ORIGINAL RESEARCH

The Effect Of Maternal Obesity And Lipid Profile On First-Trimester Serum Progesterone Levels

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Abstract
Background: Prepregnancy overweight increases the risk of adverse perinatal outcomes. Maternal lipid profile plays a key role in the production of pregnancy hormones. The influence that obesity has on the specific mechanisms that may be involved and the potential associations with abnormal conditions in pregnancy are still poorly understood.
OBJECTIVE: This study aimed to evaluate the effect of maternal body mass index and lipid profile on first-trimester serum progesterone levels.
Study Design: This was a prospective cohort study including 734 pregnant people. First-trimester maternal serum progesterone, cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were measured between 9 and 11 weeks' gestation. Free b-hCG, PAPP-A, age, body mass index, smoking status, gestational age at delivery, fetal sex, and birthweight were also recorded. Pregnant people were classified according to their body mass index into underweight (n=21), normal weight (n=395), overweight (n=221), obesity class I (n=64), and obesity class II/III (n=33) groups.
Results: Gestational age at sampling was 10.0 4§1.12 weeks. Serum progesterone levels decreased as maternal body mass index increased (35.84§12.00 ng/mL, 33.08§11.27 ng/mL, 28.04§8.91 ng/mL, 24.37§ 8.56 ng/mL, and 19.87§11.00 mL for underweight, normal weight, overweight, obesity class I, and obesity class II/III groups, respectively; P<.0000001). There were statistically significant negative correlations between maternal progesterone and body mass index, triglycerides, and cholesterol/ high-density lipoprotein cholesterol ratio, and positive correlations with gestational age at sampling, maternal age, cholesterol, high-density lipoprotein cholesterol, crown−rump length, free b-hCG, and PAPP-A. Linear regression showed that the only independent predictor variables for progesterone levels were body mass index (P<.0000001).
Conclusion: First-trimester serum progesterone levels were lower in overweight pregnant people and markedly decreased in those with obesity, especially obesity class II/III. Maternal high-density lipoprotein cholesterol was independently related to progesterone levels as a protective factor. Benefits of progesterone supplementation in pregnant people with obesity need further evaluation.
Keywords: high-density lipoprotein cholesterol, lipids, miscarriage, obesity, placental metabolism, pregnancy, pregnancy complications, progesterone.

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Introduction

Obesity has been described as the new worldwide epidemic. In Asian countries, this condition is increasing rapidly and becoming a major health problem. From the obstetrical perspective, prepregnancy overweight increases the risk of adverse perinatal outcomes, including congenital malformations, miscarriage, late fetal death, macrosomia, pregnancy-induced hypertension, and cesarean delivery.1 Specifically, the risk for miscarriage before the first live-born child in pregnant people with obesity has been described as being as high as 25% to 37%.2 The exact mechanism by which obesity may contribute to the risk of miscarriage is poorly understood. A meta-analysis demonstrated this increased risk in spontaneously conceived pregnancies, and in cases of induction of ovulation or after oocyte donation. 2 Although the evidence was not strong enough in cases of patients treated with in vitro fertilization, most of the studies have found that miscarriage rate is also higher in people with obesity using assisted reproductive techniques, and thus weight loss is always encouraged in these patients.3,4 The cause of these pregnancy losses is probably related to altered endometrial receptivity rather than a

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direct effect on either oocytes or embryos,3 although the latter cannot be ruled out. It is unclear if this effect of obesity on the endometrium may be because of a deficit in progesterone production, although other factors such as hyperglycemia and inflammation clearly related to the presence of obesity should be considered.5,6 Progesterone is essential for correct implantation and early embryo development. Moreover, it is critical for maintaining uterine quiescence and regulating maternal−fetal and placental metabolism. During the first weeks of pregnancy, it is produced by the corpus luteum, but at approximately 6 to 8 weeks of pregnancy, the placenta takes over the corpus luteum as the main source of progesterone production.7 In this period, progesterone may be critical to regulate the actions of other important hormones and mediators such as estrogen, prostaglandins, and oxytocin. A loss of this balance, resulting from reduced progesterone levels before 10 weeks of gestation, has been observed in pregnant people before abortion.8 Defects in the production of progesterone by the corpus luteum, and the activity of the receptors of this hormone have been studied in relation to infertility and sterility, in the context of the condition called luteal phase deficiency. The potential failure of the progesterone production by the placenta is less known. Whether this deficiency exists, the specific mechanisms that may be involved, and the potential association with abnormal conditions in pregnancy remain to be clarified. In addition, maternal plasma progesterone level beyond 9 weeks has been evaluated as a biomarker for predicting several maternal complications. Low serum level at 9 weeks has been found to be a predictor of miscarriage at 12 weeks' gestation.9 Beyond miscarriage, progesterone has been linked to other pregnancy complications such as pregnancy-induced hypertension and intrauterine growth restriction.10,11 However, neither progesterone nor 5-alpha-dihydroprogesterone concentrations in plasma are of value in identifying women at risk of developing pregnancy-induced hypertension,12 and maternal progesterone levels cannot discriminate between normal-grown and intrauterine growth−restricted fetuses.13 Because progesterone therapy is used for preventing preterm labor, and there is evidence that prolonged administration of progesterone minimizes the ability of the uterus to contract as a syncytium,14 maternal levels of progesterone have been investigated as predictors of preterm labor. It has been reported that progesterone metabolites 11-deoxycorticosterone and 16 alpha-hydroxyprogesterone, when combined with patient demographic and obstetrical history known during the pregnancy, are predictive of preterm delivery−associated neonatal morbidity,15 although these results should still be validated. However, concerning maternal progesterone levels, the results have been inconclusive and even contradictory. Although some authors found high levels of progesterone at 28 to 32 weeks' gestation in pregnant people having preterm labor,16 others have found the contrary— low levels in both plasma17 and in saliva.17 Therefore, the role and the predictive capability of progesterone for these complications remain unclear. Cholesterol is essential for the placental biosynthesis of progesterone. Most of this cholesterol is derived from the maternal lipoproteins; therefore, variations in lipid levels may influence progesterone production. It is not clear whether alterations in the maternal lipid levels in the first trimester are related to pregnancy complications.18 A better understanding of the relationships among progesterone, maternal body mass index (BMI) status, and lipids is important for further hypothetical applications. These include potential use as biomarkers for pregnancy complications and potential therapeutic uses for preventing or treating these conditions. For this, it is essential to evaluate these interactions in a multivariate model given that maternal BMI and lipid profile may be related. This study aimed to: (1) test the hypothesis that progesterone levels may be decreased in cases of maternal obesity, and (2) evaluate the relationship between first-trimester maternal serum progesterone and lipid profile in a multivariate model.

Materials and Methods

Study design and population

We performed a population-based prospective cohort study including consecutive pregnant people with singleton pregnancies undergoing first-trimester combined screening for aneuploidies. According to the study protocol, an additional blood sample was requested at the time of extraction for biochemical screening (9−11 weeks) to determine the rest of the analytes included in the study. Exclusion criteria included twin or multiple pregnancy, assisted reproduction techniques (ART), progesterone therapy, and familial dyslipidemia. The local ethical and research committees approved the study on April 22, 2009 (PS09/02178), and the approval was in accordance with the Declaration of Helsinki.

All pregnant people participating in the study signed a written consent form. All pregnant people were followed up until the end of pregnancy, and the following clinical variables were recorded: maternal age and BMI, gestational age at delivery, mode of delivery, fetal sex, and birthweight. All cases with miscarriage, elective termination of pregnancy, fetal demise, and loss to follow-up were excluded from the analysis.

Outcome measures

All biochemical parameters were analyzed using reagents and modular systems from Diagnostics. Triglycerides, total cholesterol, and high-density lipoprotein cholesterol (HDL-c) were measured by standard enzymatic methods (cobas t 711 system; Roche Diagnostics). Low-density lipoprotein cholesterol (LDL-c) was calculated using the

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Friedewald−Fredrickson formula. Progesterone levels were measured by electrochemiluminescence immunoassay (ECLIA) (cobas c 170 system; Diagnostics). Free b-hCG (beta-human chorionic gonadotropin) and PAPP-A (pregnancy-associated plasma protein-A) were determined by automated standardized methods, using an enzyme-linked immunosorbent assay (ELISA) kit with the cobas e 601 system Diagnostics.

Statistical analysis

Numeric variables are expressed as mean§standard deviation. Categorical variables are shown as number and percentage. Comparisons between 2 groups were done using the Student t-test. When >2 groups were compared, analysis of variance (ANOVA) was used, followed by LSD (least significant difference) test as post hoc analysis. Because both PAPPA and free b-hCG were not normally distributed, log-transformed values were used for analysis. The relationships between variables were analyzed using the Pearson linear correlation coefficient. For linear regression, fetal sex was categorized as a numeric variable, assigning the value 0 for male and 1 for female fetuses. Likewise, smoking habit was converted to a binary variable, assigning the value 0 to nonsmokers and 1 to smokers. To account for covariables that may act as confounders, we performed a linear regression to find independent predictor variables for first-trimester progesterone plasma levels. Statistical significance was set at 95% level (P <95) and analyses were performed with IBM SPSS Statistics software, version 20.0 .

Results

Initially, 973 eligible pregnant people accepted to participate in the study. A total of 20 cases of twin pregnancies and 20 cases using progesterone after ART (6 of them with twin pregnancy) were excluded. Thus, 939 pregnant people were initially included; 15 were excluded because of their biochemical analyses, which were performed out of the normal gestational-age range. In addition, 38 pregnant people who had miscarriage or voluntary termination of pregnancy, 3 pregnant people with fetal demise, and 149 cases of partial or total loss to follow-up were also excluded. Finally, 734 pregnant people (75.44%) were included in the study (Figure 1). Maternal characteristics and basic perinatal outcomes are shown in Table 1. Gestational age at sampling was 10.04§1.12 weeks. The values of maternal lipid plasma levels, progesterone, b-hCG, and PAPP-A are shown in Table 2. Serum progesterone levels were lower in smokers in comparison with nonsmokers (27.47§9.11 vs 30.95§11.34 ng/mL; P<.0001 and in pregnant people bearing female fetuses compared with those with male fetuses (29.19§ 10.25 vs 30.97§11.22 ng/mL; P=.03). Pregnant people were categorized according to their BMI into 5 groups: underweight (n=21), normal weight (n=395), overweight (n=221), obesity class I (n=64), and obesity class II/III (n=33) (Table 3). There were statistically significant differences in serum progesterone among groups according to their BMI status (P<.00001). Post hoc analysis comparing groups found that progesterone was significantly lower in the overweight, obesity class I, and obesity class II/III groups in comparison with normalweight and underweight groups. Descriptive statistics and differences between paired groups are shown in Table 3 and Figure 2. All groups were significantly different from each other, with the exception of underweight and normal-weight groups, which had similar serum progesterone concentrations. In total, there were 27 miscarriages and 11 voluntary terminations of pregnancy. Table 3 also shows progesterone levels in cases of spontaneous miscarriage. Progesterone was significantly higher in normal pregnancies compared with all other groups, and the levels decreased as BMI increased; however, comparisons among groups could not demonstrate statistically significant differences, probably because of the low number of cases (eg, only 1 case in class II/III obesity). There were 48 cases of preterm labor. Neither lipid profile nor progesterone levels differed significantly between women with and without preterm delivery. There were statistically significant negative correlations between first-trimester maternal serum progesterone and maternal BMI, triglycerides, and total cholesterol/HDL-c ratio, and significant positive correlations with gestational age at sampling, maternal age, total cholesterol, HDL-c, crown−rump length (CRL) measurements, free b-hCG, and Pearson correlation coefficients and P values are shown in Table 4. The most important correlations were those with PAPP-A and BMI (Figures 3 and 4). Linear regression using all variables that showed significant correlations in the univariate analysis found that the only independent predictor variables were maternal BMI (P<.0000001).PAPP-A. The values of the Pearson correlation coefficients and P values are shown in Table 4. The most important correlations were those with PAPP-A and BMI Linear regression using all variables that showed significant correlations in the univariate analysis found that the only independent predictor variables were maternal BMI (P<.0000001). (Figures 3 and4).

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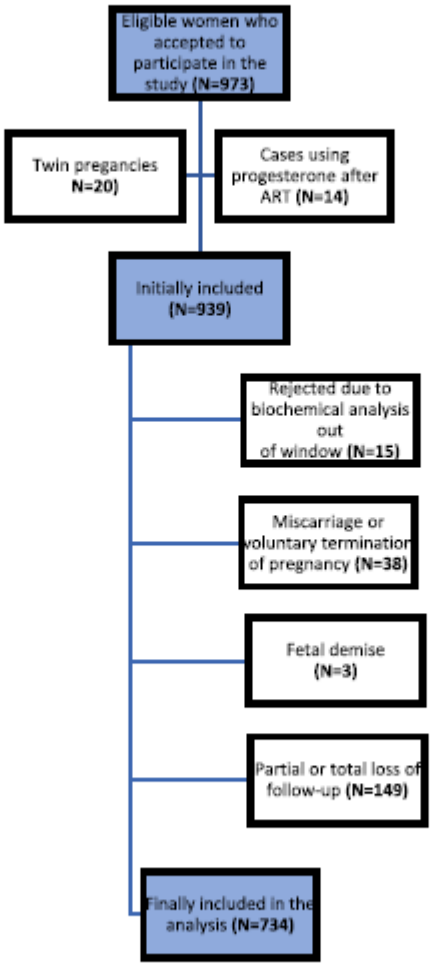
FIGURE 1
Flowchart of the studied population



ART, assisted reproduction techniques.

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TABLE 1
Maternal characteristics and basic perinatal outcomes (n=734)

Variable	Underweight (n=21)	Normal weight (n=395)	Overweight (n=221)	Obesity class I (n=64)	Obesity class II/III (n=33)	*P* value
Maternal age (y)	29.27 ± 6.37	31.89 ± 5.28	31.73 ± 5.47	32.43 ± 5.56	31.97 ± 5.55	.21
BMI (kg/m^2)	17.04 ± 1.22	22.17 ± 1.68	26.94 ± 1.24	32.01 ± 1.35	39.50 ± 4.18	<.001
GA at sampling (wk)	10.40 ± 0.86	10.01 ± 1.09	10.06 ± 1.12	10.32 ± 1.23	10.02 ± 0.98	.25
GA at delivery (wk)	38.75 ± 2.42	39.13 ± 2.06	39.48 ± 1.55	38.87 ± 1.90	39.36 ± 1.39	.08
Preterm delivery (<37 wk)	3 (14.28%)	28 (7.08%)	10 (4.52%)	6 (9.37%)	1 (3.03%)	.25

BMI, body mass index; *GA*, gestational age.

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TABLE 2
Biochemical variables (n=734)

Variable	Results
Free β-hCG (UI/mL)	68.02 ± 52.65
Log free β-hCG	1.79 ± 0.27
PAPP-A (UI/mL)	1412.81 ± 1261.09
Log PAPP-A	2.99 ± 0.39
Progesterone (ng/mL)	30.16 ± 11.03
Total cholesterol (mg/dL)	177.39 ± 29.06
HDL-c (mg/dL)	72.43 ± 13.64
LDL-c (mg/dL)	89.10 ± 23.47
Triglycerides (mmol/L)	79.55 ± 34.54
Ratio of total cholesterol to HDL-c (mg/dL)	2.50 ± 0.51

Data are presented as mean±standard deviation.

β-hCG, beta-human chorionic gonadotropin; *HDL-c*, high-density lipoprotein cholesterol; *LDL-c*, low-density lipoprotein cholesterol; *PAPP-A*, pregnancy-associated plasma protein-A.

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Discussion

Principal findings

In this study, first-trimester serum progesterone levels were lower in overweight pregnant people and markedly decreased in obesity, especially in obesity class II/III. In addition, they were also lower in smokers in comparison with nonsmokers and in pregnant people bearing female fetuses compared with those with male fetuses. Furthermore, first-trimester maternal serum progesterone was negatively correlated with maternal BMI, triglycerides, and total cholesterol/HDL-c ratio, and significantly positively correlated with gestational age at sampling, maternal age, total cholesterol, HDL-c, CRL measurements, free b-hCG, and PAPP-A. After multivariate adjustment, the only significant parameters influencing progesterone levels were BMI, HDL-c as a protective factor, and both placental proteins: PAPP-A and b-hCG. Cases of miscarriage were analyzed separately correlation with maternal age was very weak, although significant, probably because of the high number of cases; however, this association was no longer significant after adjustment for the remaining variables. Thus, it could probably depend on correlation with other variables such as cholesterol level or BMI.

Results and clinical and research implications

Obesity is a costly and increasingly prevalent condition. In the fields of reproduction and obstetrics, it is associated with many complications. Different mechanisms are involved in the poor reproductive performance of patients with obesity. Concerning miscarriage, both direct effect on either oocytes or embryo and altered endometrial receptivity have been reported.20,21 In people with obesity and pregnancy loss after in vitro fertilization or intracytoplasmic sperm injection, it has been reported that the risk is, to some extent, related to the lower number of collected oocytes in people with obesity.6 However, an altered endometrial function and morphology may also be present. This could be the main mechanism for miscarriage in people with obesity with spontaneous conception. It has been demonstrated that in people with recurrent miscarriage, there is a significant negative correlation between endometrial glandular leukemia inhibitory factor concentration, a key factor for implantation, and the BMI.7 This effect may be mediated by the action of progesterone, as demonstrated in animal models.22 We found a significant decrease in progesterone concentration in pregnant people with obesity, in line with other published data.23,24 This was a large prospective observational cohort study. Because of the large sample, we were able to categorize people into 5 groups according to their BMI status. The decreases in progesterone concentration were already significant in overweight people, more pronounced in those with obesity, and markedly lower in pregnant people with obesity class II/III. In these pregnant people, progesterone levels fell to 57% of the normal concentration. It has been published that plasma estradiol and progesterone concentrations at term were significantly lower in pregnant people with obesity as compared with lean people.24,25 Maliqueo et al24 showed some alternations in the placental protein expression enzymes of people with obesity compared with control patients, specifically in those that synthesize progesterone and estrogen. Moreover, these variations differed by fetal sex. We also found a

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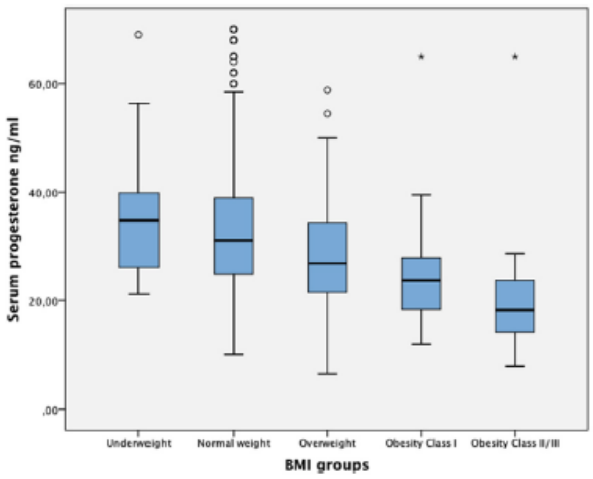
statistically significant although not clinically relevant difference in progesterone levels according to fetal sex. However, this difference disappeared after multivariate adjustment. Lassance et al25 also reported that in placentas of people with obesity, the placental mitochondrial cholesterol concentration was 40% lower, and the mitochondrial translocator protein (TSPO) was decreased. This indicates that obesity could impair mitochondrial steroidogenic function through the negative regulation of mitochondrial TSPO. Thus, the low progesterone concentration that we found in the first trimester of pregnancy in people with obesity could be because of a deficit of production rather than a consequence of simple hemodilution. Except in the first weeks, placental cholesterol is the source of sex steroids during pregnancy. Because placental cells have limited capacity for de novo synthesis of cholesterol, they use cholesterol derived from maternal lipoproteins as a source for progesterone synthesis. In addition, a study examining cultured human term placenta demonstrated that LDL and HDL have a carrier function for cholesterol and stimulated placental progesterone synthesis.7 Furthermore, these lipoproteins facilitated progesterone release from placental tissue. Interestingly, we found a positive correlation between both total cholesterol and HDL-c and progesterone levels but no correlation with LDL-c levels. In another study on 22 nonsmoker patients with uncomplicated pregnancies without obesity, the authors also found correlations between lipids and placental steroid hormone, although the trimester of pregnancy in which the relationships were analyzed was not specified, and no multivariate analysis was performed. In addition, they did not find significant differences according to fetal sex.26 Cholesterol transported by maternal lipoproteins is one of the most important stimuli for progesterone production at the time when the placenta takes over the corpus luteum. However, the relationship between HDL-c and placental steroidogenesis is probably more complex. The mechanisms controlling steroidogenesis in human placental mitochondria are still unknown. Nevertheless, there is enough evidence suggesting that cholesterol transport to mitochondria and between mitochondrial membranes are rate-limiting steps.27 One significant difference between the placenta and other steroidogenic tissues is that the placenta lacks short-term modulation of progesterone synthesis by cyclic adenosine monophosphate (cAMP) and does not express all types of the steroidogenic acute regulatory (StAR) proteins that control mitochondrial cholesterol trafficking, specifically STARD1.7 It has been suggested that STARD3 is in charge of transporting cholesterol in the human placenta. This protein has to be proteolytically activated, and one of its functions is to stimulate mitochondrial progesterone production.28 In animal liver models, it has been suggested that genetic obesity lowers the expression of this protein, and that targeting STARD3 may increase circulating levels of HDL.29 Thus, it remains to be elucidated if human obesity may affect the placental expression of this protein and consequently decrease progesterone production, and if this protein is involved in the positive association between HDL-c and progesterone that we observed in this study. The relationship between HDL-c and progesterone in pregnancy complications is even less clear. An association between.

FIGURE 2
Serum progesterone according to maternal BMI group



BMI, body mass index.

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TABLE 3
First-trimester maternal serum progesterone according to maternal body mass index (n=734; analysis of variance *P*<.00001)

BMI groups	Serum progesterone (ng/mL)
Underweight (n=21)	35.84 ± 12.00
Underweight miscarriage (n=2; 8.69%)	17.72 ± 4.94
Normal weight (n=395)	33.08 ± 11.27
Normal weight miscarriage (n=16; 3.89%)	21.60 ± 13.69
Overweight (n=221)	28.04 ± 8.91
Overweight miscarriage (n=5; 2.21%)	16.51 ± 6.95
Obesity class I (n=64)	24.37 ± 8.56
Obesity class I miscarriage (n=3; 4.47%)	13.53 ± 11.15
Obesity class II/III (n=33)	19.87 ± 11.00
Obesity class II/III miscarriage (n=1; 2.94%)	7.58

Data are presented as mean±standard deviation. Patients were categorized according to their BMI (weight/height^2) into 5 groups: underweight (<18.5 kg/m^2), normal weight (18.5–25 kg/m^2), overweight (25–30 kg/m^2), obesity class I (30–35 kg/m^2), and obesity class II/III (>35 kg/m^2). ANOVA test *P*<.00001. Post hoc analysis: underweight vs normal weight: not significant (*P*=.24); underweight vs overweight: *P*=.001; underweight vs obesity class I: *P*<.0001; underweight vs obesity class II/III: *P*<.0001; normal weight vs overweight: *P*<.0001; normal weigh vs obesity class I: *P*<.0001; normal weight vs obesity class II/III: *P*<.0001; overweight vs obesity class I: *P*=.01; overweight vs obesity class II/III: *P*<.0001; obesity class I vs obesity class II/III: *P*<.0001. ANOVA test for miscarriage: *P*=.66. Chi-square test for miscarriage rate: *P*=.36.

ANOVA, analysis of variance; *BMI*, body mass index.

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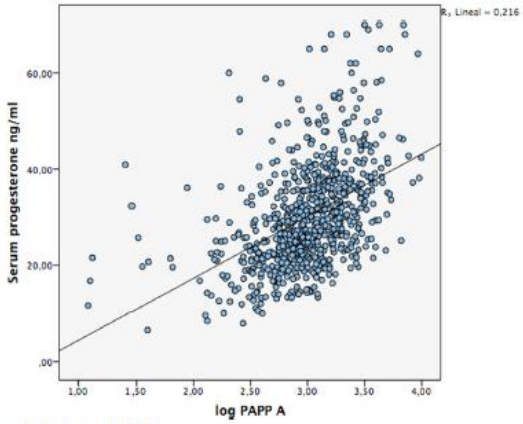
FIGURE 3
Serum progesterone and log-trasmformed PAPP-A (*r*=0.43; *P*<0.0001)



PAPP-A, pregnancy-associated plasma protein-A.

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TABLE 4
Univariate analysis: correlations between numeric variables and first-trimester serum progesterone (n=734)

Variable	r	P value
Maternal age	0.07	.04
Maternal BMI	−0.37	<.0001
Total cholesterol	0.09	.01
Triglycerides	−0.14	<.0001
HDL-c	0.32	<.0001
LDL-c	−0.02	.36
Ratio of TC to HDL-c	−0.25	<.0001
Log free β-hCG	0.22	<.0001
GA at sampling	0.24	<.0001
CRL	0.13	<.0001
Log PAPP-A	0.46	<.0001
Birthweight	0.02	.51
GA at delivery	0.01	.68

β-hCG, beta-human chorionic gonadotropin; *BMI*, body mass index; *CRL*, crown–rump length; *GA*, gestational age; *HDL-c*, high-density lipoprotein cholesterol; *LDL-c*, low-density lipoprotein cholesterol; *PAPP-A*, pregnancy-associated plasma protein-A; *TC*, total cholesterol.

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ow HDL-c and preterm labor has been previously reported,1 but whether there is association between either of the 2 and progesterone concentration is still unknown. Further studies are needed to elucidate the relationship between HDLc levels and progesterone levels in the first trimester of pregnancy and to evaluate if that relationship is maintained in the second and third trimester. We recommend further investigation into the role of cholesterol and progesterone during pregnancy, so that we could better understand their implication in some obstetrical pathologies and their potential application as early biochemical markers. In our study, first-trimester serum progesterone levels were also positively correlated with markers of placental volume and function (free b-hCG and PAPP-A). Previous studies have demonstrated correlations between serum levels of b-hCG and PAPP-A and progesterone in normal and abnormal pregnancies.30−32 When adjusted in a multivariate model, both b-hCG and PAPP-A were independently associated with progesterone concentration. HCG has many placental, uterine, and fetal functions. One of its best-known actions is the maintenance of ovarian corpus luteal cells to guarantee correct steroid synthesis. The up-regulated relationship between hCG and progesterone production by syncytiotrophoblast cells starts when there are enough of them to take over progesterone production from corpus luteal cells. This process starts approximately 3 to 4 weeks after implantation, reaches a peak at approximately 10 weeks of gestation, and then progesterone continues to be produced throughout pregnancy.30 PAPP-A is secreted by the placenta and increases during pregnancy. There is a linear positive correlation between placental volume measured by 3D ultrasound at 11 to 13 weeks of gestation and PAPP-A expression and serum concentration.33,34 Thus, the increasing levels of progesterone as PAPP-A rises may reflect a direct association between progesterone and placental size. However, the relationships between PAPP-A and progesterone and the effects of PAPP-A on the trophoblast are still not clear. PAPP-A levels decrease after administration of an antiprogesterone (mifepristone) either in vivo or in vitro. This is considered as proof that PAPPA levels in early pregnancy are progesterone-dependent.32 PAPP-A could be an autocrine factor in implantation and embryo development, and it has been reported to be up-regulated by progesterone.35 It has been described that progesterone may promote adhesion and proliferation of trophoblastic cells. Therefore, deficient progesterone production may hypothetically be related to impaired placentation by 2 mechanisms—altered endometrial receptivity and abnormal trophoblastic invasion. Considering the results of our study and the previous literature, it can be reasonably concluded that the currently available evidence is still far from conclusive. However, given the many limitations of these studies, including our low number of cases of miscarriages, not accounting for the effect of maternal hemodilution, and not having chromosomal evaluation of the miscarriages, it could be hypothesized that at least some cases of pregnant people with obesity (especially those with obesity class II/ III) and low HDL-c levels could benefit from progesterone supplementation during the first trimester of pregnancy to reduce their potential risk of miscarriage. Nevertheless, further studies are needed to reach definitive conclusions, and the findings of this study do not support any changes to clinical care, especially when considering that most cases of pregnant people with obesity had lower progesterone levels but still within the normal range.

Strengths and limitations

The strengths of this study include the originality of the results not only related to maternal obesity but also to lipid profile, the big sample size, and the evaluation of different subgroups of obesity. Moreover, we also considered other variables that could have influenced our results, such as tobacco consumption and fetal sex. In addition, biomarkers and ultrasound results were also collected. Performing

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the study in only 1 center reduced laboratory result variability. However, our study also has some limitations. Ethnicity was not evaluated, and we did not consider the circadian rhythmic variation of progesterone during pregnancy36,37 or the changes in the maternal rhythmic circulating lipid profile. In addition, we did not collect samples during the second and third trimester, or after labor. However, this was not within the study scope. Finally, another limitation may be that we did not consider the dilutional effect of BMI and blood volume on all the measurements.

Conclusions

In this study, first-trimester serum progesterone levels were lower in overweight pregnant people and markedly decreased in those with obesity, especially obesity class II/III. Apart from BMI, serum progesterone concentration was mainly associated with levels of HDL-c and markers of placental volume and function (PAPP-A and free b-hCG). Further studies are needed to clarify if pregnant people with obesity and/or low HDL-c levels could benefit from progesterone supplementation in pregnancy.

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