The details matter: personalized prediction of live birth after in vitro fertilization in women with polycystic ovary syndrome

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Objective: To derive and internally validate a clinical prediction model for live birth (LB) in women with polycystic ovary syndrome (PCOS) undergoing in vitro fertilization (IVF).
Design: Retrospective cohort study.
Setting: Four academic reproductive endocrinology clinics.
Patients: A total of 207 women with PCOS confirmed using Rotterdam criteria undergoing their first fresh IVF cycle.
Interventions: Not applicable.
Main Outcome Measure: The primary outcome was cumulative LB per IVF cycle start. This included any LB that resulted from either fresh embryo transfer or any subsequent frozen embryo transfer from embryos obtained at the index oocyte retrieval. A prediction model was derived using multivariable logistic regression. Covariates considered for inclusion in the prediction model included demographic characteristics, medical history, and prior fertility treatment. Predicted probabilities for LB were calculated using the prediction model which included the 90% shrinkage factor for each adjusted odds ratio.
Results: The final model, on the basis of maximization of the area under the receiver operating characteristic curve, included age < 35 years, White race, presence of polycystic ovaries on ultrasound (polycystic ovary morphology), normal body mass index (<25 kg/m^2), being metabolically healthy (no metabolic risk factors), and being a nonresponder to ovulation induction agents including letrozole and clomiphene citrate. The area under the receiver operating characteristic curve score for the model was 0.68 (95% confidence interval [CI]: 0.60, 0.77). Predicted probabilities of LB ranged from 8.1% (95% CI: 2.8, 21.5) for a woman who had no favorable predictors to 74.2% (95% CI: 59.5, 84.9) for a woman who had all favorable predictors.
Conclusion: Our study demonstrated that, in addition to anovulation, the underlying pathophysiology and associated comorbidities alter the likelihood of a successful pregnancy in women with PCOS undergoing IVF. Further validation of this model is needed before it can serve as a tool to personalize prediction estimates for the probability of LB in women with PCOS. (Fertil Steril® 2024;121:1010–9. ©2024 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: PCOS, IVF, prediction, metabolic

Received December 15, 2022; revised January 17, 2024; accepted January 25, 2024; published online February 1, 2024.
Supported in part by a National Institutes of Health (Bethesda, Maryland) Reproductive Epidemiology Training grant (T32-HD007440) (to L.G.C.).
Data will be made available to other researchers on request.
L.G.C. started this work at the University of Pennsylvania and completed it at the University of Wisconsin.
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Fertil Steril® Vol. 121, No. 6, June 2024 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2024.01.033

Polycystic ovary syndrome (PCOS), an endocrine disorder affecting millions of reproductive-aged women, is the most common cause of anovulatory infertility (1). Infertility therapies for women with PCOS include medication-induced ovulation with oral or injectable medication, ovarian drilling, and in vitro fertilization (IVF). Ovulation induction (OI) with letrozole or clomiphene citrate (CC), the least invasive approach, is 70%–80% effective in achieving ovulation in women with PCOS. Pregnancy, however, is only achieved within six cycles of treatment by 20%–30% of women (2–5), leading many to seek IVF ultimately. In vitro fertilization is an effective option for infertility treatment, but it is time consuming, invasive, and expensive. Furthermore, only 40% of women with PCOS achieve pregnancy after their first embryo transfer (ET) (6). Consequently, determining factors associated with a reduced likelihood of a successful IVF cycle in women with PCOS will enable physicians to intervene proactively to mitigate these risk factors. Additionally, identified risk factors could inform prediction models to improve decisions about which fertility treatment to best implement, increasing the likelihood of a successful pregnancy outcome.

Fertility prediction models have been implemented successfully for women in the general population to counsel patients regarding live birth rates (LBRs) per IVF cycle (7–10). These models have included factors such as age, pregnancy history, body mass index (BMI), race, and duration and reason for infertility. Although diagnosis of anovulation was included as a covariate in some of these models (7, 8), others did not include PCOS diagnosis in the model (9, 10). In addition, women with PCOS are inherently different from the overall population of women undergoing IVF, and their underlying pathophysiology and associated comorbidities may result in distinct factors that alter the likelihood of a successful pregnancy. Increasing age (11), obesity (12–17), and insulin resistance (15) are all known to negatively impact IVF outcomes in patients with PCOS. Recent studies in women with PCOS have demonstrated that metabolic syndrome (MetSyn), a constellation of criteria including abdominal obesity, dyslipidemia, elevated glucose, and hypertension (HTN), is associated with decreased live birth (LB) in women with PCOS undergoing OI (18) and IVF (19).

International guidelines recommend that all women with PCOS be screened for metabolic abnormalities, including obesity, HTN, impaired glucose tolerance (IGT), type 2 diabetes mellitus (T2DM), and dyslipidemia. Despite the high prevalence of metabolic comorbidities in this population and their clear importance for long-term health, previous prediction models have failed to consider whether metabolic comorbidities can be employed to predict IVF success. Thus, we had two aims: first, to use a cohort of women with PCOS-associated infertility to identify parameters associated with LB after IVF, and second, to employ those parameters to derive and internally validate a clinical prediction model for LB in women with PCOS undergoing IVF. This evidence will better inform physicians as well as patients with PCOS about deciding the optimal path toward achieving LB.

MATERIALS AND METHODS

Study design

A retrospective cohort of women with PCOS and infertility was assembled at four study sites: the University of Pennsylvania, Philadelphia, PA (Penn); Montefiore's Institute for Reproductive Medicine and Health, Albert Einstein College of Medicine, Montefiore Medical Center, Hartsdale, NY (Montefiore); the University of Rochester, Rochester, NY (Rochester); and Yale School of Medicine, New Haven, CT (Yale). Subjects at Penn, Rochester, and Yale were identified from each institution's IVF database maintained for reporting to the Society for Assisted Reproductive Technology (SART). Given that the SART does not distinguish PCOS from other disorders of ovulation, chart reviews were conducted at each site to identify patients who met PCOS criteria on the basis of Rotterdam criteria (20). Subjects from Montefiore were identified from an existing institutional database of women with PCOS who were undergoing IVF. This study was approved by the institutional review boards at all four institutions: Penn, Montefiore, Rochester, and Yale.

Inclusion and exclusion criteria

We included women aged 18–45 years with a diagnosis of PCOS on the basis of Rotterdam criteria (20) who underwent their first oocyte retrieval for autologous IVF at one of the above institutions between 2006 and 2016. Having a concurrent non-PCOS cause for infertility was not an exclusion criterion. The availability of medical records for detailed medical and obstetric histories at each institution dictated the years that each center contributed subjects. Medical records were accessible at Penn from 2009 to 2016, at Montefiore from 2006 to 2016, at Rochester from 2010 to 2016, and at Yale from 2013 to 2016. Women undergoing an oocyte banking cycle, using a donor oocyte or a gestational carrier, were all excluded. We also excluded couples using surgically retrieved sperm, given the concern that this could affect LBRs independently and that we would not have enough data to evaluate this as a variable. Only women with at least a full year of follow-up after oocyte retrieval were considered in the final cohort. Women were not excluded when they did not return to use all frozen embryos.

Covariates

The following baseline data were extracted for each subject at the time of starting IVF: age, BMI, race, obstetric history, and use of medication, including metformin. Reports of medical comorbidities and laboratory values were extracted from the time closest to IVF start, which for many patients was at the time of the new patient evaluation or workup. Women were defined as being "metabolically healthy" when they did not have any of the following metabolic comorbidities: prediabetes and diabetes (defined on the basis of medical history, oral glucose tolerance test $\geq$ 140 mg/dL, hemoglobin A1c $\geq$ 5.7%, or fasting glucose $\geq$ 100 mg/dL), HTN (defined on the basis of medical history, use of blood pressure (BP) medication, systolic BP $>$ 140 mmHg, or diastolic BP $>$ 90 mmHg), or dyslipidemia (defined on the basis of medical history, including prior use

of a statin, total cholesterol [C] > 200 mg/dL, low-density lipoprotein C ≥ 100 mg/dL, high-density lipoprotein C < 50 mg/dL, or triglycerides (TGs) ≥ 150 mg/dL). Metformin use was not part of the diagnosis of prediabetes and diabetes, given its other uses in women with PCOS.

PCOS diagnostic criteria used were the presence of oligomenorrhea, biochemical or clinical hyperandrogenism (modified Ferriman Gallwey score ≥ 4), and polycystic ovary morphology (PCOM). Given that subjects with PCOS were diagnosed before new international guidelines updated the ultrasound criteria for PCOM (21) and we did not have data on the frequency of the ultrasound transducers used, we defined PCOM as an antral follicle count (AFC) ≥ 12 or a volume ≥ 10 cm^3 in one ovary (22) because this is what clinicians would have used for PCOS diagnosis at the time of ultrasound. To address this limitation, we included a sensitivity analysis where PCOS was defined by National Institutes of Health (NIH) criteria, which includes oligomenorrhea and hyperandrogenism but not PCOM (23) as well as one where we had confirmed PCOM on the basis of updated criteria.

Data on infertility treatments before initiating IVF were obtained, including the number of prior controlled ovarian stimulation cycles (COH) with either oral medication (CC or letrozole) or follicle-stimulating hormone (FSH) injections, as well as the number of intrauterine inseminations (IUIs). When a woman was given maximum doses of oral OI agents (CC 150 mg or letrozole 7.5 mg) but did not have evidence of ovulation, she was categorized as an "OI nonresponder."

Outcomes

The definition of IVF success has evolved over the years as the range of treatment options has expanded to include both fresh and frozen ETs. The SART reports the cumulative chance of an LB after a complete IVF cycle, which is defined as "all fresh and frozen-thawed ETs resulting from one episode of ovarian stimulation" (21). Similarly, our primary outcome was cumulative LB per complete IVF cycle. Patients with at least one LB that resulted from either a fresh ET or any subsequent frozen ET (FET) from embryos obtained at the index oocyte retrieval were coded as having an LB. Only one LB per patient was included in the primary outcome, so the percentage did not exceed 100%. Because each patient had only one outcome at the end of the follow-up period, no additional analysis was necessary for multiple outcomes per patient. A sensitivity analysis was performed only including FET cycles that were completed within a year of index oocyte retrieval (rather than allowing the inclusion of any FET that was performed regardless of time).

When ET was not performed either because the ovarian stimulation cycle was canceled before oocyte retrieval or no embryos were available for transfer, women were coded as not having an LB. This outcome was used both to identify parameters associated with LB after IVF and to employ those parameters to derive and internally validate a clinical prediction model.

Statistical analysis

Unadjusted comparisons were performed to assess for associations between baseline covariates and cumulative LB. Categorical covariates were assessed using Pearson χ^2 or Fisher's exact test. Continuous covariates were assessed using either Student's t tests and analysis of variance or Wilcoxon rank sum and Kruskal-Wallis tests as appropriate.

A prediction model was derived using multivariable logistic regression. Covariates considered for inclusion in the prediction model included demographic characteristics, medical history, and prior fertility treatment.

A priori, it was decided that age and BMI would be included in the final model. The inclusion of other covariates was based on the maximization of the area under the receiver operating characteristic curve (AUROC) score. To avoid overfitting, the initial adjusted odds ratios (aORs) were multiplied by a global shrinkage factor of 0.9 to decrease all aORs in the prediction model by 10% (21). Bootstrap resampling (n = 100) was used to compute AUROC scores with 95% confidence intervals (CIs). Predicted probabilities for LB were calculated using the prediction model, which included the 90% shrinkage factor for each aOR.

RESULTS

Study population

A total of 268 records had complete medical, obstetrics, and IVF data. Sixty-one women were excluded because they did not meet the inclusion criteria listed above (55 did not have PCOS, 2 used testicular sperm extraction, 2 were on oocyte cryopreservation cycles, one was using a gestational carrier, and 1 was doing a comaternity cycle using her oocytes and her partner carrying the pregnancy).

A total of 207 women with PCOS confirmed using Rotterdam criteria undergoing their first IVF cycle were included in the final analyses. Table 1 delineates the demographics for the entire study cohort as well as within each study site. The mean age was 32.5 ± 3.9 years, and the mean BMI was 29.5 ± 7.3 kg/m^2. Most women were White (69%), nulliparous (62%), and had a BMI in the overweight or obese range (65%). In terms of PCOS phenotype, phenotype A (hyperandrogenism, oligomenorrhea, and PCOM) was the most common (45.4%), followed by phenotype D (oligomenorrhea and PCOM; 37.2%). More than half of the cohort was metabolically unhealthy (56.5%). Preimplantation genetic testing for aneuploidy was only done in six patients and was not included as a variable in the analysis.

Primary outcome—cumulative LB

The included subjects underwent a total of 269 treatment cycles (oocyte retrieval with fresh ET [N = 207] or subsequent FETs [N = 62]). Out of the 269 treatment cycles, 11 were canceled before a transfer was attempted, leaving 258 total transfers. A little over half (52%) of the transfers resulted in a positive β human chorionic gonadotropin level. There were 92 (35.7%) LBs, 22 (8.5%) biochemical pregnancies, 15 (5.8%) clinical miscarriages, 3 (1.2%) ectopic pregnancies, 2 (0.8%) therapeutic abortions, and 1 (0.4%) stillbirth. When evaluating the primary outcome, 42.5% achieved a cumulative LB. Ninety percent of women either achieved a pregnancy

TABLE 1

Demographics by study site.

Overall population (N = 207)	Overall (N = 207)	Penn (N = 105)	Montefiore (N = 49)	Rochester (N = 31)	Yale (N = 22)
Clinical covariates					
Demographics					
Mean age (y)	32.5 (3.9)	32.3 (3.7)	33.4 (4.6)	32.0 (3.6)	32.5 (3.5)
Age < 35 y	147 (71.0)	78 (74.3)	30 (61.2)	23 (74.2)	16 (72.7)
Mean BMI (kg/m^2)	29.7 (7.2)	28.4 (7.0)	31.2 (7.5)	31.4 (7.6)	29.9 (6.1)
BMI (kg/m^2)					
Underweight (<18.5)	3 (1.5)	2 (1.9)	1 (2.0)	0	0
Normal (18.5–24.9)	69 (33.3)	44 (41.9)	10 (20.4)	9 (29.0)	6 (27.3)
Overweight (25.0–29.0)	35 (16.9)	19 (18.1)	10 (20.4)	3 (9.7)	3 (13.6)
Obese (>30.0)	100 (48.3)	40 (38.1)	28 (57.1)	19 (61.3)	13 (59.1)
Race[a]					
Black	16 (8.0)	10 (9.5)	6 (14.0)	0	0
Other[b]	46 (22.9)	22 (21.0)	11 (25.6)	3 (9.7)	10 (45.5)
White	139 (69.2)	73 (69.5)	26 (60.5)	28 (90.3)	12 (54.6)
Pregnancy history					
Prior pregnancy	78 (37.7)	35 (33.3)	22 (44.9)	11 (35.5)	10 (45.5)
Prior full-term delivery	25 (12.1)	11 (10.5)	7 (14.3)	4 (12.9)	3 (16.4)
Prior miscarriage	47 (22.7)	22 (21.0)	11 (22.5)	7 (22.6)	7 (31.8)
Medical history					
Depression	17 (8.2)	11 (10.5)	0	5 (16.1)	1 (4.6)
Anxiety	22 (10.6)	11 (10.5)	2 (4.1)	6 (19.4)	3 (13.6)
Hypertension	41 (19.8)	25 (23.8)	8 (16.3)	6 (19.4)	2 (9.1)
Diabetes	11 (5.3)	4 (3.8)	5 (10.2)	2 (6.5)	0
Currently taking metformin	74 (35.8)	33 (31.4)	23 (46.9)	4 (12.9)	14 (63.6)
Metabolically healthy	90 (43.5)	38 (36.2)	17 (34.7)	22 (71.0)	13 (59.1)
PCOS specific covariates					
Polycystic ovary morphology (PCOM)	190 (91.8)	96 (91.4)	44 (89.8)	28 (90.3)	22 (100)
Oligoanovulation (OA)	188 (90.8)	91 (86.7)	47 (95.9)	30 (96.8)	20 (90.9)
Hyperandrogenism (HA)	130 (62.8)	70 (66.7)	34 (69.4)	9 (29.0)	17 (77.3)
PCOS phenotype					
Phenotype A (HA, OA, PCOM)	94 (45.4)	47 (44.8)	27 (55.1)	5 (16.1)	15 (68.2)
Phenotype B (HA, OA)	17 (8.2)	9 (8.6)	5 (10.2)	3 (9.7)	0
Phenotype C (HA, PCOM)	19 (9.2)	14 (13.3)	2 (4.1)	1 (3.2)	2 (9.1)
Phenotype D (OA, PCOM)	77 (37.2)	35 (33.3)	15 (30.6)	22 (71.0)	5 (22.7)
Fertility treatment history					
Total oral OI cycles (median [IQR])	3 (2, 5)	3 (2, 5)	2 (1, 4)	3 (3, 4)	4 (1, 5)
More than three prior oral OI cycles	92 (45.8)	51 (48.6)	16 (36.4)	14 (45.2)	11 (52.4)
Total IUI cycles (median [IQR])	3 (0, 4)	3 (1, 4)	2 (0, 4)	4 (3, 7)	0 (0, 2)
More than three prior IUI cycles	74 (36.8)	40 (38.1)	14 (31.8)	20 (64.5)	0
Any prior FSH COH cycles	71 (34.3)	26 (24.8)	21 (42.9)	23 (67.7)	3 (13.6)
OI nonresponder	32 (15.5)	17 (16.2)	4 (8.2)	6 (19.4)	5 (22.7)
Year of first oocyte retrieval					
2006–2010	57 (27.5)	35 (33.3)	16 (32.7)	6 (19.4)	0
2011–2016	150 (72.5)	70 (66.7)	33 (67.4)	25 (80.7)	22 (100)

Note: Continuous variables presented as mean (±SD) unless otherwise noted. Categorical variables presented as n (%). BMI = body mass index; FSH COH = follicle-stimulating hormone controlled ovarian hyperstimulation; IQR = interquartile range; IUI = intrauterine insemination; OI = ovulation induction; PCOS = polycystic ovary syndrome.

[a] Six values missing, all from Montefiore.

[b] Other includes American Indian or Alaskan Native, Asian, and Native Hawaiian or Pacific Islander.

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or used all embryos from the index oocyte retrieval during FETs. Only 10% of patients had embryos remaining and did not return to use them in the time frame of the study.

Table 2 shows candidate predictors of outcome and their association with LB. The final model, on the basis of maximization of the AUROC scores, included age < 35 years, White race, presence of polycystic ovaries on ultrasound (PCOM), normal BMI (<25 kg/m^2), being metabolically healthy (no metabolic risk factors), and being an OI nonresponder (Table 3). Because five subjects had missing data for race, they were not included in the final model. The AUROC score was 0.68 (95% CI: 0.60, 0.77) both before applying the shrinkage factor and afterward. In the sensitivity analysis only evaluating those with PCOS diagnosed using NIH criteria, 111 women (53.6%) met the criteria for inclusion. The AUROC score for our model was 0.67 (95% CI: 0.56, 0.78). Similarly, 135 (65.2%) had enough data to confirm PCOM on the basis of the criteria of follicle count ≥ 20. The AUROC score for our model was 0.66 (95% CI: 0.58, 0.75).

We performed a sensitivity analysis only, including outcomes from FET cycles that were started within a year of the index oocyte retrieval. This analysis impacted the outcome of

TABLE 2

Predictors of cumulative LB after the first oocyte retrieval.

Covariates	No LB (N = 115)	LB (N = 92)	*P* value
Clinical covariates			
Demographics			
Mean age (y)	32.9 (4.5)	32.1 (3.1)	.18
Age < 35 y	76 (66.1)	71 (77.2)	.08
Mean BMI (kg/m^2)	30.7 (7.8)	28.4 (6.4)	.03[c]
BMI (kg/m^2)			.18
Underweight (<18.5)	2 (1.7)	1 (1.1)	
Normal (18.5–24.9)	31 (27.0)	38 (41.3)	
Overweight (25.0–29.0)	22 (19.1)	13 (14.1)	
Obese (>30.0)	60 (52.2)	40 (43.5)	
Race[a]			.01[c]
Black	11 (9.8)	5 (5.6)	
Other[b]	33 (29.5)	13 (14.6)	
White	68 (60.7)	71 (79.8)	
Pregnancy history			
Prior pregnancy	43 (37.4)	35 (38.0)	.92
Prior full-term birth	14 (12.2)	11 (12.0)	.96
Prior miscarriage	24 (20.9)	23 (25.0)	.48
Medical history			
Depression	7 (6.1)	10 (10.9)	.21
Anxiety	12 (10.4)	10 (10.9)	.92
Hypertension	26 (22.6)	15 (16.3)	.26
Diabetes	9 (7.8)	2 (2.2)	.07
Currently taking metformin	38 (33.0)	36 (39.1)	.36
Metabolically healthy	42 (36.5)	48 (52.2)	.02[c]
PCOS specific covariates			
Polycystic ovary morphology (PCOM)	101 (87.8)	89 (96.7)	0.02[c]
Oligoanovulation (OA)	103 (89.6)	85 (92.4)	0.48
Hyperandrogenism (HA)	79 (68.7)	51 (55.4)	0.05[c]
PCOS Phenotype			0.05[c]
Phenotype A (HA, OA, PCOM)	53 (46.1)	41 (44.6)	
Phenotype B (HA, OA)	14 (12.2)	3 (3.3)	
Phenotype C (HA, PCOM)	12 (10.4)	7 (7.6)	
Phenotype D (OA, PCOM)	36 (31.3)	41 (44.6)	
Fertility treatment history			
Total oral OI cycles (median [IQR])	3 (2, 5)	3 (2, 5)	0.48
More than three prior oral OI cycles	48 (43.6)	44 (48.4)	0.50
Total IUI cycles (median [IQR])	3 (0, 4)	3 (0, 4)	0.70
More than three prior IUI cycles	38 (34.6)	36 (39.6)	0.46
Any prior FSH COH cycles	37 (32.2)	34 (37.0)	0.47
OI nonresponder	13 (11.3)	19 (20.7)	0.07
Year of first oocyte retrieval			0.10
2006–2010	37 (32.2)	20 (21.7)	
2011–2016	78 (67.8)	72 (78.3)	

Note: Continuous variables presented as mean (±SD) unless otherwise noted. Categorical variables presented as N (%). BMI = body mass index; FSH COH = follicle-stimulating hormone controlled ovarian hyperstimulation; IQR = interquartile range; IUI = intrauterine insemination; LB = live birth; OI = ovulation induction; PCOS = polycystic ovary syndrome.
[a] Six values missing, all from Montefiore.
[b] Other includes American Indian or Alaskan Native, Asian, and Native Hawaiian or Pacific Islander.
[c] *P* value indicate statistically significant.

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four subjects whose LB occurred from an FET over a year from the index oocyte retrieval. The AUROC score for our model was 0.68 (95% CI: 0.60, 0.76).

Table 4 shows the potential uses of this model to predict the probability of LB across several clinical scenarios for various combinations of covariates. For example, a White woman younger than 35 years old with PCOM would have a 74.2% (95% CI: 59.5, 84.9) chance of cumulative LB after her first IVF cycle when she was an OI nonresponder, had normal weight, and was metabolically healthy. The same woman would only have a 43.9% (95% CI: 36.8, 51.1) chance of LB when she had responded to OI, was overweight and obese, and was not metabolically healthy. For a woman who has a non-White race, the same probabilities are 54.9% (95% CI: 46.3, 63.2) and 24.8% (95% CI: 16.2, 36.1), respectively.

The impact of the clinic as a potential confounder was evaluated by comparing the final prediction models with and without the clinic added. The models were not different (*P* value using the likelihood-ratio test = .17).

DISCUSSION

This multicenter study of women with PCOS highlighted the importance of evaluating metabolic health and resistance to OI agents in predicting LB and confirmed previously

TABLE 3

Adjusted OR and shrinkage OR for final model predicting live birth.

Patient characteristics	Adjusted OR (95% CI)	OR after applying 90% shrinkage factor (95% CI)
Age < 35 y[a]	1.2 (0.6, 2.3); *P*=.70	1.0
White[b]	2.3 (1.2, 4.5); *P*=.02	2.0
PCOM[c]	3.2 (0.9, 12.3); *P*=.08	2.9
Ovulation induction nonresponder[d]	1.9 (0.8, 4.4); *P*=.12	1.7
Normal BMI (<25 kg/m^2)[e]	1.6 (0.8, 3.0); *P*=.18	1.4
Metabolically healthy[f]	1.3 (0.7, 2.4); *P*=.40	1.2

Note: BMI = body mass index; CI = confidence interval; OR = odds ratio; PCOM = polycystic ovary morphology.
Compared with reference groups of [a]age ≥ 35 y, [b]non-White, [c]no PCOM, [d]BMI ≥ 25 kg/m^2, and [e]not metabolically healthy.

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identified predictors such as normal BMI, PCOM, and White race (7–10). These factors were leveraged in a model to determine predictive probabilities with reasonable confidence to inform patients regarding the likelihood of cumulative LB resulting from one IVF cycle.

Prediction models have been used to predict LB in women with PCOS undergoing OI using data from the Pregnancy in Polycystic Ovary Syndrome I and II (PPCOS-I and PPCOS-II) trials, two randomized controlled trials (RCTs) evaluating different OI methods (PPCOS-I: CC, metformin, or their combination, and PPCOS-II: letrozole or CC). They found that younger age, lower BMI, shorter duration of attempting conception, and hormonal levels indicative of less insulin resistance and hyperandrogenism were all found to be predictive of ovulation, implantation, clinical pregnancy, and/or LB with an AUROC score of 0.66–0.76 (22, 24). We were unable to evaluate the duration of conception in our model, but interestingly, we found that women who had undergone prior OI cycles and did not ovulate with letrozole or CC had higher rates of LB. From a patient's perspective, failure to respond to OI agents can be stressful and disheartening. Although women in this category respond typically to injectable gonadotropins, these are associated with a higher risk of multiple gestations. Thus, being able to counsel this subset of patients that they have a good prognosis with IVF may help increase their comfort with fast-tracking to IVF.

A reliable prediction model for LB after IVF can be extremely valuable in informing discussions between clinicians and infertile women with PCOS to optimize interventions for achieving a successful pregnancy. Factors such as age, race, and PCOM are not modifiable, but weight and metabolic health can be addressed before initiating IVF. For a woman who is both overweight and obese and has a metabolic risk factor, her LB rate could be 15% lower than that of a woman with similar demographic characteristics who is metabolically healthy and of normal weight. Given the time and expense associated with IVF, evidence-based counseling and upfront conversations about success between physicians and patients are vital.

Obesity increases the time to conception by 2 months (25); however, the effectiveness of lifestyle (LS) changes before fertility treatment is debated. A study of overweight and obese women with PCOS (N = 149) evaluated the effectiveness of a 16-week LS intervention (caloric restriction with meal replacement and weight loss medication) compared with oral contraceptives pills (OCPs), or combined treatment (LS and OCPs) (OWL-PCOS). Women in the LS group had greater weight loss (6.1 vs. 1.1 kg; *P*<.001) and improved 2-hour glucose and insulin sensitivity, although the OCP group had higher TG levels and rates of MetSyn at the completion of the study (26). Lifestyle increased cumulative ovulation rates after four cycles of CC and intercourse. Live birth was higher when the two groups with LS were combined compared with the OCP alone group (*P*=.05), suggesting a potential benefit to delayed conception (26). In a post hoc analysis, when data from the LS and combined groups of OWL-PCOS (delayed conception) were compared with those from PPCOS-II (immediate conception), they found that women in the delayed conception group had 2.5-fold higher odds of LB (LS vs. PPCOS-II: 25% vs. 10.2%; *P*=.01 combined vs. PPCOS-II: 25.5% vs. 10.2%; *P*=.01) (27). These studies suggest a potential fertility benefit of weight loss in overweight and obese women with PCOS before using oral OI medications.

A larger RCT (LIFEstyle study) of 574 women (BMI ≥ 29 kg/m^2) compared immediate fertility treatment, including OI and IVF, to a 6-month LS intervention where participants were instructed to decrease their calorie intake by 600 kcal daily and were given exercise guidelines. This study was not restricted to women with PCOS, although 47% of women had anovulatory infertility and 75% of these were reported to have PCOS. In the overall study, women in the LS group lost more weight (4.4 vs. 1.1 kg; *P*<.001), but surprisingly, the frequency of LB within 24 months after randomization was lower in the LS group than in the control group (27.1 vs. 35.2%; rate ratio: 0.77; 95% CI: 0.60–0.99). One of the limitations of the study was that only 38% of the participants reached their target weight loss of 5%–10% of the original body weight. Post hoc subgroup analyses that were limited to women with anovulatory infertility showed no significant differences in LBRs between groups (28). Of note, women in the LS group did have a higher rate of natural conception (OR: 1.83, 95% CI: 1.21–2.76), which was seen also in the subgroup of women with anovulatory infertility (aOR: 4.15, 95% CI: 2.04–8.44). More importantly, anovulatory women who received the lifestyle intervention had increased natural

TABLE 4

Predicted probability of LB.

Sample patient characteristics							
Age < 35 y[a]	White race	PCOM	Ovulation induction nonresponder	Normal BMI (< 25 kg/m^2)	Metabolically healthy	Predicted probability of LB percent (95% CI)[b]
No	No	No	No	No	No	8.1% (2.8, 21.5)
Yes	No	No	No	No	No	8.1% (2.8, 21.5)
No	Yes	No	No	No	No	17.2% (9.1, 30.3)
Yes	No	Yes	No	No	No	24.8% (16.2, 36.1)
Yes	Yes	No	Yes	No	No	28.8% (20.3, 38.9)
Yes	Yes	Yes	No	No	No	43.9% (36.8, 51.1)
Yes	No	Yes	Yes	No	Yes	44.5% (37.4, 51.8)
Yes	No	Yes	Yes	Yes	Yes	54.9% (46.3, 63.2)
Yes	Yes	Yes	Yes	No	No	60.2% (50.0 69.5)
Yes	Yes	Yes	Yes	No	Yes	65.5% (53.6, 75.7)
Yes	Yes	Yes	Yes	Yes	No	69.6% (56.4, 80.3)
Yes	Yes	Yes	Yes	Yes	Yes	74.2% (59.5, 84.9)

Note: Only some possible variations of covariates are presented to show the contribution of individual characteristics. BMI = body mass index; CI = confidence interval; LB = live birth; PCOM = polycystic ovary morphology.

[a] More scenarios with age > 35 y are not shown because odds ratio $(OR)_{age < 35\ y} = 1.0$ and thus age has a minimal effect on the final predicted probabilities.

[b] Predicted probabilities are calculated using the prediction model which includes the 90% shrinkage factor for each OR.

Cooney. IVF Prediction for PCOS. Fertil Steril 2024.

conception rates compared with ovulatory women who received the intervention (28, 29). In another post hoc analysis of the same RCT, the investigators found that cardiometabolic health improved in the LS group and that a periconceptional decrease in BMI in obese infertile women led to a decrease in the rates of hypertensive pregnancy complications and preterm birth (30).

There are no studies specifically evaluating weight loss in women with PCOS before undergoing IVF alone. However, a large RCT of 317 women with a BMI of 30–35 kg/m^2 failed to demonstrate improved LBRs in obese women who received intensive weight reduction programs before IVF (31). In this study, women were randomized to a low-calorie liquid formula diet for 12 weeks or usual care. Their outcome was LB after one IVF cycle or spontaneous LB before initiating IVF. Those in the low-calorie liquid formula diet group lost more weight (−9.4 vs. 1.2 kg, $P<.001$) but did not have improved LB (29.6 vs. 27.5%; $P=.77$), although the weight reduction group did have more spontaneous pregnancies (10.5% vs. 2.6%; $P=.009$). A subgroup analysis of women with PCOS showed a trend in improvements in LBR in women with PCOS in the weight reduction group (n = 40) compared with the direct IVF group (n = 41); however, the study was not powered for this outcome (27.5 vs. 22.0%; $P=.75$) (31). Thus, more data are needed to identify when the possible improvement in LB after delayed conception in OI cycles in women with PCOS is seen also in IVF.

Although obesity is a hallmark symptom of PCOS, 40% of women with PCOS are of normal weight (32). Our study found a contribution of metabolic health to LBRs beyond that of overweight and obesity alone. This is consistent with results from a secondary analysis from the PPCOS-II study showing that women with MetSyn were less likely to achieve an LB (16.5% vs. 27%, $P=.001$) (18) and a secondary analysis of a large RCT (N = 1,508) evaluating fresh vs. frozen ET in women with PCOS (Frefro-PCOS), which found that MetSyn was negatively associated with cumulative LBR (OR: 0.70, 95% CI: 0.51–0.96, $P=.03$) (19). Because normal-weight women with PCOS still have increased risks of metabolic abnormalities including IGT and T2DM, dyslipidemia, HTN, and MetSyn compared with normal-weight women without PCOS (33), focusing on lifestyle interventions to improve metabolic health could be a new target to improve pregnancy rates in these women.

This association between metabolic health and IVF success has biologic plausibility. Studies of follicular fluid metabolic markers have found higher free fatty acids and lower bioactive lipids in women with PCOS (34, 35), which correlate with decreased oocyte and embryo quality (35, 36). In the general population, elevated TGs have been associated with decreased LBRs (37), although this has not been evaluated in women with PCOS. Future studies should evaluate whether there are additional serum biomarkers in women with PCOS that predict LB.

More recent treatment of obesity and metabolic dysfunction in women with PCOS has focused on the use of glucagon-like peptide-1 receptor (GLP-1R) agonists or dual glucose-dependent insulinotropic polypeptide and GLP-1R agonists. Compared with metformin, treatment with GLP-1R

agonists is associated with increased weight loss and an improvement in insulin sensitivity (38). Overall, data are mixed on whether treatment with GLP-1R agonists improves menstrual frequency (39); however, early data on pregnancy outcomes are promising. A study of 176 women with PCOS who were overweight or obese, randomized to either exenatide or metformin found a higher natural pregnancy rate in the exenatide group (40). Another study randomized 28 women with PCOS who were obese and had infertility to liraglutide or metformin and found higher pregnancy rates after IVF in the liraglutide group despite similar amounts of weight loss (41). The GLP-1R agonists are classified as pregnancy class C medications and are contraindicated during pregnancy; however, their use in the treatment of subfertility in the preconception period shows promise. Future prediction studies should focus on whether the use of these medications before IVF will improve outcomes.

The impact of race on IVF outcomes in our study was striking. Multiple previous studies have demonstrated that Black women are underrepresented among women undergoing IVF and have decreased LBRs compared with White women, likely in part because of systemic racism and racial disparities in infertility referral and treatment options. (42–44). In the PCOS population in particular, Black women with PCOS also have worse metabolic phenotypes (45, 46), which could contribute to the differences seen in IVF success rates (43). More data are needed to evaluate specifically the interaction between race and LB in women with PCOS undergoing IVF to better address modifiable factors underlying racial disparities.

Strengths of our study include recruitment from four sites with different patient demographics and characteristics, which increases generalizability to the other clinical sites. In addition, we were able to obtain detailed medical, obstetric, and infertility histories, allowing us to evaluate the contribution of factors that have not been used in prior IVF prediction models.

Our results need to be interpreted in the context of limitations. First, patients in our study were recruited when the PCOM diagnosis criterion was ≥ 12 follicles per ovary or volume was ≥ 10 cm^3. Although ultrasound reports included information to diagnose PCOM on the basis of this criterion, we did not have AFCs in all patients to perform sensitivity analyses to predict LB on the basis of total follicle number. Thus, the inclusion of PCOM in our model must be interpreted in the context of ≥ 12 follicles per ovary. Despite this, we were able to confirm that our model remained robust when looking at the more restrictive NIH criteria for PCOS. Additional limitations include a lack of routine documentation of the duration of infertility, smoking status, prior obesity treatment, and socioeconomic status. Although socioeconomic status could impact a subject's ability to return for a FET, because 90% of women either achieved pregnancy or used all embryos from the index oocyte retrieval during FETs, we do not anticipate this having a large impact. Because antimüllerian hormone (AMH) is a more recent analyte, AMH values were not available for all subjects and were not included in our model, although studies do show a strong correlation between AMH levels and AFC (47, 48). Finally, our model is derived and has internal validation, but it needs further validation in a larger and independent contemporary cohort.

CONCLUSION

Prediction of IVF success is incredibly important given that this treatment is time consuming, invasive, and expensive. We derived a prediction model that categorizes the likelihood of an LB after IVF using a variety of factors available at the time of a physician-patient IVF consultation. When this model is validated in another cohort, it could serve as a tool to personalize prediction estimates for the probability of LB in women with PCOS starting IVF. Women with overweight and obesity and poor metabolic health have decreased LBRs, but additional studies would be necessary to demonstrate whether weight loss or improving metabolic health before IVF truly leads to improved LB outcomes. In the meantime, clinicians should be reminded of the importance of screening women for IGT and T2DM, dyslipidemia, and HTN routinely in the preconception years.

CRediT Authorship Contribution Statement

Laura G. Cooney: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Iris Lee:** Writing – original draft, Formal analysis, Conceptualization. **Michelle Goldsammler:** Data curation. **Erin Scott:** Data curation. **Sarah Bjorkman:** Data curation. **Anuja Dokras:** Data curation.

Declaration of Interests

L.G.C. has nothing to disclose. M.D.S. has nothing to disclose. I.L. has nothing to disclose. M.A.C. has nothing to disclose. M.G. has nothing to disclose. E.S. has nothing to disclose. S.B. has nothing to disclose. B.T.F. reports funding from Pfizer and Merck and consulting fees from Astellas outside the submitted work. A.D. has nothing to disclose.

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Los detalles importan: predicción personalizada de nacido vivo luego de fecundación in vitro en mujeres con síndrome de ovario poliquístico.

Objetivo: Obtener y validar internamente un modelo de predicción clínica para nacido vivo (NV) en mujeres con síndrome de ovario poliquístico (SOP) que realizan fecundación in vitro (FIV).

Diseño: Estudio de cohorte retrospectivo.

Escenario: Cuatro clínicas académicas de endocrinología reproductiva.

Pacientes: Un total de 207 mujeres con SOP confirmadas mediante el criterio de Rotterdam que realizaron su primer ciclo de FIV.

Intervenciones: No aplicable.

Medida(s) de desenlace principal(es): El resultado principal fue la tasa acumulada de NV por ciclo iniciado de FIV. Esto incluyó cualquier NV que resultara de cualquiera de las transferencias embrionarias en fresco o cualquiera de las transferencias posteriores de embriones criopreservados obtenidos a partir de la misma aspiración ovocitaria. El modelo de predicción fue obtenido utilizando un análisis de regresión multivariado. Las covariables consideradas para su inclusión en el modelo de predicción fueron las características demográficas, antecedentes médicos y tratamientos de fertilidad previos. Las probabilidades previstas para NV fueron calculadas utilizando un modelo de predicción que incluía un factor de contracción del 90% para cada razón de probabilidades ajustada.

Resultados: El modelo final, basado en la maximización del área bajo la curva, incluyó edades < a 35 años, raza blanca, presencia de ovarios poliquísticos en la ecografía (morfología de ovario poliquístico), índice de masa corporal normal (< 25 Kg/m^2), ser metabólicamente saludable (sin factores de riesgo metabólico) y no responder a los agentes de inducción de la ovulación, incluidos letrozol y citrato de clomifeno. La puntuación del área bajo la curva para el modelo fue de 0.68 (intervalo de confianza 95% [IC]: 0.60, 0.77). Las probabilidades previstas de NV oscilaron entre 8.1% (IC 95%: 2.8, 21.5) para una mujer que no tenía predictores favorables y 74.2% (IC del 95 %: 59.5, 84.9) para una mujer que tenía todos los predictores favorables.

Conclusión: Nuestro estudio demostró que, además de la anovulación, la fisiopatología subyacente y las comorbilidades asociadas altera la probabilidad de embarazo exitoso en mujeres con síndrome de ovario poliquístico que realizan FIV. Se necesita mayor validación de este modelo antes poder servir como herramienta para personalizar las estimaciones de predicción de la probabilidad de NV en mujeres con síndrome de ovario poliquístico.