The effect of weight and body mass index on serum progesterone values and live birth rate in cryopreserved in vitro fertilization cycles

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Objective: To determine if weight or body mass index (BMI) affects the serum progesterone level at the time of the pregnancy test in cryopreserved blastocyst transfer cycles and to determine if those serum progesterone levels affect live births.
Design: Retrospective cohort study.
Setting: US academic medical center.
Patient(s): Six hundred thirty-three patients undergoing their first cryopreserved embryo transfer cycle.
Intervention(s): None.
Main Outcome Measure(s): The primary outcome was the serum progesterone level on the day of the pregnancy test by patient weight and BMI. Our secondary analysis assessed the serum progesterone effect on live birth rate (LBR) in a clinic where progesterone supplementation was increased if the progesterone level was <15 ng/mL on the day of the pregnancy test.
Results(s): There was a strong negative correlation between serum progesterone level and both BMI and weight, with BMI accounting for 27% and weight accounting for 29% of the variance in progesterone level. Serum progesterone level on the day of the pregnancy test was <15 ng/mL in 3% of women weighing <68 kg compared with 29% of women weighing ≥ 90.7 kg. Among women weighing ≥ 90.7 kg, live birth occurred in 47% whose serum progesterone level was <15 ng/mL on the day of the pregnancy test compared with 49% in those with serum progesterone level of 15–19 ng/mL and 44% in those with serum progesterone level of ≥ 20 ng/mL.
Conclusion(s): Body weight was a significant factor in serum progesterone level at the time of the pregnancy test, with nearly 30% of patients weighing ≥ 90.7 kg having serum progesterone level of <15 ng/mL, a value associated with lower LBRs in prior studies. However, we found no effect of low progesterone levels on LBR after cryopreserved embryo transfer cycles in a clinic where progesterone dosing was increased if serum progesterone levels were <15 ng/mL. (Fertil Steril Rep® 2021;2:195–200. ©2021 by American Society for Reproductive Medicine.)
Key Words: Body mass index, obesity, IVF, in vitro fertilization, progesterone, infertility

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As of 2016, there were 93.3 million adults affected by obesity in the United States (1). There is a high rate of reproductive age women meeting the criterion for obesity—34.8% of women aged 20–34 years and 43.4% of women aged 35–44 years (2). A multitude of health problems are linked to obesity, including issues with reproduction. Obesity is thought to impact fertility through effects on ovulation, oocyte numbers and quality, as well as miscarriage rates (3–8). Assisted reproductive technology success is also negatively impacted by obesity, even when using top-quality autologous blastocysts or using donor oocytes (7, 9).

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Obesity is often diagnosed by using a patient's height and weight to calculate their body mass index (BMI). Physical characteristics and pharmacokinetics vary in overweight and obese patients (10). For example, a 2014 study by Shah et al. (11) revealed that standard 1.5-inch (3.81 cm) needles for intramuscular injections did not reach the gluteal muscle in 36.3% of the obesity study participants. Additionally, it is known that obese patients require larger doses of gonadotropins in comparison with their normal-weight counterparts (3, 9, 12). Bioavailability and serum

levels of both exogenous and endogenous human chorionic gonadotropin are negatively affected by increasing BMI and body weight in obese individuals (11, 13, 14).

Just as gonadotropins and human chorionic gonadotropin are affected by obesity, so is progesterone. Progesterone supplementation is important for mimicking the natural cycle, stabilizing the endometrium, supporting early pregnancy, improving pregnancy rates, as well as decreasing uterine contractions at the time of embryo transfer to help reduce the likelihood of embryo displacement from the uterine cavity (15–17). Nonpregnant women with obesity have been shown to have luteal progesterone levels approximately 75%–80% lower than those of normal-weight women (18). Pregnant women with obesity have serum progesterone levels inversely related to their BMI, and it has been postulated that this may influence the increased miscarriage rate noted among obese pregnant women (19, 20). Overweight and obese patients using progesterone supplementation during fresh donor in vitro fertilization (IVF)/intracytoplasmic sperm injection cycles required increases in the progesterone dosage, because they were shown to have lower progesterone levels in comparison with those of their normal-weight counterparts (21). Additionally, a study revealed that increasing body weight was associated with lower levels of progesterone in early pregnancy after blastocyst transfer (14).

Much of the research regarding progesterone supplementation for IVF/ intracytoplasmic sperm injection cycles has focused on dosage and route of administration for the general infertility population but has not specifically examined possible differences in serum progesterone for patients with obesity. There is a need to better understand how to best care for our patients with obesity as the majority of American infertility patients meet the criteria for overweight or obesity (22). Anecdotally, our program has noticed that women with higher weight and BMI tend to require an increase in progesterone dosage. As it is important to know whether we are adequately supplementing progesterone for our patients, the aim of our study was to determine if weight or BMI affects the serum progesterone level at the time of the pregnancy test in cryopreserved IVF/intracytoplasmic sperm injection embryo transfer cycles and if those serum progesterone levels affect live birth in a clinic at which the dose of progesterone is increased if the serum progesterone level is <15 ng/mL on the day of the pregnancy test.

MATERIALS AND METHODS

The University of Iowa institutional review board approved this retrospective cohort study (IRB 201303841). Patients undergoing their initial vitrified cryopreserved blastocyst embryo transfer cycle between January 2015 and December 2018 were included in both the serum progesterone level and live birth analyses. The upper BMI limit for IVF treatment at the clinic during that time was 50 kg/m^2. To prepare for cryopreserved blastocyst transfer, patients were started on oral estradiol (estradiol 2 mg three times daily) starting on cycle day 1 or 2. Intramuscular progesterone in oil (50 mg) was initiated 5 days before embryo transfer, starting at noon, with the same dose given at 8 PM the same day and continued daily at 8 PM. Patients were included if their initial dose of supplemental progesterone was 50 mg intramuscular daily. Patients were excluded if their weight or serum progesterone level on the day of the pregnancy test were unavailable. The serum progesterone levels on the day of the pregnancy test were measured using an electrochemiluminescence immunoassay.

The primary objective was to stratify the serum progesterone level on the day of the pregnancy test by weight and BMI and to determine which might be more impactful on the serum progesterone level. We decided to look at both weight and BMI because a prior study by Mejia et al. (14) found that weight had a greater effect than BMI on hormone levels in early pregnancy. We used the same weight stratifications as were published in that article (14). Our secondary objective was to determine the effect of serum progesterone levels on live birth rate (LBR) in a clinic that increased the dose of progesterone supplementation to 75 mg in response to a serum progesterone level of <15 ng/mL on the day of the pregnancy test. We also examined the effect of the serum progesterone level on miscarriage and ectopic and biochemical pregnancies.

Chi-square test, Student's t test, and Kruskal-Wallis test were used to compare demographics, serum progesterone level, and pregnancy outcome data between groups. Ectopic pregnancy, biochemical pregnancy, and miscarriage were grouped together as "abnormal pregnancy" because of low numbers. Spearman's rank correlation was used to assess the relationship between the serum progesterone level and both weight and BMI. A power analysis determined that 281 cases would be sufficient to detect differences in LBR previously reported by serum progesterone level (45% in serum progesterone level of <15 ng/mL; 64% for serum progesterone level of >15 ng/mL) (21) using 2-tailed chi-square test with 80% power and $\alpha = 0.05$ and assuming a distribution of 1:3. Logistic regression was performed to examine the relationship between progesterone level and live birth while controlling for age, parity, smoking history, anovulation diagnosis, and weight. Chi-square test with a post hoc z-test using Bonferroni correction was used to determine the differences between weight classifications at various progesterone levels. We repeated all analyses with the sample stratified by BMI instead of weight because a majority of the prior literature has focused on the BMI.

RESULTS

A total of 633 patients met the inclusion criteria and were included in the analysis. The BMI of the patients ranged from 17.6 to 50.1 kg/m^2, with a median of 26.1 (interquartile range 22.7–31.6) kg/m^2. Patient weights ranged from 100 to 323 lbs, with a median weight of 157 (interquartile range 138–190) lbs. Spearman's rank correlation revealed a negative correlation between BMI and serum progesterone level at the time of the pregnancy test (rho $= -0.521$, $P<.001$), with BMI accounting for 27% of the variance in the progesterone level. Weight was found to be a better predictor of progesterone level, with weight accounting for 29% of the variance in the progesterone level at the time of the pregnancy test

(rho = −0.536, $P<.001$). As weight was more predictive of the progesterone level, we focused on weight for the remaining results.

Demographic characteristics by weight category are shown in Table 1 and demographic characteristics by BMI are shown in Table 2. There were no significant differences in mean age, race, gravidity, or number of previous IVF cycles across the categories. Both history of smoking and diagnosis were found to differ by weight and BMI category, with the high weight and BMI groups being more likely to have a history of smoking and a diagnosis of anovulation.

The progesterone levels at the time of the pregnancy test can be seen listed by weight and BMI category in Table 3. In general, higher weight categories were associated with lower progesterone levels. Serum progesterone levels of <15 ng/mL were found in 3% of women weighing <68 kg compared with 29% of women weighing ≥90.7 kg ($P<.001$). Only 27% of the women weighing ≥90.7 kg had progesterone levels of ≥20 ng/mL.

We did not find a difference in the odds ratio for live birth between women with a progesterone level of <15 ng/mL and those with a progesterone level of 15–19.9 ng/mL (adjusted odds ration [AOR], 95% confidence interval [CI]: 0.86, 0.47–1.60) or ≥20 ng/mL (AOR, 95% CI: 1.06, 0.58–1.92) when controlling for age, smoking history, parity, a diagnosis of anovulation, and weight group. Similarly, we found no significance difference in LBR between women with a progesterone level of <15 ng/mL and those with a progesterone level of 15–19.9 ng/mL (AOR, 95% CI: 0.89, 0.48–1.64) or ≥20 ng/mL (AOR, 95% CI: 1.05, 0.58–1.90) when BMI group was included in the model instead of weight.

Information for pregnancy outcomes by progesterone level at the time of the pregnancy test for subgroups of women weighing ≥90.7 kg and BMI ≥30 kg/m^2 is presented in Table 4. Among women weighing ≥90.7 kg, there was no significant correlation between the progesterone level at the time of the pregnancy test and the pregnancy outcome. The LBR was 47% for women with serum progesterone level of <15 ng/mL at the time of the pregnancy test compared with 49% for women with serum progesterone level of 15–19.9 ng/mL and 44% for women with serum progesterone level of ≥20 ng/mL (Table 4). In women weighing ≥90.7 kg, there were no ectopic pregnancies. Abnormal pregnancies did not differ among serum progesterone levels in women weighing ≥90.7 kg. No significant differences were found for these outcomes within the subsample of patients with BMI ≥30 kg/m^2.

DISCUSSION

The primary objective of our study was to determine whether the serum progesterone level was influenced by increasing BMI or weight in cryopreserved embryo transfer cycles, when patients rely on progesterone supplementation. We discovered that both increasing BMI and increasing weight negatively affected the serum progesterone levels on the day of the pregnancy test and that increasing weight was more influential than BMI. This was in agreement with the findings from a prior study at our institution (14). We hypothesized that this could be because of an increased volume of distribution for progesterone or perhaps the inability of standard-length needles to reach the muscular layer of the

TABLE 1

Participant characteristics by weight.

Characteristic	Weight <68 kg (n = 248)	Weight 68-90.3 kg (n = 266)	Weight ≥90.7 kg (n = 119)	*P* value
Age (y)	33.70 ± 4.58	34.03 ± 4.74	33.88 ± 4.52	.720
White	219 (89%)	243 (92%)	105 (90%)	.649
History of smoking	36 (15%)	50 (19%)	31 (26%)	.030
Current smoker	2 (1%)	10 (4%)	3 (3%)	.099
Gravidity	1 (0–2)	1 (1–2)	1 (0–2)	.066
Parity	1 (0–1)	1 (0–1)	0 (0–1)	.151
Previous cycles	1 (1–1)	1 (1–2)	1 (1–1)	.311
Diagnosis[a]				
Advanced maternal age	16 (7%)	20 (8%)	3 (3%)	.155
Anovulation	40 (16%)	58 (22%)	38 (32%)	.003
Diminished ovarian reserve	24 (10%)	22 (8%)	18 (15%)	.128
Endometriosis	27 (11%)	27 (11%)	11 (9%)	.872
Male factor	80 (33%)	97 (37%)	48 (40%)	.320
Tubal factor	39 (16%)	43 (16%)	21 (18%)	.916
Uterine factor	8 (3%)	12 (5%)	17 (14%)	<.001
Unexplained	63 (26%)	50 (19%)	15 (13%)	.011
Other	33 (14%)	35 (13%)	17 (14%)	.969
No. of embryos transferred	1 (1–1)	1 (1–1)	1 (1–1)	.274
Use of preimplantation genetic testing	26 (11%)	40 (15%)	14 (12%)	.285

Note: Data are presented as mean ± standard deviation with *P* values for analysis of variance, number (%) with *P* values for chi-square test, or median (interquartile range) with *P* values for Kruskal-Wallis test.

[a] Two hundred participants in the dataset had multiple diagnoses, so sum across diagnoses categories will not total 100%; 42 cases did not have any diagnosis specified.

Whynott. BMI effect on serum progesterone in IVF. Fertil Steril Rep 2021.

TABLE 2

Participant characteristics by BMI.

Characteristic	BMI <30 kg/m² (n = 438)	BMI ≥30 kg/m² (n = 194)	*P* value
Age (y)	33.94 ± 4.56	33.76 ± 4.81	.656
Caucasian	396 (91%)	170 (89%)	.518
History of smoking	67 (15%)[a]	50 (26%)	.003
Current smoker	8 (2%)[b]	7 (4%)	.254[c]
Gravidity	1 (0–2)	1 (1–2)	.764
Parity	1 (0–1)	1 (0–1)	.044
Previous cycles	1 (1–1)	1 (1–1)	.527
Diagnosis[d]			
Advanced maternal age	31 (7%)	8 (4%)	.220
Anovulation	81 (19%)	55 (29%)	.006
Diminished ovarian reserve	39 (9%)	25 (13%)	.157
Endometriosis	47 (11%)	18 (9%)	.698
Male factor	151 (35%)	73 (38%)	.464
Tubal factor	68 (16%)	35 (18%)	.479
Uterine factor	20 (5%)	17 (9%)	.056
Unexplained	99 (23%)	29 (15%)	.039
Other	59 (14%)	26 (14%)	1.000
No. of embryos Transferred	1 (1–1)	1 (1–1)	.557
Use of preimplantation genetic testing	54 (12%)	26 (13%)	.807

Note: Data are presented as mean ± standard deviation with *P* values for Student's *t* test, number (%) with *P* values for chi-square test, or median (interquartile range) with *P* values for Mann-Whitney *U* test. BMI = body mass index.
[a] Missing data for 1 case.
[b] Missing data for 16 cases.
[c] *P* value for Fisher's exact test as the expected counts for chi-square test were not met.
[d] Two hundred participants in the dataset had multiple diagnoses; so sum across diagnoses categories will not total 100%. Moreover, 42 cases did not have any diagnosis specified.

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tissue to provide an actual intramuscular injection in women weighing ≥90.7 kg or with a BMI >30 kg/m^2.

Our secondary objective was to determine if the LBR would be affected by differences in serum progesterone level in women weighing ≥90.7 kg in a program that automatically increases the progesterone supplementation (to 75 mg) if the serum progesterone level is noted to be <15 ng/mL on the day of the pregnancy test. Previous studies have suggested that lower serum progesterone levels can decrease the LBR in both frozen and fresh embryo transfer cycles (21, 23–25). Although prior studies have typically measured the progesterone level on the day of transfer, this is not consistent in practice, with some clinics measuring the level on the day of the pregnancy test. The route of progesterone supplementation is also not standardized across IVF programs. Our goal was to determine if the lower progesterone levels on the day of the pregnancy test were associated with a higher rate of an abnormal pregnancy (miscarriage or biochemical or ectopic pregnancy) or decreased LBRs. This determination was made in the context of a clinical policy of increasing the dose of intramuscular progesterone in anyone with a serum progesterone level of <15 ng/mL. We did not find evidence of a difference in live birth between serum progesterone levels on the day of the pregnancy test when intramuscular progesterone supplementation was increased for those with serum progesterone levels of <15 ng/mL. Our findings suggest that intramuscular progesterone in oil (50 mg) is sufficient to allow for implantation regardless of serum progesterone levels and patient weight or BMI; however, because we did not have a comparison group that did not receive additional supplementation if the serum progesterone level was <15 ng/mL, we do not know if increasing the supplementation changed the live birth outcome. In the prior study by Brady et al. (21), intramuscular progesterone was used as well, although the starting dose of progesterone ranged from 50 to100 mg without an explanation of the dose choice or of how many patients received each starting dose. Differences in our outcomes may be because of our larger patient sample, a standardized starting dose of progesterone, our analysis of cryopreserved embryo cycles instead of fresh embryo transfer cycles, or our testing of the serum progesterone level on the day of the pregnancy test instead of the day of the embryo transfer.

Given the increasing prevalence of overweight and obesity in the United States, it is important to evaluate how increasing weight or BMI affects treatment outcomes and to determine adjustments that can be made to accommodate and improve the success rates of IVF in this population.

TABLE 3

Progesterone level outcomes by weight and BMI.

Progesterone level at the time of the pregnancy test (ng/mL)	Grouped by Weight			Grouped by BMI	
	Weight <68 kg (n = 248)	Weight 68-90.3 kg (n = 266)	Weight ≥90.7 kg (n = 119)	BMI <30 kg/m² (n = 308)	BMI ≥30 kg/m² (n = 124)
<15	8 (3%)[a]	20 (8%)[a]	34 (29%)[b,c]	15 (3%)[d]	47 (24%)[e]
15–19.9	19 (8%)[a,c]	72 (27%)[a,b]	53 (45%)[b,c]	70 (16%)[d]	74 (38%)[e]
≥20	221 (89%)[a,c]	174 (65%)[a,b]	32 (27%)[b,c]	353 (81%)[d]	73 (38%)[e]

Note: Data are presented as number (%). *P* values are for chi-square test of independence. BMI = body mass index.
[a] Proportion differs significantly from the weight ≥90.7 kg group at .05 level.
[b] Proportion differs significantly from the weight <68 kg group at .05 level.
[c] Proportion differs significantly from the weight 68-90.3 kg group at .05 level.
[d] Proportion differs significantly from the BMI ≥30 kg/m^2 group at .05 level.
[e] Proportion differs significantly from the BMI <30 kg/m^2 group at .05 level.

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TABLE 4

Pregnancy outcomes by progesterone level at the time of the pregnancy test for the subsample of patients weighing 90.7 kg and with BMI ≥30 kg/m^2.

Pregnancy Type	Progesterone < 15 ng/mL	Progesterone 15-19 ng/mL	Progesterone 20+ ng/mL	*P*
Subsample weighing ≥90.7 kg				
n	34	53	32	
No pregnancy	9 (27%)	11 (21%)	7 (22%)	.879
Abnormal pregnancy[a]	9 (27%)	14 (26%)	11 (34%)	
Clinical pregnancy	16 (47%)	28 (53%)	14 (44%)	
Live birth	16 (47%)	26 (49%)	14 (44%)	.893
Subsample with BMI ≥30 kg/m^2				
n	47	74	73	
No pregnancy	12 (25%)	19 (26%)	21 (29%)	.972
Abnormal pregnancy[a]	11 (23%)	17 (23%)	14 (19%)	
Clinical pregnancy	24 (51%)	38 (51%)	38 (52%)	
Live birth	24 (51%)	36 (49%)	37 (51%)	.956

Note: Data are presented as number (%). *P* values are for chi-square test of independence. BMI = body mass index.
[a] Abnormal pregnancy was defined as biochemical or ectopic pregnancy or miscarriage.

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A recent meta-analysis revealed that female obesity negatively impacts the IVF success rate (26). Several theories have been postulated for this finding, including decreased oocyte quality, inadequate folliculogenesis, poorer embryo development, and an impaired endometrial environment (26). We hypothesized from our findings that the endometrial environment, in part, can be optimized with adequate progesterone dosing, and that women with obesity may have higher progesterone supplementation requirements. Our study suggests that increasing intramuscular progesterone supplementation in the setting of a serum progesterone level of <15 ng/mL on the day of pregnancy test is adequate to maintain excellent LBRs after cryopreserved embryo transfer cycles; however, a randomized, controlled trial is needed to confirm these findings. A potential area of investigation would be to start women weighing ≥90.7 kg on a higher initial progesterone dose and evaluate the serum progesterone levels as well as live birth outcomes. However, for the purposes of cost saving and patient satisfaction, future studies might also examine the use of longer needles for intramuscular progesterone administration to allow for the same dosage of medication to be used in this population.

The limitations of our study include our retrospective design and inclusion of only 1 center with a predominately white population. As the success of assisted reproductive technologies can vary by race and/or ethnicity, this may impact the generalizability of our findings (27). Additionally, some IVF patients may be unable to tolerate an intramuscular progesterone regimen; additional research is needed to determine adequate dosing for alternative progesterone administration routes for those in higher weight classes in those situations.

CONCLUSION

Body weight was a significant factor affecting the serum progesterone level at the time of the pregnancy test after a cryopreserved embryo transfer cycle as nearly 30% of patients weighing ≥90.7 kg had a serum progesterone level of <15 ng/mL, a value associated with lower LBRs in prior studies. However, we did not find evidence for a 19% reduction in LBR among patients with low progesterone levels after cryopreserved embryo transfer cycle in a clinic where progesterone dosing was started at 50 mg intramuscularly daily and increased if levels were <15 ng/mL on the day of the pregnancy test.

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