REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

Effect of body mass index on in vitro fertilization outcomes in women with polycystic ovary syndrome

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OBJECTIVE: The objective of the investigation was to study the effect of body mass index (BMI) on in vitro fertilization (IVF) outcomes within a polycystic ovary syndrome (PCOS) population.

STUDY DESIGN: This was a retrospective cohort study including 101 cycles from 79 women younger than 40 years old with a clinically documented diagnosis of PCOS by Rotterdam criteria undergoing IVF at a university-based infertility clinic from 2001 through 2010. All participants were stratified by BMI calculated from height and weight recorded within 3 months of cycle start: lean (18.7-24.9 kg/m^2, n = 51), overweight (25-29.9 kg/m^2, n = 19), and obese (≥30 kg/m^2, n = 31). Linear, logistic, and Poisson regressions were used as appropriate to estimate the effect of a range of BMIs on IVF outcomes while adjusting for potential confounders.

RESULTS: Obese PCOS women had 69% lower odds of clinical pregnancy per cycle start (odds ratio [OR], 0.31; 95% confidence interval [CI], 0.11—0.86; $P = .02$) and 77% lower odds of clinical pregnancy per embryo transfer (OR, 0.23; 95% CI, −0.08 to 0.68; $P = .008$) compared with lean PCOS women. Among obese PCOS women, the odds of live birth were 71% lower per cycle start (OR, 0.29; 95% CI, 0.10—0.84; $P = .02$) and 77% lower per embryo transfer (OR, 0.23; 95% CI, 0.07—0.71; $P = .01$) compared with lean PCOS women. There was a trend toward decreased ovarian hyperstimulation syndrome incidence with increasing BMI among women with PCOS: 19.6% in lean, 10.5% in overweight, and 3.2% in obese.

CONCLUSION: PCOS is a broad syndrome, with our results demonstrating 2 distinct populations, lean and obese, which have different IVF outcomes including ovarian hyperstimulation syndrome risk profiles. This information is important for clinicians because it informs treatment decisions.

Key words: assisted reproduction, body mass index, in vitro fertilization, polycystic ovary syndrome, weight

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Polycystic ovary syndrome (PCOS) affects 4-6% of women.[1-3] It is the most common endocrinopathy among reproductive-age women and accounts for a large proportion of patients seeking assisted reproductive technologies.[4] Of those affected by PCOS, 50% are obese with a body mass index (BMI) of 30 kg/m^2 or greater.[5] Yet this disease is a multifactorial condition that includes different pathophysiological pathways. One possible pathway is via increased luteinizing hormone pulse frequency in both lean and obese women with PCOS compared with normally cycling women,[6] which may have effects on the follicular cohort that is recruited. Other physiological and hormonal events contributing to the dysfunction differ across a spectrum of weights.

In a non-PCOS population, BMI is known to affect in vitro fertilization (IVF) outcomes.[7,8] Although weight reduction improves fertility in PCOS patients attempting spontaneous conception,[9-11] studies of PCOS patients to date do not fully evaluate the impact of a range of BMIs on IVF outcomes.[12-22] One study quantified the negative impact of morbid obesity on pregnancy outcomes in a group of women with PCOS, although a lean-only PCOS population was not included for comparison.[12]

In 2011, Marquard et al[13] found that obesity and PCOS were both independently associated with smaller oocyte diameter among 8 obese and 5 nonobese PCOS patients, although only patients undergoing intracytoplasmic sperm injection (ICSI) were included. A 2001 study from Norway evaluated 100 cycles from 56 PCOS patients categorized by insulin-resistance status, which did not correlate completely with BMI. Those findings showed that insulin resistance was associated with a lower oocyte count and increased follicle stimulating hormone (FSH) requirement; however, the data analysis controlled for

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TABLE 1
2003 Rotterdam ESHRE/ASRM Criteria[23]

(2 of the 3 required for PCOS diagnosis)
Oligoovulation or anovulation
Clinical (acne, hirsutism) and/or biochemical signs of hyperandrogenism
Total testosterone >70 ng/dL
Androstenedione >245 ng/dL
Dehydroepiandrosterone sulfate >248 ug/dL
Polycystic ovaries
≥12 follicles 2-9 mm in diameter in each ovary

ASRM, American Society for Reproductive Medicine; *ESHRE*, European Society for Human Reproduction and Embryology; *PCOS*, polycystic ovary syndrome.

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body weight.[14] A 2008 study of lean and obese PCOS and non-PCOS patients found that more oocytes were retrieved from lean than from obese PCOS patients, although the findings were limited by low PCOS prevalence (19%), which may have contributed to the lack of significant differences in clinical outcomes (implantation, miscarriage, live birth, and multiple birth rates).[15]

The increased incidence of ovarian hyperstimulation syndrome (OHSS) in PCOS patients is also well documented[16] but not differentiated with regard to BMI-adjusted risk. So the full effects of a spectrum of body masses among reproductive-aged women with PCOS remain poorly studied.

Considering that 50% of PCOS patients are not obese,[5] characterizing associations of a range of BMIs with ovarian response and clinical IVF outcomes could inform the management of PCOS patients. Specifically, characterizing any relationships between BMI and OHSS would lay the groundwork for investigation of how BMI-dependent dosing of gonadotropins might reduce morbidity because of OHSS, a serious disease for which PCOS patients are at elevated risk.[23]

We hypothesized that PCOS is a broad syndrome comprised of unique BMI-determined subpopulations that exhibit differences in IVF outcomes. Our secondary hypothesis was that there is a higher incidence of OHSS in the lean PCOS group when gonadotropin dosing is not BMI adjusted. This information would be important for clinicians with respect to making treatment decisions.

Materials and Methods

We investigated these hypotheses in a retrospective cohort study within an urban academic medical center's IVF practice that included 101 cycles from 79 women younger than 40 years old who started a fresh, autologous IVF cycle with or without ICSI between January 2001 and December 2010. This study received appropriate approval from the Partners Institutional Review Board (no. 2012P000196) prior to data collection.

Women eligible for inclusion were those with clinically measured height and weight within 3 months of their cycle start date, who also met strict diagnostic criteria for PCOS as defined by the 2003 Rotterdam European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine-sponsored PCOS consensus workshop group[24] (Table 1).

This set of diagnostic criteria was chosen to permit inclusion of a wide range of PCOS phenotypes because lean patients are more likely to have milder expressions of the disease including spontaneous ovulation. Each patient's medical record was meticulously reviewed to ensure that they fit the Rotterdam criteria for PCOS diagnosis.

Women whose embryo transfers were cancelled because of the high risk of OHSS were still included in the clinical outcomes analyses. Those with a transfer were restricted to day 3 fresh embryo transfers to allow for standardization of embryological outcomes. Multiple eligible fresh cycles for each patient were included, and all stimulation protocols were included. Infertility diagnoses were defined by physician documentation. ICSI was performed only if indicated by semen parameters.

Individual record review was performed for all patients and all cycles. Exclusion criteria included the use of in vitro maturation, FSH greater than 10 mIU/mL, uncontrolled thyroid disease as defined by thyroid-stimulating hormone of 5.7 mIU/L or greater based on our laboratory cutoff for an abnormal value, a history of chemotherapy or radiation exposure, a recurrent pregnancy loss, uterine factor, balanced translocation (in either partner), surgically documented endometriosis or pelvic adhesions, a history of pelvic inflammatory disease, adenomyosis, and submucosal myoma.

TABLE 2
Demographic characteristics by BMI category

Outcome	Lean (n = 51)	Overweight (n = 19)	Obese (n = 31)
Age, y[a]	32.0 (3.5) 23.7–39.2	32.6 (2.9) 27.5–36.8	32.4 (3.2) 24.8–38.0
BMI, kg/m^2[a]	22.2 (1.6) 18.7–24.9	27.1 (1.3) 25.1–29.4	39.0 (7.4) 30.2–59.2
Male factor[b]	15 (29.4%)	4 (21.1%)	12 (38.7%)
ICSI[b]	10 (19.6%)	2 (10.5%)	10 (32.3%)
Anovulation/oligoovulation[b]	51 (100.0%)	19 (100.0%)	31 (100.0%)
Hyperandrogenism[b]	33 (64.7%)	15 (78.9%)	26 (83.9%)
Polycystic ovaries on ultrasound[b]	19 (37.3%)	4 (21.1%)	5 (16.1%)

BMI, body mass index; *ICSI*, intracytoplasmic sperm injection.

[a] Mean (SD) and range; [b] n (percentage).

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