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Adverse effects of female obesity and interaction with race on reproductive potential

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Abstract

Across the reproductive spectrum, obesity is associated with greater risks for adverse health outcomes, including higher rates of infertility, subfertility, early pregnancy loss, fetal deaths and stillbirths, congenital anomalies, and pregnancy complications. The excess reproductive morbidity associated with obesity may increase with longer duration, making the current trends among children and young adults particularly critical in terms of their future reproductive potential. Obese women have a lower chance of pregnancy following in vitro fertilization (IVF), require higher dosages of gonadotropins, and have reduced rates of implantation, clinical intrauterine gestation, and live birth rates and increased rates of pregnancy loss, as well as greater risks for prematurity and preeclampsia even when stratified by plurality. Racial and ethnic differences by overweight and obesity in IVF outcomes have been reported. Compared with normal-weight women, failure to achieve a clinical intrauterine gestation is significantly more likely among obese women overall, normal-weight and obese Asian women, normal-weight Hispanic women, and overweight and obese Black women. Among women who do conceive, compared with normal-weight women, failure to achieve a live birth is significantly more likely among overweight and obese women overall, and among overweight and obese Asian women, overweight and obese Hispanic women, and normal-weight and obese Black women. Although weight loss should theoretically be the first line of therapy for obese women, other lifestyle factors, such as regular physical exercise, elimination of tobacco use and alcohol consumption, and stress management, may be of more immediate benefit in achieving conception.

Keywords

Obesity; prenatal growth restriction; abnormal glycemic parameters; insulin resistance; metabolic environment

According to the World Health Organization (1), obesity is a disease defined as the condition of excess body fat to the extent that health is impaired. The most widely accepted measure is the body mass index (BMI; weight (kg)/height (m)^2), with cutoff points of 25 kg/m^2

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(overweight) and 30 kg/m^2 (obese), as recommended by the National Heart, Lung, and Blood Institute's North American Association for the Study of Obesity expert committee (2). Class I, II, and III obesity are defined as BMI 30.0–34.9, 35.0–39.9, and ≥40.0 kg/m^2, respectively. In addition, this expert committee recommends using waist circumference cutoff points of 40 inches (102 cm) for men and 35 inches (88 cm) for women to define central obesity. This measure may be more useful than BMI because of its greater predictive value for future health risks, as well as ease of measurement (2-4). BMI is not the best measure to reflect body fat and does not account for racial and ethnic differences in body build nor higher BMI due to increased muscularity (5). Specifically, the proportion of Asians at high risk for type 2 diabetes and cardiovascular disease is considerable at lower BMI cutoffs for overweight. The World Health Organization Expert Consultation recommended retaining the current BMI cutoffs, but adding additional cutoff points of 23, 27.5, 32.5, and 37.5 kg/m^2 for public health action.

In the United States, two-thirds of adults are overweight or obese (6), with highest rates among Black and Hispanic populations and lowest rates among Asians (Table 1). The prevalence of obesity has more than doubled since the 1970s and is a leading cause of morbidity and mortality, second only to tobacco use (7). Obesity is associated with impaired fertility, primarily owing to disorders of the reproductive hormonal profile. United States national data from 2014 births indicated that 25.6% of women were overweight and 24.8% were obese before becoming pregnant (8). The prevalence of overweight and obesity was lowest among women <20 years of age, Asians, and women with a college degree or giving birth for the first time. Women with obesity before pregnancy were more likely to be older (40–54 years of age), be non-Hispanic Black or non-Hispanic American Indian/Alaskan Native, have had three or more previous births, and to be using Medicaid for payment of delivery. An estimated 35% of maternal deaths in the United Kingdom are related to obesity (9).

OBESITY AND REPRODUCTION/PREGNANCY

Obesity is associated with greater risks for adverse health outcomes across the reproductive spectrum (10-13), including higher rates of infertility (14-16), subfertility (increased time to pregnancy) (17-19), early pregnancy loss (20-29), fetal deaths, stillbirths and neonatal deaths (30-33), congenital anomalies (34, 35), pregnancy complications (36-38), greater risk of cesarean delivery and poor wound healing (39), and increased difficulty and shorter duration of breastfeeding (40-42). The excess reproductive morbidity associated with obesity may increase with longer duration, making the current trends among children and young adults particularly critical in terms of their future reproductive potential. In the United States, between 1988–1994 and 2011–2014, the proportion of adolescents (12–19 years of age) who were obese more than doubled, from 9.7% to 21% (6). Findings from the Study of Women's Health Across the Nation indicate that adolescent obesity is associated with a threefold increased risk of lifetime nulliparity and a fourfold increased risk of lifetime nulligravidity (43). The maternal, fetal, and neonatal complications of obesity have far-reaching adverse health implications for both the mother and her child (44-47).

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PRENATAL GROWTH, OBESITY, AND INFERTILITY

Research findings have linked prenatal growth restriction to timing of puberty and subsequent symptoms of polycystic ovary syndrome (48-56). Even after achieving a normal body size by the age of 2 years, singleton children born small for their gestational age tend to become relatively adipose, hyperinsulinemic, hypoadiponectinemic, and with physiologic evidence of low-grade inflammation (54, 55). By 6 years of age, these children are more likely to develop visceral adiposity, even with normal body weight. By 8 years of age, children born small for gestational age with catch-up growth develop high DHEAS and low SHBG levels (56). Precocious puberty (appearance of pubic hair before 8 years of age) has also been demonstrated as part of this sequence, as well as anovulatory and hyperinsulinemic hyperandrogenism in late adolescence and adulthood (51-53). Insulin resistance has been cited as a key mechanism linking prenatal growth restraint to early menarche (48), with insulin-sensitizing therapy improving ovulation rates (49, 50).

OBESITY, DIET, AND ADVERSE REPRODUCTIVE OUTCOMES

Obesity is associated with alterations in carbohydrate and fat metabolism central to the development of insulin resistance. A diet with a high glycemic index has been associated with infertility, fetal loss, birth defects, prematurity, and macrosomia. Greater carbohydrate intake and dietary glycemic load have been associated with an increased risk of infertility due to anovulation (57). Jovanovic et al. (58) demonstrated a threefold increased risk of pregnancy losses at glycemic extremes in both normal and diabetic pregnancies, as measured by plasma glycated protein and fructosamine levels. A diet with a high glycemic load is associated with a twofold increased risk of neural tube defects (59, 60); among women with BMIs >29 kg/m^2, this risk increases to more than fourfold (60). Among normal-weight women treated with the use of in vitro fertilization (IVF), Wei et al. (61) reported greater risk for preterm birth associated with abnormal preconception glycemic parameters, including higher fasting and 2-hour glucose levels, fasting insulin, and homeostasis-model assessment of insulin resistance. Maternal obesity and elevated blood glucose are associated with increased fetal fat deposition (62, 63).

Research findings indicate that in adults, insulin resistance is an indicator of inflammation driven by interleukin (IL) 1β, IL-6, and tumor necrosis factor α (64, 65). Stress (from infection, inflammation, trauma, or psychologic distress) raises plasma glucose concentrations by increasing the contrainsulin hormones (e.g., cortisol and placental growth hormone). Scholl et al. (66) suggests that high maternal glucose concentrations may be a risk factor or a risk marker for the subclinical infection that gives rise to chorioamnionitis. Subclinical infection associated with very-preterm delivery is manifested as a systemic inflammatory response that is otherwise asymptomatic. In his analysis of data from the Collaborative Perinatal Project, Naeye (67) reported that an increased risk of very-preterm delivery was associated with acute chorioamnionitis among obese gravidas. Scholl et al. (66) suggests that higher but seemingly normal maternal plasma glucose concentrations are associated with very-preterm delivery by predisposing to or acting as a marker for placental inflammation and subclinical infection, and that insulin resistance might be an underlying cause of very preterm delivery.

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Adipose tissue expresses and releases the proinflammatory cytokine IL-6, inducing low-grade systemic inflammation in overweight and obese individuals. The acute-phase C-reactive protein (CRP) is a sensitive marker for systemic inflammation. In an analysis of the Third National Health and Nutrition Examination Survey, Visser et al. (68) reported increased BMI to be associated with raised CRP levels in women, particularly those with a higher waist-to-hip ratio, because abdominal adipose tissue releases more IL-6 than subcutaneous adipose tissue (69). These findings suggest that a state of low-grade systemic inflammation is present in overweight and obese individuals. CRP concentrations are independent from pregnancy and gestational age, and CRP does not cross the placenta. Elevated CRP levels are more often found in patients who are refractory to tocolysis, suggesting an underlying infectious morbidity. A positive association has also been reported between elevated CRP levels, IL-6, impairment of endothelial function, and histologic evidence of placental inflammation, infection, and pathology (70-74).

Elevated plasma glucose concentrations during pregnancy have also been linked to the development of preeclampsia. Hsu et al. (75) reported that among pregnant women with insulin-dependent diabetes mellitus, those with elevated hemoglobin A_{1c} values (>8%) at 16–20 weeks of gestation had significantly higher incidence of preeclampsia compared with those whose mean hemoglobin A_{1c} level was normalized during this stage of gestation (46% vs. 26%). Although the mechanisms mediating the effect of glycated hemoglobin on the development of preeclampsia remain unknown, it has been suggested that generation of advanced glycated end-products may be involved, impairing vascular responses. Hyperglycemia-induced inflammation may be part of the causal pathway through which obesity predisposes to preeclampsia.

OBESITY AND IN VITRO FERTILIZATION OUTCOMES

In concert with the rise in obesity, there has been a long-term trend in delaying childbearing and an increased use of infertility treatments to achieve conception. Infertility affects an estimated 12% of reproductive-age women (76). Research suggests that perinatal outcome may be worse for women with assisted versus spontaneous conceptions, including greater risks for preterm birth (<32 weeks and <37 weeks), low birth weight and very low birth weight, small for gestational age, cesarean delivery, neonatal intensive care unit admission, and perinatal mortality (77-79). An important underlying mechanism may be a genetic predisposition to factors associated with infertility, including allelic variants in cytokine genes known to stimulate inflammation or those known to down-regulate the antiinflammatory response. Ness (80) suggests that although women with a robust inflammatory response may be more likely to survive to reproduce, their reproductive experiences may be less successful than women who are less responsive. Obesity has been shown to be a chronic inflammatory state with increased expression of proinflammatory factors and a reduction in antiinflammatory factors (81, 82).

In women with assisted conceptions, obesity may further potentiate this inflammatory response, increasing the known risks for adverse reproductive outcomes, including fetal loss and stillbirths associated with greater body weight (29-31). Inflammation and dyslipidemia early in pregnancy have been shown to be independently associated with preterm birth

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(83, 84). In the presence of obesity, these factors are even greater and include significant impairment of endothelial function (73, 85). Obese women have a lower chance of pregnancy following IVF, require higher dosage of gonadotropins, and have reduced rates of implantation, clinical intrauterine gestation, and live birth rates and increased rates of pregnancy loss (9-15, 21-27, 86-91), as well as greater risks for prematurity, even when stratified by plurality (92).

High BMI is also strongly associated with preeclampsia, and that risk is compounded in IVF pregnancies. In their study of more than 10,000 singleton pregnancies delivered from 2001 to 2008 in Montreal, Quebec, Dayan et al. (93) reported that although IVF was not independently associated with preeclampsia (odds ratio [OR] 0.6, 95% confidence interval [CI] 0.3–1.4), IVF pregnancies in obese women were at considerably higher risk than spontaneously conceived pregnancies among nonobese women (OR 6.7, 95% CI 3.3–13.8).

RESPONSE TO GONADOTROPIN STIMULATION AND CYCLE CANCELLATION

Several studies have documented a higher risk of cycle cancellation with increasing maternal BMI, with adjusted ORs for women with BMI ≥40 kg/m^2 compared with normal-weight women ranging from 2.73 (95% CI 1.49–5.00) (37) to 3.46 (95% CI 1.85–6.49) (94). Obesity impairs ovarian responsiveness to gonadotropin stimulation, requiring higher dosages and longer stimulation, and fewer mature follicles are obtained (37, 88, 94, 95) (Table 2).

ENDOMETRIAL VERSUS OOCYTE FACTORS

The endocrine and metabolic environment may influence oocyte quality and therefore embryo development and subsequent implantation and pregnancy outcome. One possible mechanism for the lower pregnancy rate associated with obesity may be altered receptivity of the uterus owing to disturbed endometrial function (21, 23). Even studies limited to obese women using donor oocytes and eliminating the potential effect of older maternal age and lower quality of the embryos have reported significantly reduced implantation and pregnancy rates and higher abortion rates (22, 95, 96). A national study of ART in the United States reported reduced clinical pregnancy rates with increasing BMIs with the use of autologous but not donor oocytes and reduced live birth rates with increasing BMIs regardless of oocyte source and embryo state (95) (Tables 3 and 4). These findings are in accord with earlier studies showing a progressive decline in pregnancy rates with rising obesity (15, 16, 21, 23, 97). Studies have also shown a more adverse effect of obesity among younger women undergoing IVF treatment (93, 98) (Table 3). The findings of an adverse effect of the maternal obese environment on a live birth outcome regardless of oocyte source point to the need for periconceptional and prenatal dietary therapies targeted at improving the metabolic environment.

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EMBRYO FACTORS

An increasing body of literature indicates that the oocyte and embryo are adversely affected by maternal overweight and obesity. Oocytes from overweight and obese women have been shown to be smaller than those from normal weight women, they reach the post-fertilization morula stage faster, and as blastocysts they show reduced glucose consumption and elevated endogenous triglyceride levels (99). Blastocyst formation rate has also been shown to be reduced in overweight and obese women compared with normal-weight women (43.6% vs. 57.2%; $P<.007$) (100). Compared with normal-BMI women, severe obesity (BMI ≥35 kg/m^2) is associated with a greater prevalence of spindle anomalies and nonaligned chromosomes in failed fertilized oocytes (101). In addition, the metabolomic profile of spent culture media of day-3 embryos of obese women differs from that of normal-weight women, with significant reductions in the concentration of saturated fatty acids (102).

RACIAL AND ETHNIC DIFFERENCES IN IVF OUTCOMES

Racial and ethnic differences in IVF outcomes have been reported in the literature (103, 104). In a national study of more than 225,000 fresh embryo transfer cycles, Baker et al. (104) reported that compared with White women, there were lower chances of live birth versus fetal loss or stillbirth after a clinical intrauterine gestation in Asian (adjusted odds ratio [AOR] 0.89, 95% CI 0.82–0.97), Hispanic (AOR 0.87, 95% CI 0.79–0.96), and Black (AOR 0.62, 95% CI 0.56–0.68) women (Table 5). When evaluated by week of gestation (≤8 wk, 9–12 wk, 13–19 wk, and ≥20 wk), Hispanic women had lower chances of a live birth outcome at 13–19 weeks and ≥20 weeks (AORs 0.64 [95% CI 0.51–0.81] and 0.58 [95% CI 0.43–0.78], respectively), and Black women had a decreasing chance of a live birth with advancing pregnancy (decreasing from AOR 0.83 [95% CI 0.73–0.94] at ≤8 wk gestation to AOR 0.28 [95% CI 0.22–0.36] at ≥20 wk gestation).

In a national analysis of 139,027 IVF cycles in the United States, Fujimoto et al. (105) reported that among singleton births, Black women had significantly greater risks of preterm birth (<29 wk: AOR 4.25, 95% CI 3.14–5.76; <32 wk: AOR 2.72, 95% CI 2.19–3.38; and <37 wk: AOR 1.79, 95% CI 1.59–2.03) and fetal growth restriction (birthweight z-score < −1: AOR 1.81, 95% CI 1.56–2.11; and birthweight z-score < −2: AOR 2.17, 95% CI 1.47–3.19). Hispanic women had greater risks for preterm birth (<37 wk: AOR 1.22, 95% 1.08–1.37) and fetal growth restriction (birthweight z-score < −1: AOR 1.36, 95% 1.17–1.58; and birthweight z-score < −2: AOR 1.64, 95% CI 1.11–2.42); Asian women had greater risks for fetal growth restriction (birthweight z-score < −1: AOR 1.78, 95% CI 1.58–2.01; and birthweight z-score < −2: AOR 2.05, 95% CI 1.50–2.80).

Few studies have examined the combined effects of a woman's BMI and race/ethnicity on IVF outcomes. In a national study of 31,672 embryo transfers, Luke et al. (103) reported significant disparities in pregnancy and live birth rates according to race and ethnicity, even within BMI categories (Table 6). Compared with normal-weight White women, failure to achieve a clinical intrauterine gestation was significantly more likely among obese women overall (AOR 1.22, 95% CI 1.13–1.32), normal-weight and obese Asian women (AORs 1.36 [95% CI 1.22–1.53] and 1.73 [95% CI 1.21–2.47], respectively), normal-weight Hispanic

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women (AOR 1.21, 95% CI 1.03–1.42), and overweight and obese Black women (AORs 1.34 [95% CI 1.10–1.65] and 1.47 [95% CI 1.18–1.83], respectively). Among women who did conceive, compared with normaL weight White women, failure to achieve a live birth was significantly more likely among overweight and obese women overall (AORs 1.16 [95% CI 1.02–1.31] and 1.27 [95% CI 1.10–1.47], respectively), overweight and obese Asian women (AORs 1.56 [95% CI 1.07–2.27] and 2.20 [95% CI 1.18–4.08], respectively), overweight and obese Hispanic women (AORs 1.57 [95% CI 1.12–2.20] and 1.76 [95% CI 1.16–2.67], respectively), and normal-weight and obese Black women (AORs 1.45 [95% CI 1.02–2.06] and 1.84 [95% CI 1.25–2.71], respectively). Evaluating the interaction of race/ethnicity and obesity on the risk of prematurity in IVF pregnancies would be a useful extension of this research. If such an association could be confirmed, it would provide strong support for single-embryo transfer in these high-risk women.

OBESITY AND IVF THERAPY

Editorials have called for excluding women with high BMIs from receiving IVF, suggesting a cutoff of 35 kg/m^2 as the upper limit for initiation of treatment (106, 107), and others have advocated that weight loss be incorporated into the treatment for infertility, but before conception (108). Others have argued that the potential advantage achieved with weight loss in older women should be balanced against the greater loss in fertility due to age (109). A recent United States survey reported that 35% of IVF clinics used a BMI or body weight cutoff to determine eligibility (mean BMI cutoff was 38.4 kg/m^2; mean body weight cutoff was 286 lb.) (110), but 46% of those clinics did not provide weight loss recommendations for patients.

Weight loss theoretically should be the first-line treatment for overweight women considering pregnancy, particularly with a history of recurrent miscarriages (111). The research on weight loss and IVF outcomes, though, has been discouraging. A recent Dutch randomized trial for weight loss among obese infertile women did not show improved birth rates compared with prompt infertility treatment within 24 months of randomization (112), and the use of very-low-calorie diets has been shown to have a negative effect on IVF outcomes (113). In a small United States study of 170 women undergoing IVF, short-term weight loss was related to higher yield of mature oocytes but did not improve live birth outcomes (114).

In addition to dietary modifications to facilitate weight loss, lifestyle factors such as regular physical exercise, elimination of tobacco use and alcohol consumption, and stress management may be of benefit (115-118). A recent study by Palomba et al. (118) reported more than threefold higher pregnancy and live birth rates for obese women who exercised regularly compared with obese women who were not physically active (AOR 3.22 [95% CI 1.53–6.78] vs. AOR 3.71 [95% CI 1.51–9.11], respectively). Because exercise reduces the oxidative stress characteristic of overweight and obesity, it may represent the best therapy currently available.

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CONCLUSION

Overweight and obesity are associated with greater risks for adverse health outcomes across the reproductive spectrum, including higher rates of subfertility, infertility, early pregnancy loss and fetal deaths, stillbirths and neonatal deaths, congenital anomalies, and prematurity as well as greater risks of cesarean delivery and poor wound healing, and increased difficulty and shorter duration of breastfeeding. Obese women have a lower chance of pregnancy following IVF, require higher dosages of gonadotropins, and have reduced rates of implantation, clinical intrauterine gestation, and live birth, increased rates of pregnancy loss, and greater risks for prematurity, even when stratified by plurality. Racial and ethnic differences according to BMI in IVF outcomes have been reported, with greater risks of failure to achieve a live birth among obese women overall and among overweight and obese Asian, Hispanic, and Black women. Weight loss should theoretically be the first line of therapy for obese women, but other lifestyle factors, such as regular physical exercise, elimination of tobacco use and alcohol consumption, and stress management, may be of more immediate benefit. The maternal, fetal, and neonatal complications of obesity have far-reaching adverse health implications for both the mother and her child. Attaining normal body weight for height is optimal for reproduction and long-term health.

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TABLE 1

Prevalence (%) of normal weight, overweight, and obesity in the United States, adults aged ≥20 years, 2011–14.

		BMI Category (kg/m^2)					
Sex	**Racial/ethnic group**	**Normal weight, 18.5–24.9**	**Overweight and obese, ≥25.0**	**Obese, ≥30.0**	**Obese (class I), 30.0–34.9**	**Obese (class II), 35.0–39.9**	**Obese (class III), ≥40.0**
Male	All	26.0	73.0	34.5	22.0	7.6	4.9
	White	25.6	73.7	34.6	19.6	7.8	4.7
	Black	29.0	69.6	37.9	22.0	8.9	7.0
	Asian	50.2	46.9	11.3	9.4	–	–
	Hispanic	19.5	79.6	39.1	27.2	7.3	4.7
Female	All	31.7	66.2	38.1	19.3	9.9	8.9
	White	34.3	63.5	34.0	21.4	9.1	8.2
	Black	16.0	82.0	56.5	24.9	15.1	16.5
	Asian	60.5	34.4	11.9	8.9	2.1	–
	Hispanic	22.3	77.1	45.6	24.1	13.5	8.1

Note: Dashes indicate unreliable estimates owing to low numbers. Adapted from: National Center for Health Statistics. Health, United States, 2015: with special feature on racial and ethnic health disparities. Hyattsville, MD: 2016. BMI = body mass index.

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TABLE 2

Effect of maternal BMI on risk of cycle cancellation and cancellation due to poor response.

	All cycle starts (n = 152,500 cycles)			Autologous oocytes only (n = 137,708 cycles)		
BMI category (kg/m^2)	**% Cancelled**	**AOR**	**95% CI**	**% Cancelled**	**AOR**	**95% CI**
All cancellations						
Underweight (<18.5)	9.2	1.05	0.95–1.17	9.4	1.04	0.93–1.16
Normal weight (18.5–24.9)	9.3	1.00	Reference	9.6	1.00	Reference
Overweight (25.0–29.9)	9.8	1.05	1.01–1.10	10.3	1.06	1.02–1.11
Obese, class I (30.0–34.9)	10.5	1.16	1.10–1.23	10.8	1.17	1.10–1.25
Obese, class II (35.0–39.9)	11.2	1.29	1.19–1.39	11.6	1.31	1.20–1.42
Obese, class III						
40.0–44.9	12.1	1.43	1.26–1.62	12.5	1.46	1.29–1.66
45.0–49.9	10.4	1.22	0.97–1.53	11.2	1.30	1.03–1.64
≥50.0	15.5	1.92	1.39–2.65	16.1	1.97	1.42–2.74
Cancellations due to low response						
Underweight (<18.5)	62.8	0.78	0.63–0.97	65.4	0.80	0.63–1.01
Normal weight (18.5–24.9)	68.9	1.00	Reference	71.5	1.00	Reference
Overweight (25.0–29.9)	72.9	1.28	1.17–1.41	75.4	1.31	1.19–1.45
Obese, class I (30.0–34.9)	69.1	1.12	1.00–1.27	71.6	1.16	1.02–1.32
Obese, class II (35.0–39.9)	73.1	1.45	1.22–1.72	75.5	1.52	1.26–1.82
Obese, class III						
40.0–44.9	73.9	1.59	1.22–2.09	76.2	1.70	1.27–2.26
45.0–49.9	85.7	3.46	1.85–6.49	86.7	3.48	1.81–6.70
≥50.0	77.8	1.95	0.94–4.02	77.3	1.81	0.87–3.77

Note: Models were adjusted for woman's age, race/ethnicity, height, nulligravidity, and infertility diagnoses. All tests of equality of AORs within each outcome were significant at $P<.0001$. Adapted from: Luke B, Brown MB, Missmer SA, Bukulmez O, Leach R, Stern JE. The effect of increasing obesity on the response to and outcome of assisted reproductive technology: a national study. Fertil Steril 2011; 96:820–5. AOR = adjusted odds ratio; BMI = body mass index; CI = confidence interval.

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TABLE 3

Failure to achieve a clinical intrauterine gestation, and failure to achieve a live birth after IVF According to maternal age, BMI, and oocyte source.

		Failure to achieve a clinical intrauterine gestation						Failure to achieve a live birth					
		Oocyte source				Test of equality of AORs		Oocyte source				Test of equality of AORs	
		Autologous		Donor				Autologous		Donor			
Age (y)	BMI category (kg/m^2)	AOR	95% CI	AOR	95% CI	Autologous	Donor	AOR	95% CI	AOR	95% CI	Autologous	Donor
<35	Underweight (<18.5)	1.00	0.84–1.19	–	–	*P*<.001	–	0.93	0.64–1.35	–	–	*P*<.001	–
	Normal weight (18.5–24.9)	1.00	Reference	–	–			1.00	Reference	–	–		
	Overweight (25.0–29.9)	1.07	1.00–1.16	–	–			1.16	1.00–1.35	–	–		
	Obese, class I (30.0–34.9)	1.21	1.10–1.34	–	–			1.48	1.23–1.80	–	–		
	Obese, class II (35.0–39.9)	1.38	1.20–1.60	–	–			1.72	1.32–2.25	–	–		
	Obese, class III (≥40.0)	1.80	1.46–2.23	–	–			1.64	1.08–2.48	–	–		
≥35	Underweight (<18.5)	1.00	0.82–1.21	–	–	NS	NS	0.88	0.60–1.30	–	–	*P*<.05	NS
	Normal weight (18.5–24.9)	1.00	Reference	1.00	Reference			1.00	Reference	1.00	Reference		
	Overweight (25.0–29.9)	1.00	0.93–1.08	1.03	0.88–1.22			1.20	1.05–1.37	1.28	0.95–1.72		
	Obese, class I (30.0–34.9)	1.07	0.97–1.18	0.92	0.72–1.16			1.26	1.04–1.51	1.33	0.89–1.99		
	Obese, class II (35.0–39.9)	1.25	1.08–1.45	1.18	0.81–1.71			1.15	0.86–1.52	1.70	0.89–3.25		
	Obese, class III (≥40.0)	1.31	1.05–1.64	0.91	0.55–1.50			1.34	0.88–2.04	1.61	0.71 –3.64		

Live birth of ≥22 week's gestation and birthweight ≥300 grams; models adjusted for race and ethnicity, day of embryo transfer, number of embryos transferred, and infertility diagnoses. Dashed lines indicate insufficient sample size. Adapted from: Luke B, Brown MB, Stern JE, Missmer SA, Fujimoto VY, Leach R. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. Hum Reprod 2011; 26:245–52. NS = not significant; other abbreviations as in Table 2.

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TABLE 4

Effect of BMI on failure to achieve a clinical intrauterine pregnancy and a live birth.

	Autologous oocytes											
	Fresh embryos						Thawed embryos					
	Not pregnant (n = 101,531)			Fetal loss/stillborn (n = 42,699)			Not pregnant (n = 22,643)			Fetal loss/stillborn (n = 8,649)		
BMI category (kg/m^2)	**%**	**AOR**	**95% CI**	**%**	**AOR**	**95% CI**	**%**	**AOR**	**95% CI**	**%**	**AOR**	**95% CI**
Underweight (<18.5)	57.2	1.07	0.99–1.16	15.3	0.98	0.83–1.15	59.5	0.98	0.84–1.14	21.3	1.18	0.87–1.59
Normal weight (18.5–24.9)	57.0	1.00	Reference	16.6	1.00	Reference	61.6	1.00	Reference	19.4	1.00	Reference
Overweight (25.0–29.9)	58.0	1.03	1.00–1.06	18.5	1.10	1.03–1.17	60.7	0.95	0.89–1.02	21.1	1.05	0.93–1.20
Obese, class I (30.0–34.9)	59.4	1.14	1.09–1.19	20.7	1.25	1.15–1.36	63.4	1.09	0.99–1.19	27.4	1.51	1.27–1.79
Obese, class II (35.0–39.9) Obese, class III	60.8	1.26	1.18–1.34	21.4	1.34	1.18–1.51	63.0	1.06	0.93–1.22	32.7	1.83	1.44–2.32
40.0–44.9	63.0	1.41	1.27–1.57	22.6	1.39	1.14–1.69	65.6	1.18	0.93–1.48	30.7	1.78	1.18–2.69
45.0–49.9	62.4	1.40	1.17–1.67	26.0	1.67	1.21–2.31	71.1	1.60	1.06–2.41	30.3	1.80	0.85–3.83
≥50.0	64.5	1.53	1.13–2.06	31.4	2.29	1.37–3.83	57.6	0.77	0.39–1.55	14.3	0.54	0.12–2.43
	Donor oocytes											
	Fresh embryos						Thawed embryos					
	Not pregnant (n = 9,366)			Fetal loss/stillborn (n = 5,812)			Not pregnant (n = 3,975)			Fetal loss/stillborn (n = 1,565)		
Underweight (<18.5)	35.2	0.96	0.72–1.27	12.3	1.00	0.59–1.69	63.0	1.11	0.72–1.72	26.5	1.72	0.77–3.82
Normal weight (18.5–24.9)	37.0	1.00	Reference	12.5	1.00	Reference	59.9	1.00	Reference	18.9	1.00	Reference
Overweight (25.0–29.9)	38.0	1.00	0.90–1.11	15.4	1.26	1.06–1.51	60.9	1.03	0.88–1.21	22.3	1.23	0.91–1.66
Obese, class I (30.0–34.9)	42.0	1.16	0.99–1.35	17.9	1.51	1.16–1.96	60.3	1.00	0.79–1.25	27.2	1.61	1.07–2.43
Obese, class II (35.0–39.9) Obese, class III	41.0	1.13	0.89–1.42	17.7	1.49	1.01–2.20	58.8	0.92	0.67–1.26	19.2	1.03	0.55–1.90
40.0–44.9	37.0	0.98	0.65–1.47	23.4	2.18	1.21–3.94	72.3	1.76	1.01–3.06	17.6	0.87	0.24–3.10
45.0–49.9	37.5	0.97	0.51–1.86	12.0	0.94	0.28–3.16	77.8	2.26	0.73–6.97	–	–	–
≥50.0	36.4	0.76	0.22–2.64	28.3	2.44	0.46–12.91	100.0	–	–	–	–	–

Note: Models were adjusted for woman's age, race/ethnicity, height, nulligravidity, infertility diagnoses, and number of embryos transferred. Adapted from: Luke B, Brown MB, Missmer SA, Bukulmez O, Leach R, Stern JE. The effect of increasing obesity on the response to and outcome of assisted reproductive technology: a national study. Fertil Steril 2011; 96:820–5. Abbreviations as in Table 2.

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TABLE 5

Effect of race and ethnicity on optimal outcome (live birth) versus adverse outcome (fetal loss or stillbirth) in IVF pregnancies according to gestational period when adverse outcome occurred.

Period of adverse outcome	**All**			**≤8 wk**			**9–12 wk**			**13–19 wk**			**≥20 wk**		
	15,077			**8,657**			**3,711**			**1,770**			**939**		
No. of adverse outcomes	**AOR**	**95% CI**	***P* value**	**AOR**	**95% CI**	***P* value**	**AOR**	**95% CI**	***P* value**	**AOR**	**95% CI**	***P* value**	**AOR**	**95% CI**	***P* value**
White	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
Asian	0.89	0.82–0.97	**	0.95	0.85–1.06	NS	0.96	0.82–1.13	NS	0.63	0.52–0.78	***	0.82	0.60–1.11	NS
Hispanic	0.87	0.79–0.96	**	0.98	0.86–1.11	NS	0.91	0.76–1.08	NS	0.64	0.51–0.81	***	0.58	0.43–0.78	***
Black	0.62	0.56–0.68	***	0.83	0.73–0.94	**	0.61	0.51–0.71	***	0.38	0.31–0.46	***	0.28	0.22–0.36	***

Note: Study population limited to cycles of fresh embryo transfers using autologous oocytes and partner semen. Models were adjusted for maternal age, number of embryos transferred, assisted hatching and intracytoplasmic sperm injection, reproductive history, and infertility diagnoses. Adapted from: Baker VL, Luke B, Brown MB, Alvero R, Frattarelli JL, Usadi R, et al. Multivariate analysis of factors affecting probability of pregnancy and live birth with in vitro fertilization: an analysis of the Society for Assisted Reproductive Technology Clinic Outcome Reporting System. Fertil Steril 2010; 94:1410–6. Abbreviations as in Tables 2 and 3.

** $P<.01$

*** $P<.00$.

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TABLE 6

Effect of maternal BMI within race/ethnic groups on IVF outcomes.

	BMI category (kg/m^2)											
	All[a]			Normal weight (18.5–24.9)			Overweight (25.0–29.9)			Obese (30.0–46.0)		
Race/ethnicity	**AOR**	**95% CI**	***P* value**	**AOR**	**95% CI**	***P* value**	**AOR**	**95% CI**	***P* value**	**AOR**	**95% CI**	***P* value**
Treatment outcome: failure to achieve CIG												
All[b]				1.00	Reference		1.03	0.97–1.10	NS	1.22	1.13–1.32	***
White	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
Non-White[c]	1.30	1.22–1.39	***	1.31	1.20–1.43	***	1.17	1.03–1.33	*	1.36	1.16–1.59	***
Asian	1.38	1.25–1.52	***	1.36	1.22–1.53	***	1.21	0.98–1.50	NS	1.73	1.21–2.47	**
Hispanic	1.10	0.99–1.24	NS	1.21	1.03–1.42	*	0.92	0.75–1.13	NS	1.04	0.81–1.33	NS
Black	1.43	1.27–1.61	***	1.18	0.97–1.44	NS	1.34	1.10–1.65	**	1.47	1.18–1.83	***
Pregnancy outcome: failure to achieve live birth												
All[b]				1.00	Reference		1.16	1.02–1.31	*	1.27	1.10–1.47	***
White	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
Non-White[c]	1.38	1.22–1.56	***	1.24	1.04–1.47	**	1.52	1.20–1.93	***	1.86	1.40–2.47	***
Asian	1.33	1.11–1.60	**	1.21	0.96–1.51	NS	1.56	1.07–2.27	*	2.20	1.18–4.08	**
Hispanic	1.39	1.14–1.69	***	1.14	0.84–1.56	NS	1.57	1.12–2.20	**	1.76	1.16–2.67	**
Black	1.43	1.16–1.77	***	1.45	1.02–2.06	*	1.35	0.92–1.98	NS	1.84	1.25–2.71	**

Note: Models were adjusted for woman's age, gravidity, oocyte source, day of embryo transfer, number of embryos transferred, and infertility diagnoses. Adapted from: Luke B, Brown MB, Stern JE, Missmer SA, Fujimoto VY, Leach R. Racial and ethnic disparities in assisted reproductive technology pregnancy and live birth rates within body mass index categories. Fertil Steril 2011; 95:1661–6. CIG = clinical intrauterine pregnancy; other abbreviations as in Tables 2 and 3.

* *P*<.05

** *P*<.01

*** *P*<.001.

[a] Models additionally adjusted for BMI.

[b] Models additionally adjusted for race and ethnicity.

[c] Non-White includes Asian, Hispanic, and Black.

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