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ASSISTED REPRODUCTION TECHNOLOGIES

The effect of female body mass index on in vitro fertilization cycle outcomes: a multi-center analysis

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Abstract

Purpose The aim of this study is to examine the impact of female body mass index (BMI) on IVF cycle outcomes.

Methods This is a retrospective cohort study including 51,198 women who initiated their first autologous IVF cycle in 13 fertility centers in the USA between 2009 and 2015. The effect of underweight, overweight, and obese BMI on four different IVF cycle outcomes (cycle cancellation, oocyte and embryo counts, and ongoing clinical pregnancy [OCP]) was evaluated in logistic or Poisson regression analyses with confounders adjusted.

Results Women with an overweight or obese BMI experienced worse outcomes than those with a normal BMI. These differences included (1) greater odds of cycle cancellation (aOR [95%CI] 1.17 [1.08, 1.26] for overweight, 1.28 [1.15, 1.41] for class-I obesity, and 1.50 [1.33, 1.68] for class-II/III obesity, $P < .001$ for all); (2) fewer oocytes retrieved (aIRR [95%CI] 0.98 [0.98,0.99] for class-I obesity, 0.93 [0.92,0.94] for class-II/III obesity, $P < .001$ for both); (3) fewer usable embryos (aIRR [95%CI] 0.98 [0.97,0.99] for overweight, 0.97 [0.96,0.99] for class-I obesity, 0.95 [0.93,0.97] for class-II/III obesity, $P < .01$ for all); and (4) lower odds of OCP (aOR [95%CI] 0.89 [0.83,0.95] for class-I obesity, 0.86 [0.79,0.93] for class-II/III obesity, $P < .001$ for both). In a subgroup analysis based on primary infertility diagnosis, these trends persisted in those with male or uterine factor and were especially pronounced in women with ovulatory dysfunction or PCOS.

Conclusions A BMI above the normal range was an independent negative prognostic factor for multiple outcomes, including cycle cancellation, oocyte and embryo counts, and OCP. These negative outcomes were most profound in women with class-II/III obesity, ovulatory dysfunction, or PCOS.

Keywords Infertility · IVF/ICSI outcome · Body mass · Polycystic ovaries · Obesity · PCOS

Introduction

As reproductive medicine continues to advance, with continual improvement in in vitro fertilization (IVF) success rates [1], some fundamental physiological questions, such as whether body mass index (BMI) impacts fertility and pregnancy outcomes, still remain unanswered. Approximately half of reproductive-aged women in the USA and Europe are overweight (BMI 25.00–29.99 kg/m^2) or obese (BMI ≥ 30.00 kg/m^2); therefore, understanding this potential impact of BMI remains critically important [2, 3]. Compared to women with a normal BMI (18.50–24.99 kg/m^2), women with an elevated BMI are more likely to experience disruption in the hypothalamic-pituitary-ovarian axis, irregular menstrual cycles, and ovulatory dysfunction, all of which lead to higher rates of infertility [4, 5]. Obesity is also associated with higher

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rates of obstetric complications [6–10], and these effects may be compounded by racial and ethnic disparities [11].

Studies exploring the potential effects of elevated BMI on fertility treatment outcomes have demonstrated conflicting results. Surprisingly, multiple studies and two systematic reviews reported no significant adverse effects of elevated BMI on IVF outcomes [12–17]. Other studies, however, including two recent meta-analyses have associated elevated BMI with higher gonadotropin requirement, fewer oocytes collected, higher cancellation rates, reduced pregnancy and live birth rates, as well as higher miscarriage rates [18–27]. In the most recent meta-analysis, from 2011, overweight or obese women undergoing IVF were observed to have a lower relative risk (RR) of clinical pregnancy (RR = 0.90, $P < 0.0001$) and live birth (RR = 0.84, $P = 0.0002$), with a higher miscarriage rate (RR = 1.31, $P < 0.0001$), when compared to women with a normal BMI [28]. In an analysis of nearly 500,000 cycles reported to the Society for Assisted Reproductive Technologies (SART), both obese and underweight women had lower rates of clinical pregnancy and live birth after fresh autologous transfers (adjusted RR 0.97 and 0.95 for underweight, 0.94 and 0.87 for obese women, respectively), as well as higher rates of low birth weight and premature deliveries. Meanwhile, in the study, only obese women had a higher miscarriage rate [29].

Some studies have tried to identify the specific mechanisms by which excess weight might affect IVF outcomes by exploring associations with egg quality, embryo quality, or uterine function. For example, preliminary data has associated maternal obesity with decreased oocyte size [30] or dysregulation of meiotic spindle formation [31]. Meanwhile, Comstock and colleagues demonstrated a significantly better blastocyst formation rate in normal-weight controls versus overweight or obese individuals (57.2 vs. 43.6%, $P < 0.007$) and further showed that the blastocysts of overweight women with metabolic dysfunction did as poorly as those of the obese women [32].

Given these results and the higher spontaneous miscarriage rates that have been observed in obese women [17], some researchers have speculated that increased meiotic errors might underlay these pregnancy losses. However, higher miscarriage rates were also observed in one study of women who had pre-implantation screened embryos transferred after IVF [33].

It has long been hypothesized that environments of excess adiposity may negatively impact implantation. Ovum donation cycles have provided one way to study the possible impact of obesity on implantation in a more well-controlled way. A 2012 meta-analysis showed no impact of obesity on success rates in ovum recipients [34], but two subsequent large studies demonstrated that implantation, pregnancy, and live birth rates were inversely correlated with BMI [35, 36]. Thus, further research is needed to help determine whether and how excess weight may affect various stages of development from oocyte growth through implantation.

Finally, the additional impact of polycystic ovary syndrome (PCOS) in overweight/obese women has been explored in several independent cohorts. A study of Chinese women with PCOS demonstrated that being obese was associated with lower clinical pregnancy rates and higher miscarriage rates as compared to non-obese counterparts [37]. Two additional studies in similar populations also concluded that women with PCOS who were either overweight or obese had a poorer prognosis [38, 39]. A study of 653 women with PCOS in Turkey showed that obesity had a negative impact on IVF outcomes, but the differences were not statistically significant [27]. A small US-based study also showed that morbidly obese women with PCOS had lower clinical pregnancy rates than women with PCOS who had a BMI < 40.00 kg/m^2 [40]. In a study using SART data, among patients in which PCOS was the only infertility-related diagnosis, pregnancy loss was the only outcome with a statistically significant association with increasing BMI, although trends for all other outcomes also worsened with increasing BMI [41].

With regard to underweight BMI, the data to date are very limited, and a firm consensus in the literature has not yet been reached. Therefore, the aim of this study was to perform the first large-scale investigation of the relationship between the full spectrum of BMI categories and IVF-related outcomes using detailed patient-level clinical information rather than more limited registry data.

Materials and methods

Study population and IVF treatment

We performed a retrospective review of women who initiated their first autologous IVF cycle with conventional insemination or intracytoplasmic sperm injection (ICSI) at 1 of 13 geographically distinct fertility treatment centers in the USA between 2009 and 2015. We excluded frozen transfers of supernumerary embryos, cycles using pre-implantation genetic screening, and cycles that were missing BMI data. Institutional Review Board (IRB) exemption was obtained.

Women underwent IVF with or without ICSI per individual clinic guidelines. Controlled ovarian hyperstimulation was achieved using one of several protocols (most commonly, a GnRH antagonist protocol) with hCG and/or leuprolide trigger administration according to established practice conventions at each clinic. The trigger was administered when the largest follicle measured 18–24 mm, and oocytes were retrieved transvaginally 35–36 h afterwards. Conventional insemination or ICSI was performed by standard techniques, and embryos were then cultured for either 3 days (cleavage stage, ~20% of transfers) or 5 days

(blastocyst stage, ~80% of transfers). In some cases, embryos were cultured for 6 or 7 days after oocyte retrieval to allow more time for blastocyst development.

For fresh embryo transfer cycles, luteal support was initiated after retrieval, and embryos were then transferred into the uterus. Embryos were cryopreserved according to established practice protocols at each clinic.

Data set

BMI was documented for all individuals included in the study before the start of their IVF cycle. BMI was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). We used the BMI categories defined by the World Health Organization: < 18.50 kg/m^2 (underweight), 18.50–24.99 kg/m^2 (normal), 25.00–29.99 kg/m^2 (overweight), 30.00–34.99 kg/m^2 (obese class-I), 35.00–39.99 kg/m^2 (obese class-II), and ≥ 40.00 kg/m^2 (obese class-III) [42].

The demographic and baseline clinical information collected included the following: age of female patient intending pregnancy, primary infertility diagnosis (according to what was stated in the medical record as primary cause of infertility), anti-Müllerian hormone (AMH) levels, basal follicle-stimulating hormone (FSH) levels, basal luteinizing hormone (LH) levels, basal estradiol (E_2) levels, basal antral follicle count (BAFC), sperm volume, total motile sperm, sperm morphology, stimulation protocol, total gonadotropin dose used, peak serum E_2 levels, number of oocytes retrieved, use of ICSI, number of usable embryos (either transferred or cryopreserved), stage of embryo at transfer (cleavage stage vs. blastocyst), number of embryos transferred, and pregnancy outcome.

Outcome measures

The primary outcome of interest was ongoing clinical pregnancy, defined as the presence of an intrauterine sac with visible heartbeat from ultrasound at the time that care was transferred from the reproductive endocrinologist to the obstetrician (usually between 8 and 12 weeks gestational age, depending on the clinic). Secondary outcomes included cycle cancellation, number of oocytes retrieved, and number of usable embryos. The primary outcome was only assessed in cycles that underwent fresh embryo transfer. Cycle cancellation was assessed in the entire cohort of first autologous IVF cycles, number of oocytes retrieved was assessed only in patients that reached the oocyte retrieval stage, and number of useable embryos quantified embryos used in fresh transfers as well as cryopreserved embryos.

Statistical analysis

Baseline characteristics of the study population were examined by BMI categories. Continuous variables are presented as mean ± SD or median (interquartile range) for normally distributed and skewed data, respectively. Categorical variables are presented as frequency and percentages. The least absolute shrinkage and selection operator (LASSO) regression was used to select confounders that were statistically significantly ($P < 0.05$) associated with each outcome measure. For cycle cancellation, the analysis controlled for the following factors: female age, gravidity, BAFC, basal FSH and E_2 levels, AMH, total gonadotropin used, infertility diagnosis, and clinic. Number of oocytes retrieved was adjusted for female age, parity, BAFC, basal FSH, LH and E_2 levels, AMH, total gonadotropin used, infertility diagnosis, and clinic. When evaluating number of usable embryos, we controlled for female age, BAFC, basal FSH, LH and E_2 levels, AMH, gravidity, parity, ICSI, number of oocytes retrieved, embryo stage at the end of culture, total gonadotropin used, infertility diagnosis, and clinic. Lastly, the analysis of ongoing pregnancy rate controlled for the following factors: female age, basal E_2 levels, parity, infertility diagnosis, total gonadotropin used, number of oocytes retrieved, embryo stage at transfer, number of usable embryos, number of embryos transferred, and clinic.

Logistic or Poisson regression was used to calculate the unadjusted and multivariate adjusted odds ratio (aOR; for cycle cancellation and ongoing clinical pregnancy) or adjusted incidence rate ratio (aIRR; for number of oocytes retrieved and number of usable embryos), respectively, with their 95% confidence interval (CI); normal BMI served as the reference category.

The same regression analysis was also performed for eight subpopulations based on primary infertility diagnoses reported by the clinic (diminished ovarian reserve [DOR], endometriosis, idiopathic, male factor, ovulatory dysfunction, PCOS, tubal factor, and uterine factor). These infertility diagnoses were designated in the electronic medical record by clinicians, and the subgroups based on primary infertility diagnosis were mutually exclusive in our study. Sensitivity analyses for number of usable embryos and ongoing clinical pregnancy were performed among cycles that transferred only blastocyst stage embryos. Statistical analysis was performed using R (version 3.2.4). Statistical significance in this study was defined as $P < 0.05$ (two-sided).

Results

A total of 51,198 women who initiated their first autologous IVF cycle were divided into 5 categories based on their BMI: underweight ($n = 1377$, 2.7%); normal ($n = 27{,}945$, 54.6%); overweight ($n = 12{,}283$, 24.0%); obese class-I ($n = 5791$,

11.3%); and obese class-II/III ($n = 3802$, 7.4%). Obese class-II and class-III were combined in our study because of the limited sample size in the obese class-III group ($n = 755$). Baseline characteristics, IVF cycle details, and outcome by BMI groups are presented in Table 1.

Cycle cancellation

Of the 51,198 cycles included, 8694 cycles were cancelled. After adjusting for potential confounders, we found that overweight and obesity categories are associated with an increase odds of cycle cancellation. For those with BMI ≥ 18.5 kg/m^2, odds of cycle cancellation increased with rising BMI (overweight vs. normal weight aOR 1.17, 95% CI 1.08–1.26, $P < 0.001$; obese class-I vs. normal weight aOR 1.28, 95% CI 1.15–1.41, $P < 0.001$), with obese class-II/III women having the highest aOR for cycle cancellation compared to those of normal weight (aOR 1.50, 95% CI 1.33–1.68, $P < 0.001$). The odds of cycle cancellation were comparable between underweight and normal weight women ($P = 0.23$) (Table 2).

Number of oocytes retrieved

Among 45,950 women that reached oocyte retrieval, obese individuals had fewer oocytes retrieved compared to those of normal weight after adjustment for confounders (Table 2). In a comparison of the number of oocytes retrieved between obese class-I and normal weight women, aIRR was 0.98 (95% CI 0.98–0.99, $P < 0.001$), while aIRR comparing obese class-II/III with normal weight was 0.93 (95% CI 0.92–0.94, $P < 0.001$). Underweight and overweight women had similar number of oocytes retrieved compared to those of normal weight ($P = 0.11$ and $P = 0.19$, respectively).

Number of usable embryos

After adjustment for confounders, among 45,767 women with one or more oocytes retrieved, underweight, overweight, and obese individuals had fewer usable embryos that were transferred or cryopreserved compared to those of normal weight (underweight vs. normal weight aIRR 0.95, 95% CI 0.92–0.97, $P < 0.001$; overweight vs. normal weight aIRR 0.98, 95% CI 0.97–0.99, $P = 0.006$; obese class-I vs. normal weight aIRR 0.97, 95% CI 0.96–0.99, $P < 0.001$) (Table 2). Obese class-II/III women had an impact on number of usable embryos (aIRR = 0.95, 95% CI 0.93–0.97, $P < 0.001$). When only blastocyst cycles were analyzed, the difference in number of usable blastocysts was not statistically significant between overweight and normal weight women, whereas those who were underweight and obese had fewer usable blastocysts than the normal weight individuals (Supplementary Table S1).

Ongoing clinical pregnancy

Among 39,055 women with a fresh embryo transfer, obese individuals had lower odds of ongoing clinical pregnancy compared to those of normal weight after adjustment for confounders (Table 2). In a comparison of the odds of ongoing clinical pregnancy between obese class-I and normal weight women, aOR was 0.89 (95% CI 0.83–0.95, $P < 0.001$), while an aOR comparing obese class-II/III and normal weight women was 0.86 (95% CI 0.79–0.93, $P < 0.001$). Underweight and overweight women did not have significantly lower odds of ongoing clinical pregnancy compared to those of normal weight ($P = 0.21$ and $P = 0.09$, respectively). When only blastocyst transfers were included, results remained consistent, with obese women having lower odds of ongoing clinical pregnancy (Supplementary Table S1).

Subgroup analyses

We next examined the effect of BMI on IVF cycle outcomes for subgroups with different primary infertility diagnoses: DOR, endometriosis, idiopathic, male factor, ovulatory dysfunction, PCOS, tubal factor, and uterine factor. We found that the effect of BMI on IVF cycle outcomes was more pronounced for PCOS, ovulatory dysfunction, male factor, and uterine factor (Supplementary Tables S2-S5).

PCOS For cycles in which the patient's primary diagnosis was PCOS, the odds of cycle cancellation were higher in women with obese BMI compared to normal BMI (obese class-I vs. normal weight: aOR 2.59, 95% CI 1.40–4.78, $P = 0.002$; obese class-II/III vs. normal weight: aOR 2.56, 95% CI 1.35–4.84, $P = 0.004$) (Fig. 1, Supplementary Table S2). Both overweight and obese women had fewer oocytes retrieved compared to normal weight individuals (overweight vs. normal weight: aIRR 0.96, 95% CI 0.94–0.98, $P = 0.001$; obese class-I vs. normal weight: aIRR 0.93, 95% CI 0.90–0.96, $P < 0.001$; obese class-II/III vs. normal weight: aIRR 0.85, 95% CI 0.82–0.88, $P < 0.001$) (Fig. 1, Supplementary Table S3). Overweight and obese women also had fewer usable embryos compared to normal weight individuals (overweight vs. normal weight: aIRR 0.95, 95% CI 0.91–0.99, $P = 0.03$; obese class-I vs. normal weight: aIRR 0.89, 95% CI 0.84–0.94, $P < 0.001$; obese class-II/III vs. normal weight: aIRR 0.84, 95% CI 0.79–0.89, $P < 0.001$) (Fig. 2, Supplementary Table S4). For ongoing clinical pregnancy, only obese class-II/III women had a poorer outcome than normal weight individuals (aOR 0.56, 95% CI 0.42–0.74, $P < 0.001$) (Fig. 2, Supplementary Table S5).

Table 1 Descriptive characteristics of study population

	BMI (kg/m^2) categories				
	Underweight < 18.5	Normal 18.5–24.9	Overweight 25.0–29.9	Obese class-I 30.0–34.9	Obese class-II/III ≥ 35.0
N	1377	27,945	12,283	5791	3802
Female age (year)	34.40 ± 4.47	35.34 ± 4.52	35.76 ± 4.59	35.72 ± 4.64	35.63 ± 4.64
BMI (kg/m^2)	17.75 ± 0.73	21.99 ± 1.69	27.15 ± 1.44	32.22 ± 1.42	38.48 ± 3.04
Gravidity	0.53 ± 1.04	0.64 ± 1.09	0.78 ± 1.24	0.84 ± 1.35	0.77 ± 1.25
Parity	0.19 ± 0.51	0.21 ± 0.53	0.26 ± 0.64	0.29 ± 0.73	0.26 ± 0.65
Diagnosis, *n* (%)					
DOR	202 (14.7)	4514 (16.2)	1901 (15.5)	776 (13.4)	488 (12.8)
Endometriosis	102 (7.4)	1707 (6.1)	620 (5.0)	241 (4.2)	87 (2.3)
Idiopathic	57 (4.1)	1192 (4.3)	373 (3.0)	145 (2.5)	86 (2.3)
Male factor	282 (20.5)	5583 (20.0)	2552 (20.8)	1167 (20.2)	742 (19.5)
Ovulatory dysfunction	168 (12.2)	2560 (9.2)	1094 (8.9)	657 (11.3)	584 (15.4)
PCOS	33 (2.4)	940 (3.4)	552 (4.5)	383 (6.6)	405 (10.7)
Tubal factor	58 (4.2)	1247 (4.5)	645 (5.3)	327 (5.6)	188 (4.9)
Uterine factor	271 (19.7)	5480 (19.6)	2010 (16.4)	812 (14.0)	463 (12.2)
Other	115 (8.4)	2289 (8.2)	984 (8.0)	474 (8.2)	330 (8.7)
Missing	89 (6.5)	2433 (8.7)	1552 (12.6)	809 (14.0)	429 (11.3)
BAFC	14.12 ± 8.39	14.33 ± 8.74	14.57 ± 9.30	15.59 ± 9.87	16.39 ± 10.55
Basal FSH (mIU/mL)	7.68 ± 2.89	7.59 ± 2.74	7.35 ± 2.68	7.02 ± 2.45	6.76 ± 2.37
Basal LH (mIU/mL)	5.93 ± 3.37	5.71 ± 3.15	5.39 ± 3.01	5.01 ± 2.95	4.64 ± 2.86
Basal E_2 (pg/mL)	50.56 ± 20.28	50.89 ± 20.09	52.28 ± 20.16	53.10 ± 19.62	55.66 ± 19.71
Peak E_2 (pg/mL), median [IQR]	2493.33 [1710.06, 3376.00]	2291.00 [1600.00, 3171.00]	2137.00 [1515.00, 3025.00]	2041.00 [1434.67, 2951.50]	1913.50 [1385.25, 2770.00]
AMH (ng/mL)	3.26 ± 2.81	2.90 ± 2.69	2.87 ± 2.79	3.01 ± 2.87	3.15 ± 3.07
Total gonadotropin dose (IU), median [IQR]	3000.00 [1950.00, 4875.00]	3225.00 [2100.00, 4950.00]	3375.00 [2250.00, 5100.00]	3465.00 [2384.00, 5187.50]	3675.00 [2550.00, 5325.00]
ICSI, n (%)	281 (20.4)	5313 (19.0)	2380 (19.4)	1141 (19.7)	826 (21.7)
Number of embryos transferred	1.38 ± 0.95	1.46 ± 0.97	1.50 ± 0.99	1.52 ± 0.98	1.49 ± 0.97
Stage of embryo transfer					
Cleavage stage	315 (22.9)	6103 (21.8)	2785 (22.7)	1322 (22.8)	892 (23.5)
Blastocyst	1062 (77.1)	21,842 (78.2)	9498 (77.3)	4469 (77.2)	2910 (76.5)

Data presented as mean ± SD or *n* (%) or median [IQR]. *IQR* interquartile range, *DOR* diminished ovarian reserve, *PCOS* polycystic ovary syndrome, *IQR* interquartile range, *ICSI* intracytoplasmic sperm injection, *BAFC* basal antral follicle count, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, E_2 estradiol, *AMH* antimüllerian hormone

Table 2 The effect of BMI on IVF success

BMI (kg/m^2) categories		Total *N*	*N* (%) of cases or mean ± SD	Unadjusted model		Multivariate adjusted model	
				OR or IRR (95% CI)	*P* value	aOR or aIRR (95% CI)	*P* value
Cancellation (*N* = 51,198)							
Underweight	< 18.5	1377	125 (9.1)	0.95 (0.79, 1.15)	0.60	1.13 (0.92, 1.39)	0.23
Normal	18.5–24.9	27,945	2660 (9.5)	1.00 (reference)		1.00 (reference)	
Overweight	25.0–29.9	12,283	1356 (11.0)	1.19 (1.11,1.27)	< .001	1.17 (1.08, 1.26)	< .001
Obese class-I	30.0–34.9	5791	648 (11.2)	1.20 (1.10,1.31)	< .001	1.28 (1.15, 1.41)	< .001
Obese class-II/III	≥ 35.0	3802	459 (12.1)	1.31 (1.18,1.45)	< .001	1.50 (1.33, 1.68)	< .001
Number of oocytes retrieved (*N* = 45,950)							
Underweight	<1 8.5	1252	14.3 ± 8.9	1.01 (1.00, 1.03)	0.08	0.99 (0.97, 1.00)	0.11
Normal	18.5–24.9	25,285	14.1 ± 8.5	1.00 (reference)		1.00 (reference)	
Overweight	25.0–29.9	10,927	13.9 ± 8.5	0.99 (0.98, 1.00)	< .001	1.00 (0.99, 1.00)	0.19
Obese class-I	30.0–34.9	5143	14.0 ± 8.7	0.99 (0.99, 1.00)	0.16	0.98 (0.98, 0.99)	< .001
Obese class-II/III	≥ 35.0	3343	13.2 ± 7.9	0.94 (0.93, 0.95)	< .001	0.93 (0.92, 0.94)	< .001
Number of usable embryos (*N* = 45,767)							
Underweight	< 18.5	1249	3.6 ± 3.4	0.96 (0.93, 0.99)	0.006	0.95 (0.92, 0.97)	< .001
Normal	18.5–24.9	25,191	3.8 ± 3.6	1.00 (reference)		1.00 (reference)	
Overweight	25.0–29.9	10,891	3.7 ± 3.4	0.97 (0.96, 0.99)	< .001	0.98 (0.97, 0.99)	0.006
Obese class-I	30.0–34.9	5117	3.7 ± 3.4	0.97 (0.96, 0.99)	< .001	0.97 (0.96, 0.99)	< .001
Obese class-II/III	≥ 35.0	3319	3.5 ± 3.3	0.92 (0.90, 0.94)	< .001	0.95 (0.93, 0.97)	< .001
Ongoing clinical pregnancy (*N* = 39,055)							
Underweight	< 18.5	1011	465 (46.0)	0.95 (0.83, 1.07)	0.40	0.92 (0.81, 1.05)	0.21
Normal	18.5–24.9	21,219	10,050 (47.4)	1.00 (reference)		1.00 (reference)	
Overweight	25.0–29.9	9411	4264 (45.3)	0.92 (0.88, 0.97)	0.001	0.96 (0.91, 1.01)	0.09
Obese class-I	30.0–34.9	4481	1959 (43.7)	0.86 (0.81, 0.92)	< .001	0.89 (0.83, 0.95)	< .001
Obese class-II/III	≥ 35.0	2933	1254 (42.8)	0.83 (0.77,0.90)	< .001	0.86 (0.79, 0.93)	< .001

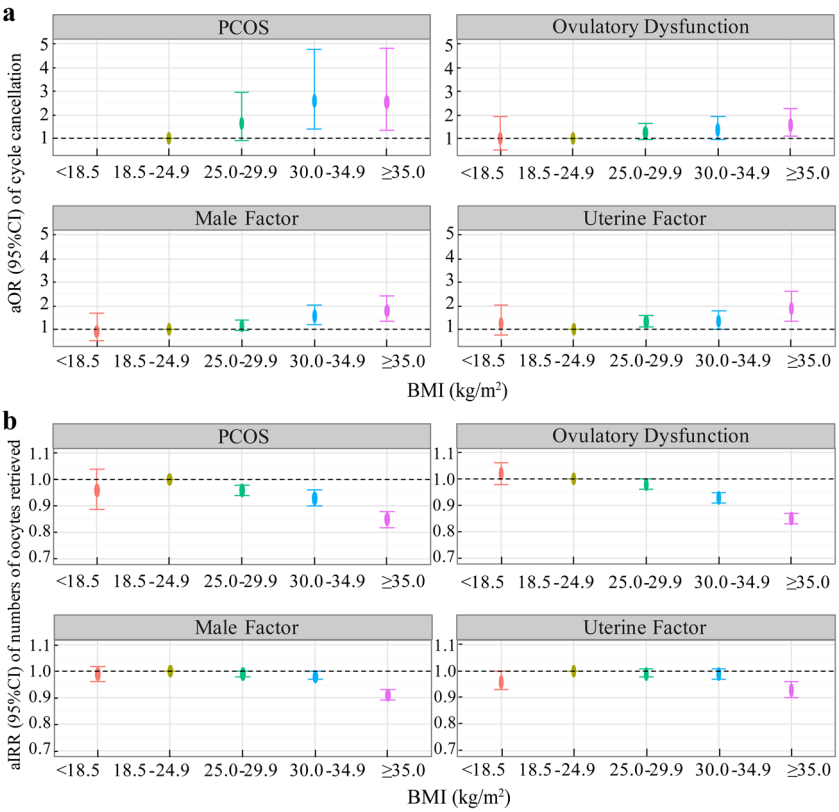

Fig. 1 The effect of BMI on cycle cancellation (**a**) and number of oocytes retrieved (**b**) among women with a diagnosis of PCOS, ovulatory dysfunction, male factor, or uterine factor

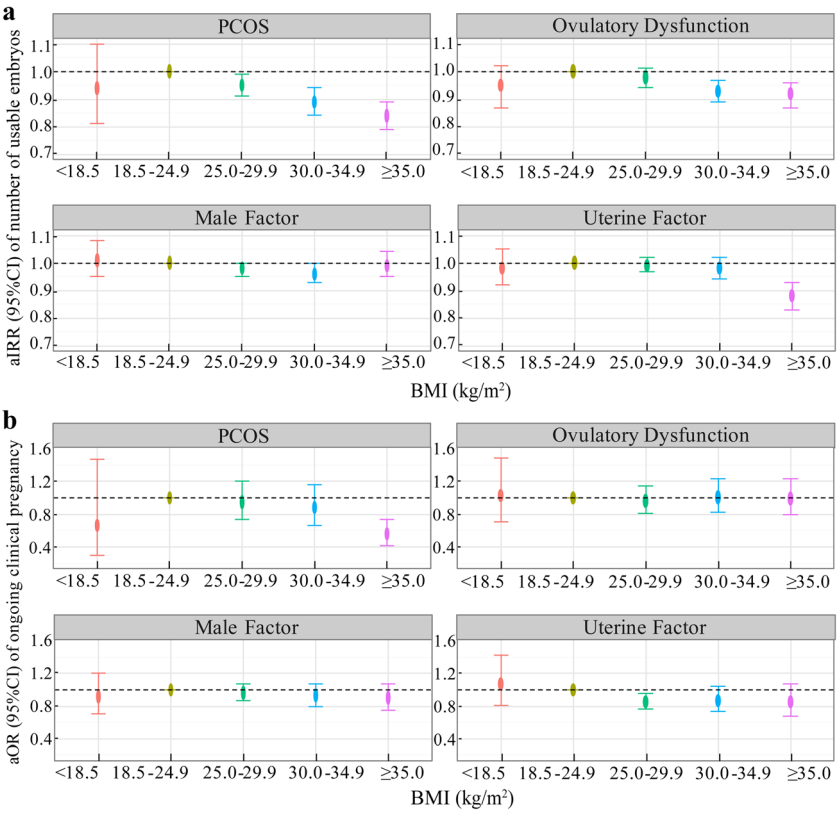

Fig. 2 The effect of BMI on number of usable embryos (**a**) and ongoing clinical pregnancy (**b**) among women with a diagnosis of PCOS, ovulatory dysfunction, male factor, or uterine factor

Ovulatory dysfunction For cycles in which the patient's primary diagnosis was ovulatory dysfunction, the odds of cycle cancellation were higher in obese class-II/III women compared to those of normal weight (aOR 1.58, 95% CI 1.10–2.26, $P = 0.01$) (Fig. 1, Supplementary Table S2). Both overweight and obese women had fewer oocytes retrieved compared to normal weight individuals (overweight vs. normal weight: aIRR 0.98, 95% CI 0.96–0.99, $P = 0.01$; obese class-I vs. normal weight: aIRR 0.93, 95% CI 0.91–0.95, $P < 0.001$; obese class-II/III vs. normal weight: aIRR 0.85, 95% CI 0.83–0.87, $P < 0.001$) (Fig. 1, Supplementary Table S3). Obese women also had fewer usable embryos compared to those of normal weight (obese class-I vs. normal weight: aIRR 0.93, 95% CI 0.89–0.97, $P = 0.002$; obese class-II/III vs. normal weight: aIRR 0.92, 95% CI 0.87–0.96, $P < 0.001$) (Fig. 2, Supplementary Table S4). For ongoing clinical pregnancy, underweight, overweight, and obese women had a similar outcome compared to normal weight individuals (Fig. 2, Supplementary Table S5).

Male factor For cycles in which the couple's primary diagnosis was male factor, the odds of cycle cancellation were higher in obese women compared to those of normal weight (obese class-I vs. normal weight: aOR 1.57, 95% CI 1.22–2.02, $P < 0.001$; obese class-II/III vs. normal weight: aOR 1.80, 95% CI 1.34–2.42, $P < 0.001$) (Fig. 1, Supplementary Table S2). Obese class-II/III women had fewer oocytes retrieved compared to normal weight individuals (aIRR 0.91, 95% CI 0.89–0.93, $P < 0.001$) (Fig. 1, Supplementary Table S3), while obese class-I women had fewer usable embryos compared to those of normal weight (aIRR 0.96, 95% CI 0.93–0.99, $P = 0.04$) (Fig. 2, Supplementary Table S4). For ongoing clinical pregnancy, underweight, overweight, and obese women had a similar outcome compared to normal weight individuals (Fig. 2, Supplementary Table S5).

Uterine factor For cycles in which the patient's primary diagnosis was uterine factor, the odds of cycle cancellation were higher in overweight and obese women compared to normal weight individuals (overweight vs. normal weight: aOR 1.33, 95% CI 1.09–1.61, $P = 0.004$; obese class-I vs. normal weight: aOR 1.35, 95% CI 1.03–1.77, $P = 0.03$; obese class-II/III vs. normal weight: aOR 1.90, 95% CI 1.37–2.63, $P < 0.001$) (Fig. 1, Supplementary Table S2). Compared to those of normal weight, obese class-II/III women had fewer oocytes retrieved (aIRR 0.93, 95% CI 0.90–0.96, $P < 0.001$) (Fig. 1, Supplementary Table S3), and fewer usable embryos (aIRR 0.88, 95% CI 0.83–0.93, $P < 0.001$) (Fig. 2, Supplementary Table S4). Odds of ongoing clinical pregnancy of underweight, overweight, and obese women were not statistically significantly different from their normal weight counterparts (Fig. 2, Supplementary Table S5).

Discussion

This study is the first to utilize detailed patient-level, multi-center data to demonstrate that obesity is associated with a significantly increased probability of cycle cancellation, as well as a lower number of oocytes retrieved, number of usable embryos, and odds of clinical pregnancy. The magnitude of these differences is greater in women with class-II/III obesity. Overweight individuals were also more likely to have their cycles cancelled, while both over- and underweight women had fewer usable embryos. This study is the first to use rich clinical metrics to study the impact of BMI on each phase of IVF separately and to control for prior cycle outcomes in each subsequent analysis. This approach allowed for a more independent assessment at each stage. Furthermore, to our knowledge, no prior studies have investigated all diagnostic subgroups with regard to the impact of BMI. In the analysis by primary diagnosis, the negative impact of elevated BMI was particularly profound in those with PCOS or ovulatory dysfunction. Prior studies have shown that PCOS may be a negative risk factor for IVF outcomes including fertilization, pregnancy, miscarriage, and cycle cancellation [43], and our data further suggest that oligo- or anovulatory women, even those without PCOS, do worse when burdened with excess weight. Overall, from the perspective of patient counseling, given the conflicting data in prior studies, our data help estimate a risk for overweight and obese women undergoing IVF, such as the 50% higher odds of cycle cancellation associated with class-II/III obesity.

The study does, however, have several limitations that warrant follow up work. Some diagnoses had a smaller sample size than others, which may have prevented a signal from emerging. Furthermore, variations in how clinics define primary infertility diagnosis may also diminish the signal. Although the study included multiple centers, the sites may not have been representative of all fertility practices nationally or internationally. Most cycles utilized only a few common protocols and primarily performed blastocyst transfer, but as with all real-world evidence, practice variations exist within these data. The data may also include some misclassification; for example, though some with an anovulatory diagnosis may actually meet PCOS criteria, without more complete data, further characterization of this group is not possible. Another limitation is that we were unable to investigate live birth outcomes because data were not available for the entire cohort. Finally, though some clinical outcomes, such as number of oocytes retrieved, may demonstrate small absolute differences, the cumulative impact of obesity at multiple stages throughout the treatment journey appears to result in the highly clinically significant disparity in clinical pregnancy rates observed by BMI stratification.

With regard to possible mechanisms at play in the diagnosis-specific analysis, we theorize that the impact of male factor may be secondary. Obese women may be more likely to have obese male partners [44], and paternal obesity is also a known risk factor for poorer IVF outcomes [45]. We also found a BMI effect in women with a uterine factor diagnosis, even prior to implantation. Although uterine factor encompasses a wide variety of diagnoses, the body habitus combined with a bulky myomatous or adenomyomatous uterus could possibly complicate oocyte retrieval and lead to fewer oocytes being retrieved. Further prospective studies are needed to confirm these findings and to detail the mechanisms whereby these groups seemed particularly vulnerable to the impact of BMI.

Overall, these results provide a detailed picture of the relationship between BMI and IVF cycle outcomes, which is greatly needed to provide infertility patients with the most accurate clinical prognosis and guidance. These numbers identify and could help to motivate those who have the most to gain from lifestyle improvement, which has been previously demonstrated to have a positive impact, including in PCOS women specifically [46–49]. Understanding patterns around the total number of usable embryos may also help in counseling patients who hope to obtain enough embryos in one stimulation cycle to achieve their entire family-building goals. Finally, our data could help to clarify the risk profile associated with underweight women, who have been far less studied than women on the other side of the BMI spectrum. Our data were largely reassuring on this front because the only significant finding was a statistically significant, but not clinically meaningful, lower number of usable embryos.

In conclusion, women who were classified as overweight or obese had poorer IVF cycle outcomes than those with a normal BMI. Certain diagnoses, particularly PCOS or ovulatory dysfunction, exacerbated these negative effects. Future research should aim to identify the underlying mechanisms, as well as the best patient-centered practices to help fertility patients optimize their weight prior to starting treatment.

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Compliance with ethical standards

Conflict of interest A.B.C. is an advisor for Celmatix and board member for Sema4 Genomics. P.Y.B. has a patent pending (US62460415). The other coauthors declare no conflict of interest.

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