ORIGINAL ARTICLE

Body mass index is negatively associated with a good perinatal outcome after in vitro fertilization among patients with polycystic ovary syndrome: a national study

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Objective: To evaluate the association between body mass index (BMI) and good perinatal outcomes after in vitro fertilization (IVF) among women with polycystic ovary syndrome (PCOS).
Design: Retrospective cohort study using 2012-2015 Society for Assisted Reproductive Technology Clinic Outcomes Reporting System data.
Setting: Fertility clinics.
Patient(s): To identify patients most likely to have PCOS, we included women with a diagnosis of ovulation disorder and serum antimüllerian hormone >4.45 ng/mL. Exclusion criteria included age ≥ 41 years, secondary diagnosis of diminished ovarian reserve, preimplantation genetic testing, and missing BMI or primary outcome data.
Intervention(s): None
Main Outcome Measure(s): Good perinatal outcome, defined as a singleton live birth at ≥ 37 weeks with birth weight ≥ 2,500 g and ≤ 4,000 g.
Result(s): The analysis included 9,521 fresh, autologous IVF cycles from 8,351 women. Among women with PCOS, the proportion of cycles with a good perinatal outcome was inversely associated with BMI: underweight 25.1%, normal weight 22.7%, overweight 18.9%, class I 18.4%, class II 14.9%, and class III or super obesity 12.2%. After adjusting for confounders, women in the highest BMI category had 51% reduced odds of a good perinatal outcome compared with normal weight women (adjusted odds ratio 0.49, 95% confidence interval 0.36-0.67).
Conclusion(s): Among women with PCOS undergoing fresh, autologous IVF, the odds of a good perinatal outcome decline with increasing BMI. Women with PCOS should be counseled that the odds of achieving a good perinatal outcome decrease as their weight increases. (Fertil Steril Rep® 2022;■:■–■. ©2022 by American Society for Reproductive Medicine.)
Key Words: PCOS, obesity, IVF outcomes, perinatal outcomes

The prevalence of obesity in the United States has steadily risen over the past two decades, yielding an increasing prevalence of obesity among women entering pregnancy (1, 2). Maternal obesity contributes to poor obstetrical outcomes, including miscarriage, stillbirth, gestational diabetes, and preeclampsia (3-7). Obesity is also associated with adverse outcomes after assisted reproductive technology (ART), including a reduction in live birth rates with increasing body mass index (BMI) (8, 9).

Polycystic ovary syndrome (PCOS) is a common endocrinopathy associated with obesity and infertility. The prevalence of infertility is approximately 50% among women with PCOS, whereas obesity rates range from 30 to 60% (10, 11). Women with PCOS undergoing IVF are at higher risk of miscarriage and obstetrical complications such as gestational diabetes, hypertensive disorders of pregnancy, preterm delivery, and large or small for gestational age infants (12–15).

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Despite the known association between PCOS and obesity, there are limited data on the effect of obesity on in vitro fertilization (IVF) outcomes among women with PCOS, and no prior studies have examined adverse perinatal outcomes such as multiple birth, prematurity, or extremes of birth weight (16–18). As obesity rates continue to climb, we expect to see a growing number of women with obesity and PCOS seeking treatment for infertility. Thus, we aimed to examine the association between BMI and the odds of a good perinatal outcome after fresh autologous IVF in women with PCOS. We hypothesized that the odds of a good perinatal outcome would decrease with increasing BMI.

MATERIALS AND METHODS

This was a retrospective cohort study and was declared exempt by the Duke Health institutional review board (Pro00100912) as the data were de-identified. All 2012-2015 fresh, autologous IVF cycles with patient age <41 and no use of preimplantation genetic testing were queried from the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System (SART CORS). The SART CORS database contains comprehensive data from >90% of all clinics performing ART cycles in the United States. The data were collected through voluntary submission, verified by SART, and then reported to the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). The SART maintains HIPAA-compliant business associates' agreements with reporting clinics. In 2004, after a contract change with Centers for Disease Control and Prevention, SART gained access to the SART CORS data system for the purposes of conducting research. The data in the SART CORS are validated annually, with select clinics having on-site visits for chart review based on an algorithm for clinic selection (19). During each visit, data reported by the clinic were verified with information recorded in patients' charts. In 2012, records for 2,045 cycles at 35 clinics were randomly selected for full validation, along with 238 egg or embryo banking cycles (19). The full validation included a review of 1,318 cycles for which pregnancy was reported. Among the nondonor cycles, 331 were multiple-fetus pregnancies. Ten out of 11 data fields selected for validation were found to have discrepancy rates of ≤5%. The exception was the diagnosis field, which, depending on the diagnosis, had a discrepancy rate between 2.1% and 9.2% (19).

The analysis included women with a diagnosis of "ovulation disorder polycystic ovaries." Women with a secondary infertility diagnosis of diminished ovarian reserve were excluded. Women were also excluded if their indication for ART was designated as "other" with "hypothalamic," "hypogonadotropic hypogonadism," or "hypo-hypo" in the comments. The SART CORS data field "ovulation disorder polycystic ovaries" is broadly defined as "one or more disorders causing reduced fecundity associated with structural, anatomic, or functional impairment of one or both ovaries." Therefore, this category includes women with ovulatory disorders other than PCOS. Recognizing this limitation, we used antimüllerian hormone (AMH) as a surrogate marker to help differentiate PCOS from diminished ovarian reserve or primary ovarian insufficiency. Although not part of the formal diagnostic criteria, AMH is known to be higher in patients with PCOS (20–23). We selected an AMH cutoff of 4.45 ng/mL, which has been shown to have 76% sensitivity and 75% specificity for PCOS (20). Women with an AMH below this cutoff point were excluded from the analyses.

Patients were assigned to BMI categories according to the World Health Organization BMI guidelines: underweight (< 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), class I obesity (30.0–34.9 kg/m^2), class II obesity (35.0–39.9 kg/m^2), class III obesity (40.0–49.9 kg/m^2), and super obesity (≥ 50.0 kg/m^2) (24). Women were excluded if BMI data was missing. Super obesity was left as a standalone category for descriptive tables, but because of the low frequency and lack of events, this category was grouped with class III obesity for statistical analyses. Race and ethnicity were categorized as "Hispanic or Latina," "Non-hispanic White," "Non-hispanic Black," "Other," and "Unknown," as reported by each clinic to the SART CORS. The term "Unknown" was used to identify those patients without race or ethnicity documented in the medical record.

The primary outcome was a "good perinatal outcome," defined as a singleton live birth at ≥ 37 weeks with birth weight ≥ 2,500 g and ≤ 4,000 g. Women were further excluded if data were missing for any component of the composite primary outcome. Secondary outcomes included live birth rate, defined as the proportion of cycles with a live birth entered in SART CORS; multiple birth rate, calculated as the proportion of live births with two or more infants; and prematurity rate, defined as the proportion of live births occurring < 37 weeks gestational age. Low birth weight was defined as birth weight < 2,500g, and macrosomia was defined as birth weight > 4,000g. Implantation rate, as defined by SART CORS, was the greater of the number of fetal hearts on ultrasound or the number of live births plus still births, divided by the total number of embryos transferred. The clinical pregnancy rate was defined as the proportion of cycles with a gestational sac on first-trimester ultrasound. Miscarriage was defined as clinical pregnancy ending before 24 completed weeks of gestation. Ovarian hyperstimulation syndrome was defined as abdominal distension and discomfort with nausea, vomiting, diarrhea, ovarian enlargement, and ultrasonic evidence of ascites.

Analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC) at a two-tailed significance level of 0.05. All available cycles within the study period for a woman were included in the analysis. Marginal models using generalized estimating equations (GEE) were implemented to account for the correlation between repeated IVF cycles. A GEE-type model with a binomial distribution and logit link was implemented to test the association between BMI and a good perinatal outcome with and without the following covariates: age, race, parity, infertility diagnoses, and smoking status. Secondary outcomes were analyzed using GEE-type models without adjustment for covariates. An autoregressive(1) working correlation structure was used along with the robust variance estimator for all models.

TABLE 1

Demographic and baseline characteristics among women with PCOS who underwent fresh, autologous IVF, 2012-2015.

Characteristic	Underweight (N = 231)	Normal (N = 4134)	Overweight (N = 2254)	Class I Obesity (N = 1556)	Class II Obesity (N = 937)	Class III Obesity (N = 381)	Super Obesity (N = 28)	Total (N = 9521)
Age (y), mean (SD)	30.5 ± 3.6	31.3 ± 3.5	31.5 ± 3.7	31.6 ± 3.8	31.6 ± 3.7	31.7 ± 3.6	31.9 ± 4.1	31.4 ± 3.6
AMH (ng/ml), median (25th percentile, 75th percentile)	7.8 (5.8, 11.3)	8.0 (5.9, 11.5)	8.2 (6.1, 12.0)	8.0 (5.9, 11.1)	7.6 (5.9, 10.7)	7.5 (5.9, 10.0)	7.2 (5.7, 10.4)	8.0 (5.9, 11.3)
Race, N (%)								
Hispanic or Latina	3 (1.3%)	143 (3.5%)	136 (6.0%)	109 (7.0%)	81 (8.6%)	21 (5.5%)	1 (3.6%)	494 (5.2%)
Non-hispanic Black	5 (2.2%)	100 (2.4%)	150 (6.7%)	118 (7.6%)	58 (6.2%)	27 (7.1%)	5 (17.9%)	463 (4.9%)
Non-hispanic White	121 (52.4%)	2354 (56.9%)	1141 (50.6%)	820 (52.7%)	553 (59.0%)	224 (58.8%)	17 (60.7%)	5230 (54.9%)
Other	32 (13.9%)	521 (12.6%)	275 (12.2%)	157 (10.1%)	44 (4.7%)	5 (1.3%)	0 (0.0%)	1034 (10.9%)
Unknown	70 (30.3%)	1016 (24.6%)	552 (24.5%)	352 (22.6%)	201 (21.5%)	104 (27.3%)	5 (17.9%)	2300 (24.2%)
Nulligravid, N (%)	159 (68.8%)	2526 (61.1%)	1263 (56.0%)	850 (54.6%)	524 (55.9%)	216 (56.7%)	17 (60.7%)	5555 (58.3%)
Nulliparous, N (%)	192 (83.1%)	3343 (80.9%)	1783 (79.1%)	1227 (78.9%)	756 (80.7%)	293 (76.9%)	25 (89.3%)	7619 (80.0%)
Smoker, N (%)	10 (4.3%)	129 (3.1%)	111 (4.9%)	89 (5.7%)	61 (6.5%)	28 (7.3%)	3 (10.7%)	431 (4.5%)
Additional infertility diagnoses, n (%)								
Male infertility	73 (31.6%)	1339 (32.4%)	739 (32.8%)	518 (33.3%)	309 (33.0%)	119 (31.2%)	6 (21.4%)	3103 (32.6%)
Endometriosis	11 (4.8%)	251 (6.1%)	120 (5.3%)	63 (4.0%)	36 (3.8%)	12 (3.1%)	1 (3.6%)	494 (5.2%)
Uterine factor	7 (3.0%)	170 (4.1%)	108 (4.8%)	83 (5.3%)	39 (4.2%)	13 (3.4%)	1 (3.6%)	421 (4.4%)
Tubal factor	16 (6.9%)	248 (6.0%)	210 (9.3%)	154 (9.9%)	77 (8.2%)	48 (12.6%)	2 (7.1%)	755 (7.9%)
Other	15 (6.5%)	147 (3.6%)	98 (4.3%)	72 (4.6%)	31 (3.3%)	22 (5.8%)	2 (7.1%)	387 (4.1%)

SD = standard deviation; AMH = anti-Müllerian hormone.

Hynes. BMI and IVF outcomes in women with PCOS. Fertil Steril Rep 2022.

TABLE 2

Fresh autologous IVF cycle characteristics among women with PCOS, 2012-2015.

Cycle characteristic	N	Underweight	Normal	Overweight	Class I obesity	Class II obesity	Class III obesity or super obesity	P*
Total FSH dose, IU[a]	9320	1802.2 ± 832.4	1900.6 ± 899.6	2058.0 ± 926.0	2302.5 ± 1010.2	2634.3 ±1198.9	2900.6 ± 1267.6	
Beta (95% CI)		-93.7 (-209.8–22.3)	Reference	155.7 (105.5–205.8)	391.5 (333.2–449.9)	686.2 (602.6–769.9)	1022.6 (896.2–1149.1)	<.001
Oocytes retrieved[b]	9521	18.0 (13.0, 25.0)	19.0 (13.0, 26.0)	18.0 (12.0, 25.0)	18.0 (12.0, 25.0)	16.0 (10.0, 23.0)	15.0 (9.0, 22.0)	
Beta (95% CI)		-0.78 (-2.26–0.69)	Reference	-0.78 (-1.35 to -0.21)	-1.23 (-1.88 to -0.58)	-2.86 (-3.64 to -2.09)	-4.03 (-5.10 to -2.95)	<.001
Embryos cryopreserved[b]	9521	4.0 (1.0, 7.0)	3.0 (0.0, 7.0)	3.0 (0.0, 7.0)	2.0 (0.0, 6.0)	2.0 (0.0, 5.0)	2.0 (0.0, 5.0)	
Beta (95% CI)		-0.02 (-0.62–0.57)	Reference	-0.35 (-0.60 to -0.10)	-0.85 (-1.11 to -0.58)	-1.06 (-1.40 to -0.73)	-1.33 (-1.73 to -0.93)	<.001
ICSI N (%)	9521	158 (68.4)	2854 (69.0)	1593 (70.7)	1053 (67.7)	640 (68.3)	285 (69.7)	
Odds ratio (95% CI)		0.96 (0.72–1.29)	Reference	1.09 (0.97–1.22)	0.94 (0.83 – 1.07)	1.00 (0.85 – 1.17)	1.04 (0.83 – 1.31)	.488
Assisted hatching, N (%)	9521	39 (16.9)	675 (16.3)	418 (18.5)	303 (19.5)	168 (17.9)	83 (20.3)	
Odds ratio (95% CI)		1.03 (0.71–1.49)	Reference	1.18 (1.03–1.35)	1.23 (1.06 – 1.44)	1.13 (0.93 – 1.37)	1.35 (1.04 – 1.74)	.036
Blastocyst transfer[c] N(%)	6834	122 (75.3)	2146 (74.0)	1209 (74.0)	848 (73.9)	486 (71.3)	206 (66.9)	
Odds ratio (95% CI)		1.10 (0.75–1.60)	Reference	0.99 (0.86–1.14)	0.97 (0.83–1.14)	0.87 (0.72–1.05)	0.72 (0.55–0.93)	.178
Embryos transferred[b,c]	6834	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	
Beta (95% CI)		-0.03 (-0.12–0.06)	Reference	0.07 (0.04–0.11)	0.08 (0.04–0.12)	0.12 (0.08–0.17)	0.16 (0.09–0.23)	<.001

FSH = follicle stimulating hormone; ICSI = intracytoplasmic sperm injection.

* *P* value for overall association between BMI and cycle characteristic.

[a] Reported as mean (standard deviation).

[b] Reported as median (25th percentile, 75th percentile).

[c] Reported among cycles with transfer attempted.

Hynes. BMI and IVF outcomes in women with PCOS. Fertil Steril Rep 2022.

Cycles with missing values for the primary outcome were excluded from the analysis. Two cycles with missing parity were also excluded. Given that BMI was missing for > 10% of cycles, we confirmed that outcomes were clinically similar between cycles with missing and nonmissing BMI. Cycles with missing values in BMI were then excluded from the analysis. As a sensitivity analysis, an additional BMI category was created for the cycles with missing BMI. The unadjusted and adjusted primary outcome models were then refitted with this additional BMI category included as a covariate.

RESULTS

Among the 10,921 identified cycles, 118 (1.1%) were excluded because of a diagnosis of diminished ovarian reserve or hypothalamic amenorrhea (Supplemental Figure 1, available online). Forty-six (0.4%) cycles were excluded for missing good perinatal outcomes, 2 (0.02%) for missing parity, and 1,234 (11.3%) for missing BMI. A total of 9,521 cycles among 8,351 unique women were included in the analysis. The mean age across all cycles was 31.5 years, and the median AMH was 7.9 ng/mL (Table 1). Nearly half of the cycles (45.0%) had a secondary cause of infertility in addition to PCOS, most commonly male factor (32.6%).

The median number of oocytes retrieved ranged from 19 in the normal BMI group to 15 in the group with class III obesity and super obesity (Table 2). The number of supernumerary embryos cryopreserved decreased from a median of three in the normal weight and overweight categories to two in women with any stage of obesity. There were no significant differences in the use of intracytoplasmic sperm injection or cleavage stage versus blastocyst transfer between BMI categories.

With increasing BMI, women had lower rates of implantation, clinical pregnancy, and live birth (Table 3). Elevated BMI was also significantly associated with miscarriage, macrosomia, and prematurity, but not multiple birth or low birth weight. Among women with BMI in the overweight range or higher, rates of ovarian hyperstimulation syndrome declined with increasing BMI.

The proportion of cycles with a good perinatal outcome was highest in the women with underweight BMI (25.1%) and decreased with increasing BMI to a low of 12.2% in the group with class III obesity or super obesity (Table 4, unadjusted odds ratio [OR] 0.47, 95% confidence interval [CI], 0.35–0.65; $P<.001$, compared with normal weight group).

The multivariable GEE model demonstrated that BMI was significantly and inversely associated with the odds of a good perinatal outcome after adjusting for age, race, parity, infertility diagnoses other than PCOS, and smoking status (Table 4). Compared with women with normal BMI, the odds of a good perinatal outcome were reduced by 17% (OR, 0.83; 95%, CI 0.73–0.94), 19% (OR, 0.81; 95% CI, 0.70–0.94), 38% (OR, 0.62; 95% CI, 0.51–0.75), and 51% (OR, 0.49; 95% CI, 0.36–0.67) with overweight, class I obesity, class II obesity, and class III obesity or super obesity, respectively.

To confirm that the findings were not skewed by excluding cycles with missing BMI, a sensitivity analysis

TABLE 3

Associations between BMI and cycle outcomes among women with PCOS undergoing fresh, autologous IVF, 2012-2015.

Cycle outcome	N	Underweight	Normal	Overweight	Class I obesity	Class II obesity	Class III obesity or super obesity	*P**
Implantation[a]	—	0.49	0.48	0.43	0.40	0.37	0.32	—
Clinical pregnancy[b] n (%)	9521	105 (45.5)	1828 (44.2)	958 (42.5)	657 (42.2)	362 (38.6)	138 (33.7)	
Odds ratio (95% CI)		1.04 (0.80–1.35)	Reference	0.93 (0.84–1.03)	0.93 (0.82–1.04)	0.79 (0.68–0.92)	0.65 (0.52–0.81)	<.001
Live birth[b] n (%)	9521	93 (40.3)	1591 (38.5)	796 (35.3)	527 (33.9)	293 (31.3)	107 (26.2)	
Odds ratio (95% CI)		1.07 (0.82–1.39)	Reference	0.87 (0.78–0.97)	0.82 (0.72–0.93)	0.73 (0.62–0.84)	0.57 (0.45–0.72)	<.001
Miscarriage[c] n (%)	4048	11 (10.5)	208 (11.4)	148 (15.4)	112 (17.0)	67 (18.5)	30 (21.7)	
Odds ratio (95% CI)		0.80 (0.41–1.57)	Reference	1.41 (1.12–1.77)	1.67 (1.30–2.15)	1.74 (1.27–2.37)	2.31 (1.50–3.57)	<.001
Multiple birth[d] n (%)	3407	23 (24.7)	407 (25.6)	239 (30.0)	127 (24.1)	81 (27.6)	38 (35.5)	
Odds ratio (95% CI)		0.95 (0.59–1.55)	Reference	1.24 (1.03–1.50)	0.92 (0.73–1.16)	1.11 (0.84–1.47)	1.61 (1.06–2.43)	.055
Low birth weight[d] n (%)	3380	21 (22.8)	386 (24.4)	190 (24.1)	125 (23.9)	79 (27.3)	30 (28.3)	
Odds ratio (95% CI)		0.91 (0.55–1.51)	Reference	0.98 (0.81–1.20)	0.97 (0.77–1.23)	1.16 (0.88–1.54)	1.23 (0.79 –1.90)	.815
Macrosomia[d] n (%)	3380	2 (2.2)	68 (4.3)	48 (6.1)	45 (8.6)	23 (8.0)	4 (3.8)	
Odds ratio (95% CI)		0.49 (0.12–2.05)	Reference	1.42 (0.97–2.08)	2.00 (1.32–3.03)	2.07 (1.23–3.48)	0.88 (0.31–2.46)	.002
Prematurity[d] n (%)	3394	22 (23.7)	402 (25.3)	241 (30.4)	151 (28.8)	94 (32.4)	36 (33.6)	
Odds ratio (95% CI)		0.91 (0.56–1.49)	Reference	1.28 (1.06–1.55)	1.19 (0.96 – 1.49)	1.41 (1.07–1.84)	1.50 (0.99–2.28)	.024
OHSS[b] n (%)	9521	37 (16.0)	683 (16.5)	320 (14.2)	197 (12.7)	104 (11.1)	41 (10.0)	
Odds ratio (95% CI)		0.96 (0.67–1.38)	Reference	0.84 (0.72– 0.97)	0.73 (0.62 – 0.87)	0.63 (0.51 – 0.79)	0.56 (0.40 –0.79)	<.001

CI = confidence interval; OHSS = ovarian hyperstimulation syndrome.
* *P* value for overall association between BMI and outcome.
[a] Implantation rate presented as ratio of implantations per number of embryos transferred.
[b] Reported among all cycles.
[c] Reported among cycles with clinical pregnancy.
[d] Reported among cycles with live birth.

Hynes. BMI and IVF outcomes in women with PCOS. Fertil Steril Rep 2022.

TABLE 4

Association between BMI and good perinatal outcome among women with PCOS, 2012-2015.

	Good perinatal outcome[a]	Unadjusted		Adjusted*	
BMI category	**N (%)**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Underweight	58 (25.1)	1.14 (0.84–1.54)	.401	1.14 (0.84–1.55)	.396
Normal	940 (22.7)	Reference	—	Reference	—
Overweight	425 (18.9)	0.79 (0.70–0.90)	< .001	0.83 (0.73–0.94)	.005
Class I obesity	286 (18.4)	0.76 (0.66–0.89)	< .001	0.81 (0.70–0.94)	.006
Class II obesity	140 (14.9)	0.60 (0.49–0.72)	< .001	0.62 (0.51–0.75)	< .001
Class III obesity/Super obesity	50 (12.2)	0.47 (0.35–0.65)	< .001	0.49 (0.36–0.67)	< .001

BMI = body mass index; OR = odds ratio; CI = confidence intervals.
* Adjusted for age, race, parity, secondary infertility diagnoses, and smoking status.
[a] Good perinatal outcome defined as a singleton live birth at ≥ 37 weeks with birth weight ≥ 2,500 g and ≤ 4,000 g.

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including these 1,234 cycles was performed with a "missing BMI" category. When the unadjusted and adjusted primary outcome models were refit with this additional BMI category as a covariate, the results were consistent with those of the primary analysis (Supplemental Table 1, available online).

DISCUSSION

The results of this large national study demonstrate that BMI is negatively associated with the odds of a singleton, term delivery of a normal weight infant after fresh, autologous IVF among women with PCOS. Our data indicate that obesity is strongly associated with worse ART outcomes, even among a study population with a high baseline prevalence of obesity.

Our findings are consistent with those of a retrospective cohort study that used 2008-2010 SART CORS data to demonstrate a negative association between BMI and live birth rates among women with a diagnosis of ovulation disorder (9). Because the ovulation disorder diagnosis was not exclusive to PCOS, however, many women with other causes of ovulation dysfunction were inadvertently included in their analysis. Given the limitations of that study, we chose to use an AMH cutoff of > 4.45ng/mL to improve the likelihood of excluding women without PCOS (20). We also excluded women with a secondary infertility diagnosis of diminished ovarian reserve or an ART indication consistent with hypothalamic amenorrhea. Therefore, the results of the present study have greater internal validity and are more applicable to the PCOS population.

Other existing studies have been too small to categorize women into more than two or three BMI categories, and some were underpowered to detect a meaningful difference in live birth rates (16–18). Those that did compare live birth rates did not examine rates of multiple birth or associated neonatal morbidities such as prematurity and low birth weight.

The present study is strengthened by its large sample size and the use of clinically relevant WHO BMI categories. It is also strengthened by the use of a composite variable, a good perinatal outcome, advocated as the most clinically relevant measure of IVF success (25–27). The use of live birth rate as the primary outcome underestimates the morbidity associated with multiple births, specifically prematurity and low birth weight (28). Notably, the median number of embryos transferred in the present study population was two across all BMI categories despite national guidelines advocating single embryo transfer to maximize the likelihood of a healthy live birth (26, 27, 29, 30). Consequently, the multiple birth rate was as high as 36%, with up to one-third of women delivering prematurely. Even in the lowest BMI categories, only one-quarter of women experienced a good perinatal outcome. Our results accentuate the importance of performing single embryo transfer in good-prognosis patients, regardless of BMI.

The present study also has limitations, most notably the challenge of identifying a population of women with PCOS from SART CORS. We recognize that AMH level is not a traditional diagnostic criterion for PCOS. However, no distinct category existed for PCOS in SART CORS at the time of data collection. Given that previous studies did not address this limitation at all, we feel that the use of an AMH cutoff significantly reduces the risk of misclassification bias compared with those of prior SART CORS studies in which a PCOS diagnosis was incorrectly assigned to all women with ovulatory dysfunction. Despite the use of an AMH cutoff and the exclusion of women with a clear diagnosis of hypothalamic amenorrhea, we acknowledge that there was no way to definitively exclude all women without PCOS from our cohort. We also acknowledge that some women with PCOS and an AMH level on the lower end of the spectrum may inadvertently have been excluded.

Additionally, despite the large cohort, there were a limited number of women with super obesity (BMI > 50). However, this reflects reality as many IVF centers have BMI limits in place to prevent dangerous anesthesia complications or the numerous obstetric risks associated with such morbid obesity (3, 31). By combining the class III obesity and super obesity groups, we maintained the ability to show clinically meaningful differences in ART outcomes in women with morbid obesity. Notably, whereas approximately 10% of women were missing BMI data, the sensitivity analysis is reassuring that this missing data does not affect the results. However, this remains a potential source of bias if an unequal

proportion of these women with unknown BMI came from a single BMI category.

During our study period (2012-2015), the rate of missing AMH data was approximately 50%, likely based on the newness of this variable at that time. However, the proportion of missing AMH data was similar between women, with (49%) and without (50%) a diagnosis of "ovulatory disorder polycystic ovaries." Moreover, when applying our inclusion/exclusion criteria to the cohort, aside from AMH > 4.45, the rate of a good perinatal outcome was similar between the group with AMH data (19.5%) compared with the group with missing AMH data (20.1%). Taken together, these findings support a lack of bias introduced by this missing AMH data.

Although SART CORS includes abundant IVF cycle data, it does not include obstetric complications that may affect the likelihood of our composite outcome via pathways unrelated to ART; for example, iatrogenic preterm delivery for preeclampsia or macrosomia in the setting of gestational diabetes. Regardless of the causal pathway, these complications are known risks for women with obesity and PCOS and should be accounted for when counseling patients about their chances of a healthy infant after IVF.

Finally, our dataset includes only fresh cycles and may not be generalizable to subsequent frozen embryo transfers (32). However, our results show that the women with obesity have fewer cryopreserved embryos for future use, and thus, their cumulative success per oocyte retrieval is likely similarly decreased.

CONCLUSIONS

This large, national, retrospective study demonstrated that the odds of a good perinatal outcome decline with increasing BMI among women with PCOS. Women with PCOS and elevated BMI should be counseled that a decreased BMI may optimize their odds of achieving term delivery of a normal weight singleton—the ultimate goal of IVF.

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REFERENCES

1. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015-2016. NCHS Data Brief; 2017.
2. Fisher SC, Kim SY, Sharma AJ, Rochat R, Morrow B. Is obesity still increasing among pregnant women? Prepregnancy obesity trends in 20 states, 2003-2009. Prev Med 2013;56:372–8.
3. Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, et al. Obesity, obstetric complications and cesarean delivery rate–a population-based screening study. Am J Obstet Gynecol 2004;190:1091–7.
4. Salihu HM, Dunlop AL, Hedayatzadeh M, Alio AP, Kirby RS, Alexander GR. Extreme obesity and risk of stillbirth among black and white gravidas. Obstet Gynecol 2007;110:552–7.
5. Yao R, Ananth CV, Park BY, Pereira L, Plante LA. Obesity and the risk of stillbirth: a population-based cohort study. Am J Obstet Gynecol 2014;210, 457.e1–9.
6. Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. Hum Reprod 2004;19:1644–6.
7. Chu SY, Kim SY, Schmid CH, Dietz PM, Callaghan WM, Lau J, et al. Maternal obesity and risk of cesarean delivery: a meta-analysis. Obes Rev 2007;8:385–94.
8. Maheshwari A, Stofberg L, Bhattacharya S. Effect of overweight and obesity on assisted reproductive technology–a systematic review. Hum Reprod Update 2007;13:433–44.
9. Provost MP, Acharya KS, Acharya CR, Yeh JS, Steward RG, Eaton JL, et al. Pregnancy outcomes decline with increasing body mass index: analysis of 239,127 fresh autologous in vitro fertilization cycles from the 2008-2010 society for assisted reproductive technology registry. Fertil Steril 2016;105:663–9.
10. Balen AH, Conway GS, Kaltsas G, Techatraisak K, Manning PJ, West C, et al. Andrology: polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. Hum Reprod 1995;10:2107–11.
11. Ezeh U, Yildiz BO, Azziz R. Referral bias in defining the phenotype and prevalence of obesity in polycystic ovary syndrome. J Clin Endocrinol Metab 2013;98:E1088–96.
12. Sterling L, Liu J, Okun N, Sakhuja A, Sierra S, Greenblatt E. Pregnancy outcomes in women with polycystic ovary syndrome undergoing in vitro fertilization. Fertil Steril 2016;105:791–7.e2.
13. Han AR, Kim HO, Cha SW, Park CW, Kim JY, Yang KM, et al. Adverse pregnancy outcomes with assisted reproductive technology in non-obese women with polycystic ovary syndrome: a case-control study. Clin Exp Reprod Med 2011;38:103–8.
14. Yan X, Shi YH, Sheng Y, Tang R, Xu LH, Li Y, et al. [Pregnancy outcomes of patients with polycystic ovary syndrome undergoing in vitro fertilization and embryo transfer]. Zhonghua Fu Chan Ke Za Zhi 2011;46:923–7.
15. Sha T, Wang X, Cheng W, Yan Y. A meta-analysis of pregnancy-related outcomes and complications in women with polycystic ovary syndrome undergoing IVF. Reprod Biomed Online 2019;39:281–93.
16. Bailey AP, Hawkins LK, Missmer SA, Correia KF, Yanushpolsky EH. Effect of body mass index on in vitro fertilization outcomes in women with polycystic ovary syndrome. Am J Obstet Gynecol 2014;211, 163.e1–6.
17. Bu Z, Dai W, Guo Y, Su Y, Zhai J, Sun Y. Overweight and obesity adversely affect outcomes of assisted reproductive technologies in polycystic ovary syndrome patients. Int J Clin Exp Med 2013;6:991–5.
18. Jungheim ES, Lanzendorf SE, Odem RR, Moley KH, Chang AS, Ratts VS. Morbid obesity is associated with lower clinical pregnancy rates after in vitro fertilization in women with polycystic ovary syndrome. Fertil Steril 2009;92:256–61.
19. Prevention CfDCa. 2005 Assisted reproductive technology success rates: National summary and fertility clinic reports. In: American Society for Reproductive Medicine. Society for Assisted Reproductive Technology; 2007.
20. Wiweko B, Maidarti M, Priangga MD, Shafira N, Fernando D, Sumapraja K, et al. Anti-mullerian hormone as a diagnostic and prognostic tool for PCOS patients. J Assist Reprod Genet 2014;31:1311–6.
21. Pellatt L, Hanna L, Brincat M, Galea R, Brain H, Whitehead S, et al. Granulosa cell production of anti-Müllerian hormone is increased in polycystic ovaries. J Clin Endocrinol Metab 2007;92:240–5.
22. Skałba P, Cygal A, Madej P, Dąbkowska-Huć A, Sikora J, Martirosian G, et al. Is the plasma anti-Müllerian hormone (AMH) level associated with body weight and metabolic, and hormonal disturbances in women with and without polycystic ovary syndrome? Eur J Obstet Gynecol Reprod Biol 2011;158:254–9.

23. Begawy AF, El-Mazny AN, Abou-Salem NA, El-Taweel NE. Anti-Müllerian hormone in polycystic ovary syndrome and normo-ovulatory women: correlation with clinical, hormonal and ultrasonographic parameters. Middle East Fertil Soc J 2010;15:253–8.
24. Obesity: preventing and managing the global epidemic: Report of a WHO Consultation. World Health Organization; 2000.
25. Joshi N, Kissin D, Anderson JE, Session D, Macaluso M, Jamieson DJ. Trends and correlates of good perinatal outcomes in assisted reproductive technology. Obstet Gynecol 2012;120:843–51.
26. Kissin DM, Kulkarni AD, Kushnir VA, Jamieson DJ. Number of embryos transferred after in vitro fertilization and good perinatal outcome. Obstet Gynecol 2014;123:239–47.
27. Steinberg ML, Boulet S, Kissin D, Warner L, Jamieson DJ. Elective single embryo transfer trends and predictors of a good perinatal outcome–United States, 1999 to 2010. Fertil Steril 2013;99:1937–43.
28. Sunderam S, Kissin DM, Zhang Y, Folger SG, Boulet SL, Warner L, et al. Assisted reproductive technology surveillance - United States, 2016. MMWR Surveill Summ 2019;68:1–23.
29. Mersereau J, Stanhiser J, Coddington C, Jones T, Luke B, Brown MB. Patient and cycle characteristics predicting high pregnancy rates with single-embryo transfer: an analysis of the Society for Assisted Reproductive Technology outcomes between 2004 and 2013. Fertil Steril 2017;108:750–6.
30. Elective single-embryo transfer. In: Practice Committee of the Society for Assisted Reproductive Technology. Vol. 97. Fertil Steril 2012:835–842.
31. Kaye L, Sueldo C, Engmann L, Nulsen J, Benadiva C. Survey assessing obesity policies for assisted reproductive technology in the United States. Fertil Steril 2016;105:703–6.e2.
32. Chen Z-J, Shi Y, Sun Y, Zhang B, Liang X, Cao Y, et al. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. N Engl J Med 2016;375:523–33.