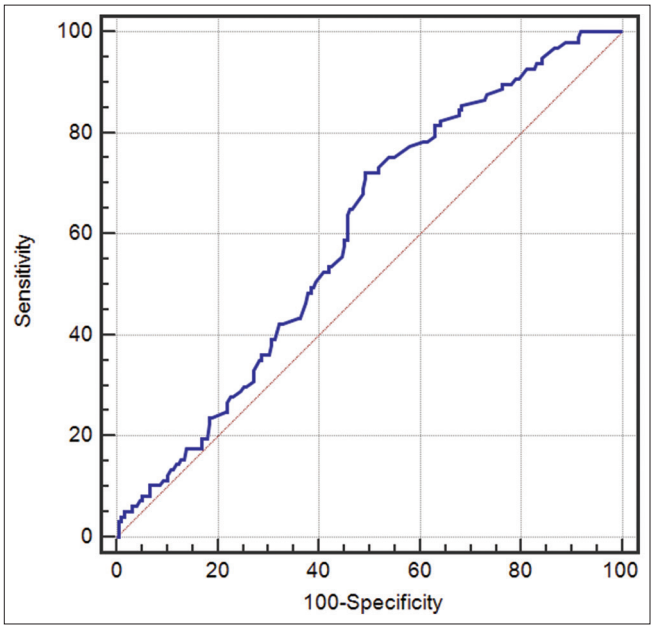
Supplementary Figure 5: Receiver operating curve for infertility duration (years) in pregnancy predictability



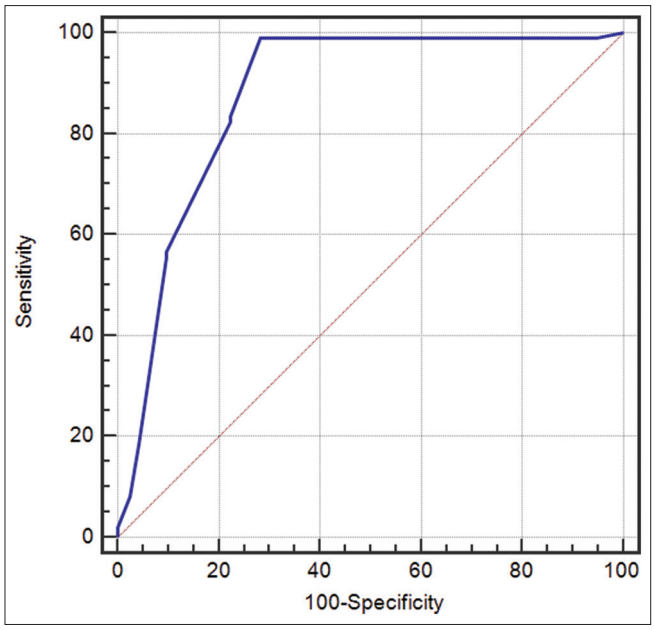
Supplementary Figure 6: Receiver operating curve for follicle-stimulating hormone in pregnancy predictability



Supplementary Figure 7: Receiver operating curve for follicle-stimulating hormone/luteinising hormone ratio in pregnancy predictability



Supplementary Figure 8: Receiver operating curve for anti-Mullerian hormone in pregnancy predictability



Supplementary Figure 9: Receiver operating curve for endometrial thickness at day of trigger in pregnancy predictability

Supplementary Table 1: Predictive value of different cycle predictors

	Cut-off	Sensitivity	Specificity	ROC AUC
Age	≤30	57.73	70.77	0.673
AFC	>9	86.60	53.85	0.736
Ovarian volume	>5.2	89.69	59.49	0.764
BMI	≤30	49.48	76.41	0.592
Infertility duration	≤10	86.60	35.90	0.656
FSH	≤6.05	72.16	57.95	0.616
FSH/LH ratio	≤2	77.32	48.72	0.623
AMH	>1.8	72.16	50.77	0.599

AFC=Antral follicle count, BMI=Body mass index, FSH=Follicle-stimulating hormone, LH=Luteinising hormone, AMH=Anti-Mullerian hormone, AUC=Area under the curve, ROC=Receiver operating curve