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Prepregnancy obesity and complement system activation in early pregnancy and the subsequent development of preeclampsia

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Abstract

OBJECTIVE: We hypothesized that women who are obese before they become pregnant and also have elevations of complement Bb and C3a in the top quartile in early pregnancy would have the highest risk of preeclampsia compared with a referent group of women who were not obese and had levels of complement less than the top quartile.

STUDY DESIGN: This was a prospective study of 1013 women recruited at less than 20 weeks' gestation. An EDTA-plasma sample was obtained, and complement fragments were measured using enzyme-linked immunosorbent assays. The data were analyzed using univariable and multivariable logistic regression analysis.

RESULTS: Women who were obese with levels of Bb or C3a in the top quartile were 10.0 (95% confidence interval, 3.3–30) and 8.8 (95% confidence interval, 3–24) times, respectively, more likely to develop preeclampsia compared with the referent group.

CONCLUSION: We demonstrate a combined impact of obesity and elevated complement on the development of preeclampsia.

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Keywords

complement system; obesity; preeclampsia

Pregnancy is associated with a physiological state of inflammation and insulin resistance, which is further amplified if the woman is overweight or obese before conception.[1,2] Obesity-driven dysregulation of inflammatory and metabolic pathways contributes to adverse sequelae for the mother, specifically hypertensive diseases of pregnancy[2–4] and gestational diabetes.[2] In addition, obesity is a significant risk factor for complications in the neonate including macrosomia and congenital defects.[2] Obesity has now become one of the most important public health issues for the perinatal health of women,[5] with 23% of women of child-bearing age in the United States now estimated to be obese.[6]

Inflammatory mediators, derived from adipocytes and adipose-resident macrophages, contribute to obesity-related systemic inflammation. Adipokines and inflammatory cytokines as mediators of inflammation have been in the spotlight of research in recent years.[7,8] Inflammatory factors associated with the complement system are also found in adipose tissue, with adipose tissue and its microenvironment a source of the complement components C3, factor B, and factor D (adipsin).[9–12] However, there is a paucity of information on the impact of complement-mediated inflammation in obesity[13] specifically in pregnancy.[14]

The complement system (described elsewhere[15,16] and in Figure 1) is a complex series of more than 30 proteins (soluble and membrane bound) that has a pivotal role in innate immunity. Specifically, it has 3 main functions: (1) it defends the host against pyogenic infections, (2) bridges innate and adaptive immunity, and (3) disposes of immune complexes, apoptotic bodies and the products of injury from inflammation, ischemia, trauma, and infection. In many diseases these protective functions are inappropriately turned against self-tissues.[15] The complement has 3 initiating mechanisms known as the classical, lectin, and alternative pathways. The biologic functions of the complement system are mediated through the production of activation fragments.

Recently, our group has made 2 independent discoveries relevant to the role of complement activation in early pregnancy and to pregnancy-related obesity and vascular disease. First, complement activation fragments (Bb and C3a) are elevated in pregnant women with obesity compared with nonobese pregnant subjects.[17] Second, elevated levels of complement activation fragments in early pregnancy are significantly associated with the subsequent development of preeclampsia,[17–19] a complex multisystem pregnancy-related vascular disease that contributes significantly to maternal and neonatal mortality and morbidity.[20] The role of the complement system in hypertensive disease of pregnancy has also been supported by other authors,[21–24] and indeed, links between the complement system have also been described in association with other complications of pregnancy.[24–27]

Building on these results, we were interested to estimate the risk of preeclampsia based on maternal preconception obesity in combination with levels of complement activation fragments in early pregnancy. We hypothesized that women who are obese before they

become pregnant and also have elevations of complement markers in early pregnancy will have the highest risk of preeclampsia later in pregnancy compared with women, who have the following: (1) obesity alone and lower levels of complement markers, (2) elevated levels of complement markers with no obesity, and (3) neither elevation of complement markers nor obesity.

Materials and Methods

This was a planned secondary analysis of data collected as part of the Denver Complement Study. This prospective cohort study (June 2005 to June 2008) was approved by the Colorado Multiple Institutional Review Board. Details of the study have been described in previous publications.[17–19] In brief, women were recruited from the University of Colorado Hospital prenatal clinics and 2 affiliated sites. Women were referred to the study by the prenatal intake nurse if they were in the first half of pregnancy. Informed consent was obtained, and additional EDTA-plasma (for complement activation fragments) was obtained with the routine prenatal labs. Data were gathered on the maternal medical and obstetrical history. The women were followed up throughout pregnancy. After delivery, outcome data were collected and the gestational age at blood draw (recruitment visit) was assigned based on the best overall obstetrical estimate incorporating assessment at the first visit and in the great majority on early ultra-sound examination.

From the analytic dataset of singleton gestations (n = 1224), we excluded women with a loss to follow-up (n = 49) and chronic medical disease (cardiac disease, chronic hypertension, type 1 diabetes, and autoimmune disease, n = 114). Women with a missing plasma sample (because of a deviation from the study protocol at the initial blood draw, n = 48) were also removed from the analysis. Following theses exclusions, 1013 women remained in the analytic dataset.

The main outcome of the study was preeclampsia, classically defined as gestational hypertension and proteinuria.[28] The definition of gestational hypertension was a systolic blood pressure greater than 140 mm Hg or a diastolic blood pressure greater than 90 mm Hg on 2 or more occasions at least 6 hours apart after 20 weeks' gestation in a woman known to have been normotensive before pregnancy and before 20 weeks' gestation.[28] Preeclampsia was defined as one of the following: (1) gestational hypertension with proteinuria (300 mg or greater per 24 hour period) or at least 1or greater on dipstick or (2) in the absence of proteinuria, gestational hypertension with cerebral symptoms, epigastric or right upper quadrant pain with nausea, or vomiting or thrombocytopenia and abnormal liver function test.[28] Hypertensive disease of pregnancy was defined as the development of either preeclampsia or gestational hypertension in pregnancy.[28]

The complement activation fragments Bb and C3a and the maternal prepregnant body mass index (BMI) were the primary risk factors examined. At the first prenatal visit (less than 20 weeks' gestation, we measured the woman's height and determined her prepregnant weight (self-reported by the woman). The maternal BMI (kilograms per square meter) was calculated from the maternal prepregnant weight, and height and was categorized as follows: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI

25–29.9 kg/m^2), and obese (BMI >30 kg/m^2).[29] Additional maternal risk factors included in the analysis were age, race/ethnicity (non-Hispanic white, Hispanic white, African American, Asian, and other), parity (nulliparous vs multiparous), and cigarette smoking at conception (yes vs no).

Complement assays

Each EDTA tube for complement was promptly centrifuged, and the plasma was separated from the cells, aliquoted, and placed in a freezer at −80°C. For testing, the specimens were thawed 1 time and kept on ice during the assay set-up procedures. The complement activation fragment Bb was measured using a quantitative sandwich enzyme-linked immunosorbent assay (Quidel, San Diego, CA). C3a fragments were measured by the BD Pharmingen OptEIA enzyme-linked immunosorbent assay (BD Pharmingen, San Diego, CA). Although we refer to C3a throughout the manuscript, the actual fragment that was measured was C3a desArg because active C3a lasts only a short amount of time in the circulation. The inter- and intraassay coefficients of variation for Bb were 6% and 4.7%, respectively, and for C3a they were 12.1% and 11.2%. The individuals performing all study assays were blinded to the participant's pregnancy outcome.

Statistical analysis

The data were analyzed in SAS 9.3 (SAS Institute, Cary, NC). Associations between dichotomous or categorical variables were tested using the χ^2 test or Fisher exact test ($P < .05$). Means for continuous variables are reported, but nonparametric methods (Wilcoxon rank sum) were used to test for differences in medians among groups.

For the initial part of the analysis, levels of the complement fragments were categorized into quartiles. A variable of maternal inflammatory/metabolic risk was categorized as follows: (1) maternal prepregnant obesity and a level of the complement marker in the top quartile at less than 20 weeks' gestation, (2) maternal obesity alone and a level of the complement marker less than the top quartile, (3) complement levels in the top quartile and nonobese, and (4) complement levels less than the top quartile and nonobese. The categories were mutually exclusive.

We chose to dichotomize at the 75th percentile (Bb >0.82 μg/mL and C3a >895 ng/L) because it was the lowest point at which both complement markers appeared to give a clinically useful result with a large enough sample of preeclamptic subjects above the cutoff to make modeling meaningful. The association of these categories with preeclampsia was examined using univariable and multivariable logistic regression analysis. Women with complement levels less than the top quartile who were not obese were the referent group. The odds ratio (OR) was used as a measure of association.

Results

In this cohort, 635 women (63%) were non-Hispanic white, 246 Hispanic (24%), 71 African American (7%), and 61 (6%) were Asian or from other races. We report that 39 (4%) were underweight, 625 (62%) were normal weight, 233 (23%) were overweight, and 116 (11%) were obese. The majority of the women (62%) were younger than 35 years of age. Only a

small proportion of women (6.4%) reported cigarette smoking at the time of conception.A high proportion of the women in the cohort had their blood drawn in the first trimester(n = 620 [61%])with a mean ± SD gestational age (weeks) at first blood draw of 11.6 ± 2.6.

We examined the distribution of categories of the complement quartiles across categories of maternal prepregnant BMI. The underweight and normal-weight categories were merged because of low numbers of women with a prepregnant BMI less than 18.5. We show in Figure 2 differences in the levels of Bb within and across the 3 categories of BMI ($P < .0001$ for trend). It is note-worthy that among women who were obese, 14% had levels of Bb in the lower quartile and 44% had levels in the upper quartile.

Within and between the 3 categories of BMI there were also differences in the levels of C3a ($P < .0001$ for trend, Figure 3). We repeated the analysis among the 928 women who remained normotensive during pregnancy and found a similar significant trend across the categories of BMI ($P < .0001$ for trend). In addition, we conducted the analysis with the women who had a BMI less than 18.5 kg/m^2 removed from the analysis and found very similar significant results ($P = .0001$ for trend). We also found a significant ($P < .0001$) difference in the levels (mean ± SD) of Bb (micrograms per milliliter) and C3a (nanograms per liter) in women with a prepregnant BMI greater than 30 kg/m^2 as compared with women with a BMI less than 25 kg/m^2 (0.8 ± 0.2 vs 0.68 ± 0.2 for Bb and 824 ± 365 vs 728 ± 417 for C3a).

For the next part of the analysis, women who developed gestational hypertension or had delivery less than 20 weeks' gestation were removed from the cohort. Thirty-four of the 932 women (3.7%) developed preeclampsia. The incidence of preeclampsia among the 4 categories of BMI was 0% for a BMI less than 18.5 kg/m^2, 2.9% for a BMI between 18.5 and 25 kg/m^2, 1.9% for a BMI of 25–30 kg/m^2, and 12% for a BMI over 30 kg/m^2 ($P < .0003$ for trend). We demonstrate in Figure 4 that the incidence of preeclampsia rose in a significant dose-dependent manner across the categories of the Bb/obesity variable ($P < .0001$ for trend). We show in the multivariable logistic regression model (Table) that adjusted for maternal race, parity, age, and cigarette smoking at conception, obesity, and a Bb level in the top quartile and obesity alone were significant risk factors for preeclampsia.

For the categories of the C3a/obesity variable, the results were similar with a high incidence of preeclampsia (17.5%) in women with C3a in the top quartile and obesity compared with the referent group (2.7%) (Figure 5, $P < .0001$ for trend). Adjusted for other covariates, the OR in this high-risk group for preeclampsia was highly significant at 8.8 ($P < .0001$; Table). A level of C3a in the top quartile with no obesity did not confer any increased risk of preeclampsia, but the number of women in this category with preeclampsia was small (n = 4). We repeated the analysis for the Bb and C3a categories with women who had a BMI less than 18.5 kg/m^2 removed from the dataset and observed a similar significant trend as seen in the entire cohort.

Results of the univariable analysis for any hypertensive diseases of pregnancy (gestational hypertension-preeclampsia, n = 85) demonstrated similar trends to those for preeclampisa. In the multivariable logistic regression analysis for this outcome, the adjusted ORs for Bb

top quartile and obesity, obesity alone and lower levels of complement factors, top quartile Bb, and no obesity were 6.7 (95% confidence interval [CI], 3–14.7; $P < .0001$), 2.3 (95% CI, 1.016–5.3; $P = .046$), and 1.8 (95% CI, 1.008–3; $P = .047$), respectively. The adjusted OR for C3a top quartile and obesity, obesity alone, and top quartile C3a/no obesity for any hypertensive disease of pregnancy were 5.3 (95% CI, 2.4–12; $P < .0001$), 2.8 (95% CI, 1.3–6; $P = .01$), and 1.7 (95% CI, 1–3; $P = .05$), respectively. We also show in the Table the data stratified by parity. The trends were all significant across the Bb and C3a metabolic/inflammatory categories for both nulliparous and multiparous women.

We also investigated the relationship of having both an elevated level (top quartile) of C3a and Bb at less than 20 weeks' gestation on the risk of preeclampsia. Seventy-four women (8%) had levels of both of these markers in the top quartile. Five of these women (6%) developed preeclampsia compared with 29 (3.4%) in the remainder of the cohort (OR, 2; 95% CI, 0.8–5; $P = .14$).

Comment

This study represents the novel use of complement biomarkers in combination with obesity, a known risk factor for preeclampsia, in the risk assessment of women for the development of preeclampsia later in pregnancy. We found a significantly higher incidence of preeclampsia in women who were obese. The risk was further enhanced when we looked at the complement/obesity composite exposure. We estimate that women with a high level of complement activation fragments in association with prepregnant obesity are 10.0 (Bb) and 8.8 (C3a) times more likely to develop preeclampsia later in pregnancy compared with women who are not obese and have lower levels of the activation fragments. The trend was similar for the composite outcome of preeclampsia and gestational hypertension.

This is the first study to show a significant impact of the combination of obesity with a complement inflammatory marker in the first half of pregnancy on the development of preeclampsia. The incidence of preeclampsia rose as this metabolic/inflammatory burden increased in early pregnancy. The study shows clearly that the pathophysiology of preeclampsia and gestational hypertension-preeclampsia was evident as early as the first trimester of pregnancy long before the clinical onset of the disease. The risk was increased for the markers on their own,[18,19] but it was greatly enhanced with the addition of the inflammatory effect of obesity (Table). This confirms the many studies showing a significant link between inflammation and preeclampsia.[30]

The results of this study add to the growing body of literature, highlighting the important contribution of the complement system to the pathophysiology of several human diseases, including pregnancy-associated atypical hemolytic uremic syndrome[31] and the HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome.[21,31,32] In our high-risk subjects, the source of the complement factors is most likely adipose tissue,[9–12] the liver,[13] and perhaps the placenta.[33] Indeed, a link between prepregnant obesity and macrophage accumulation and inflammation has been described in term placentas from women with no evidence of gestational diabetes.[34] These results have important clinical

implications and suggest an opportunity to identify in early pregnancy a subset of pregnant obese women who are substantially more likely to develop preeclampsia.

The imbalance in cytokines and adipokines in obese individuals has received a substantial amount of investigation in recent times.[7,8] In contrast, there has been very little consideration given to dysregulation of the complement system in individuals with obesity. However, high expression of complement genes in intraabdominal adipose tissue suggests that the complement system has significant links with visceral adiposity and/or contributes to the inflammatory and metabolic sequelae associated with obesity.[35] Indeed, adipose tissue and its microenvironment (tissue macrophages) is a source of the complement components C3, factor B, and adipsin.[9,36]

Adipsin is the same protein as the complement factor D.[11] Factor B, C3, and adipsin have a role in the production of the complement fragment, acyl-stimulating protein.[37] Acyl-stimulating protein, which is also known as C3a desArg, acts to influence lipid metabolism in adipose tissue toward increased fat storage. Obese human subjects have higher acyl-stimulating protein levels[38] and weight loss decreases levels of acyl-stimulating protein in obese individuals.[39]

Our data in obese pregnant women replicate what has been described in the established literature. Indeed, a recent study has shown a relationship between enhanced levels of regulators and activators (circulating factor H and complement factor B of the alternative complement pathways) with higher levels of BMI, triglycerides, inflammatory parameters, and insulin resistance.[40] In line with our previous finding of elevated levels of C3a in obesity, other authors have discussed a link between obesity and the classical pathway.[41] Although C3a could be linked with the alternative complement pathway, this activation fragment could also arise from triggers for activation of the classical or lectin pathways in the absence of an elevated Bb. Interestingly, it would appear from our data (ie, the low frequency of overlap of high values of the complement markers) that multiple complement pathways may be activated in pregnancy. Indeed, other authors have implicated the role of activation of the classical pathway through autoantibodies[42] and the manose-binding lectin pathway in preeclampsia.[43]

This study clearly demonstrates a major impact of obesity and complement fragments on the incidence of preeclampsia. Notwithstanding these important results, the study has some limitations. The main issue is sample size with a low number of cases of women who developed hypertensive disease in pregnancy. However, even with this sample size, we saw a strong and highly significant relationship of the combination of obesity and a high complement marker with hypertensive disease of pregnancy. Low sample size also limited our ability to examine other adverse outcomes of pregnancy as, for example, spontaneous preterm birth and intrauterine growth restriction.[19,27] We also found the overall rate of obesity in the cohort (11%) to be lower than that reported nationally, perhaps secondary to the lower incidence of obesity in Colorado.[44]

Another limitation is that prepregnancy weight was self-reported[45] because we were not able to confirm prepregnant weight for most of the cohort. In the future we would certainly

like to study a larger,more diverse cohort to allow stratification analysis by severity of preeclampsia, race/ethnicity, and gestational age at onset of preeclampsia. It is also our intention to study other inflammatory mediators and additional complement markers from early pregnancy through to other time points further along in pregnancy.

Obesity is a modifiable risk factor. However, to reduce the contribution of this altered metabolic state to adverse pregnancy outcomes and the long-term cardiovascular health of women will require a major public health effort through pre- or inter-conception counseling directed at preventing excessive weight gain during pregnancy and overall weight reduction in women of reproductive age. Women need to be educated on the risks of obesity for their long-term health and the health of their babies. Moreover, these interventions need to be implemented before the first pregnancy to prevent perpetuation of the problem into subsequent pregnancies and future generations.[5,46,47]

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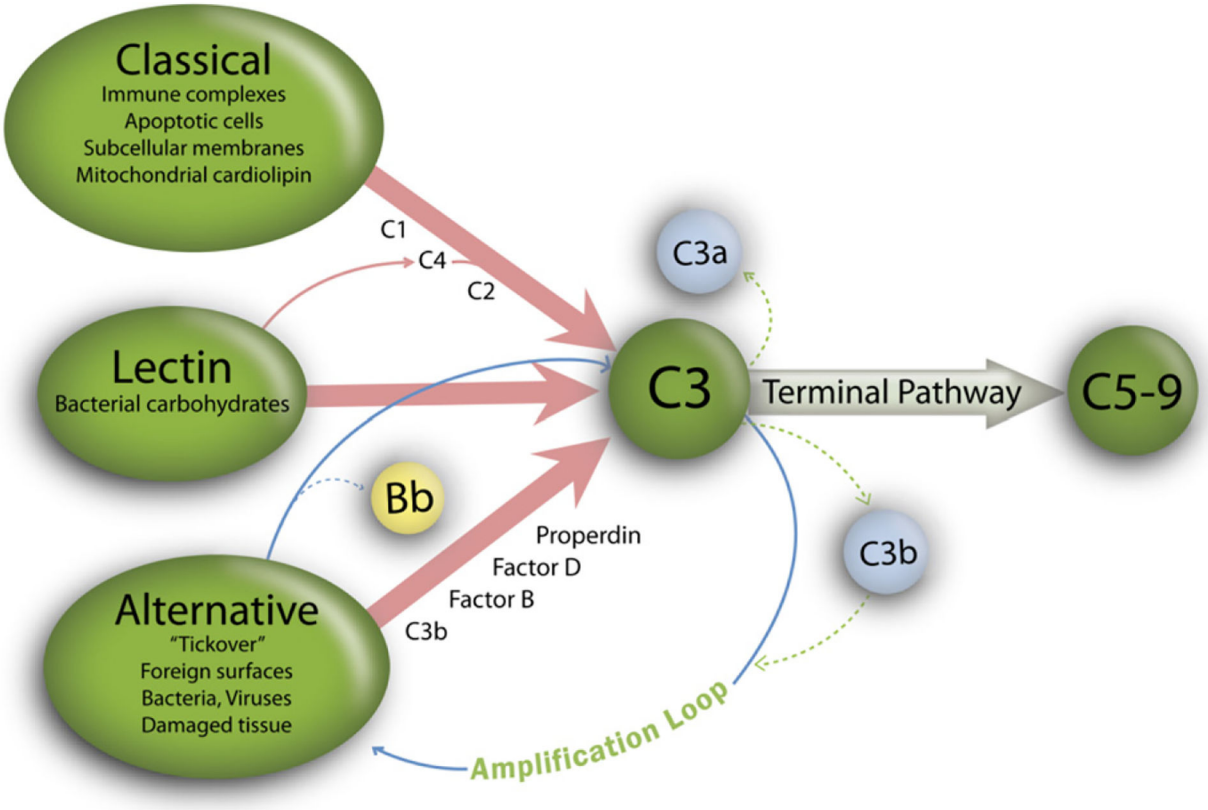

FIGURE 1.

Classical, lectin, and alternative complement pathways and triggers for activation

The classical, lectin, and alternative complement pathways and the triggers for activation (described in detail elsewhere[15]). The 3 complement pathways converge to generate C3 convertases that cleave C3, creating C3a and C3b. C3b is a major effector molecule of the complement system. C3b binds covalently to the surface of nearby cells, opsonizes the cells for phagocytosis, and initiates the reactions that lead to the formation of the membrane attack complex (C5–9). Bystander host cells are protected from excessive complement activation by cell-bound and circulating complement regulatory proteins. The alternative pathway also has the unique ability to serve as an amplification system for the classical and lectin pathways. In this study, we examined the complement activation fragment C3a, which can arise from activation of any of the 3 complement pathways and also Bb. The Bb activation fragment is primarily associated with alternative complement pathway activation but can also arise as a result of activation of initiation of the complement cascade by the classical or lectin pathways through the alternative complement pathway amplification loop. Bb is a protease generated during the sequential activation of both the alternative pathway and the activation loop and is required for further steps of the pathway. The alternative pathway and amplification loop are reviewed in detail elsewhere.[48–50]

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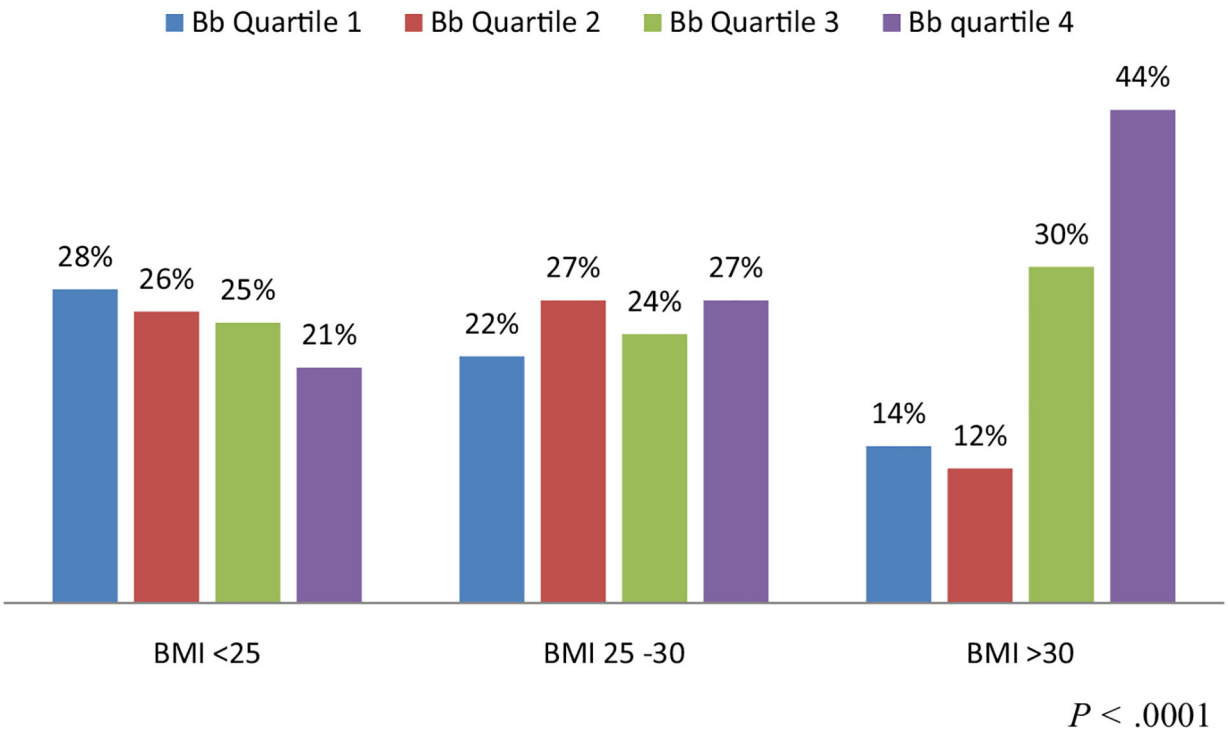

FIGURE 2.

Distribution of measures of quartiles of Bb by category of BMI (n = 1013)

Within and across the 3 categories of BMI there are differences in the levels of Bb. Among women who were obese, 14% had levels of Bb in the lower quartile and 44% had levels in the upper quartile.

BMI, body mass index.

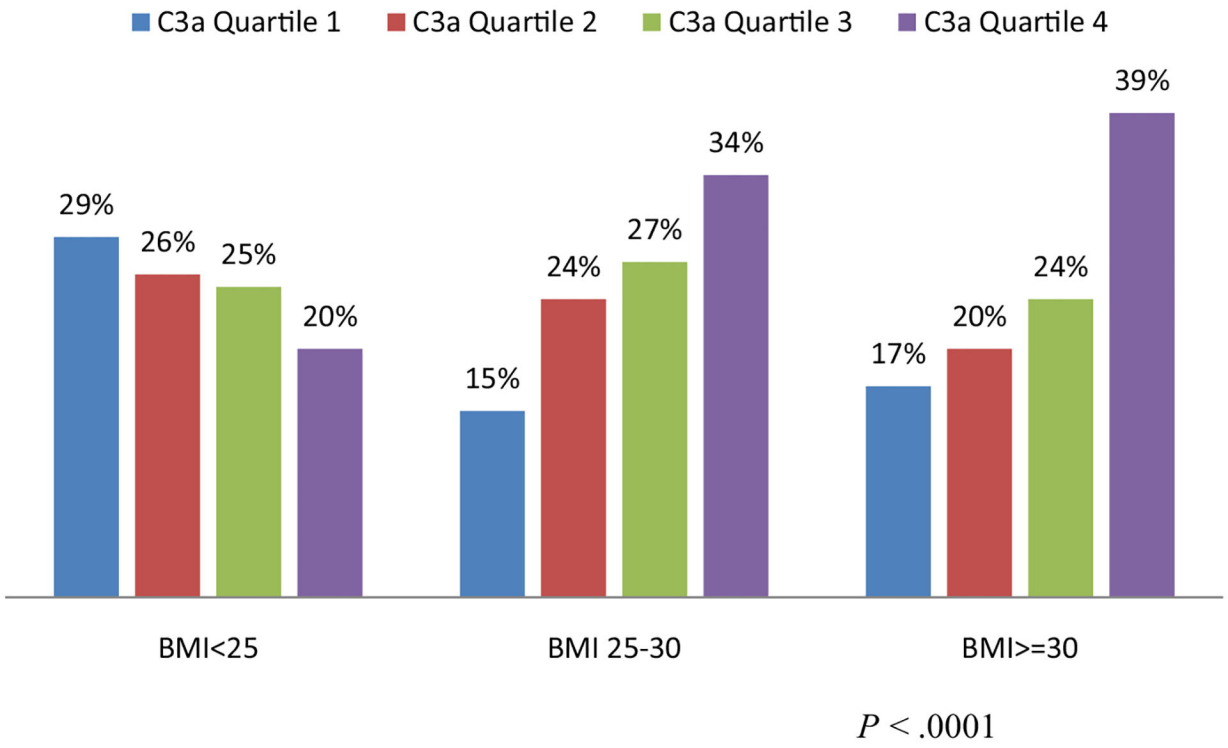

FIGURE 3.

Distribution of measures of quartiles of C3a by category of BMI (n = 1013)

Within and across the 3 categories of BMI there are differences in the levels of C3a. Among women who were obese, 17% had levels of C3a in the lower quartile and 39% had levels in the upper quartile.

BMI, body mass index.

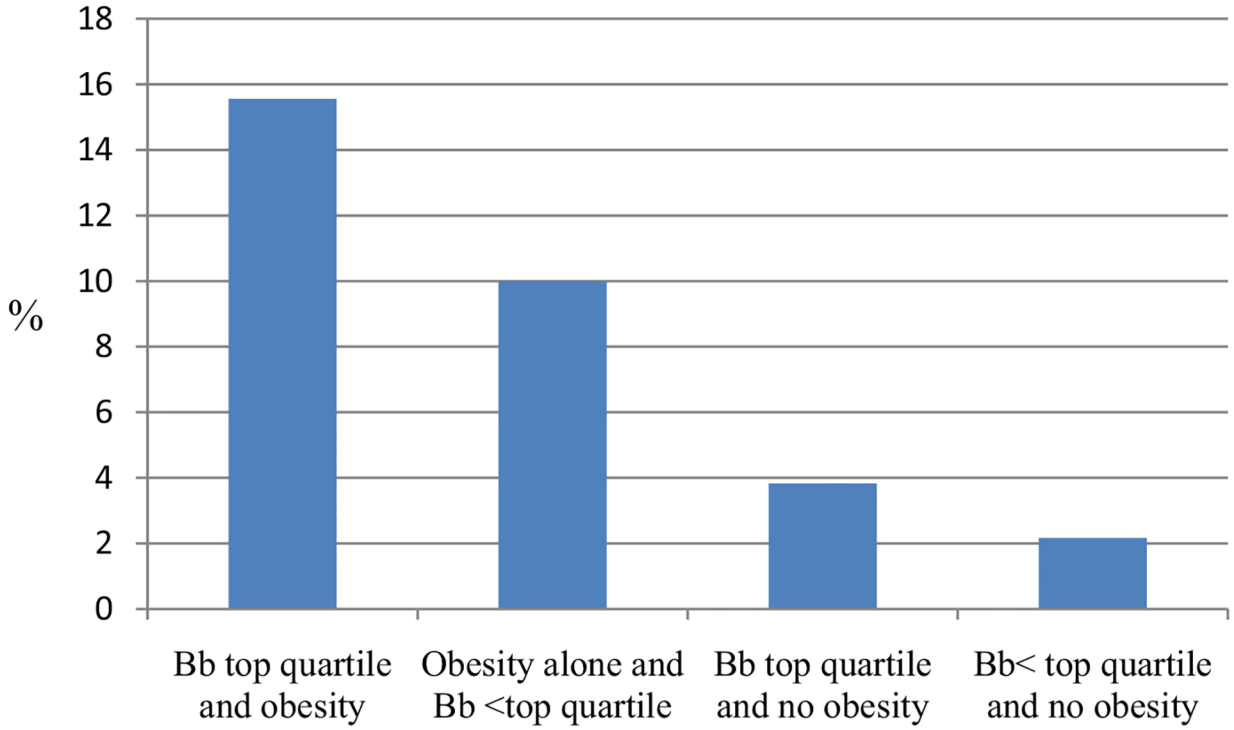

FIGURE 4.

Incidence of preeclampsia across categories of complement Bb

The incidence of preeclampsia across categories of complement Bb inflammatory metabolic risk categories.

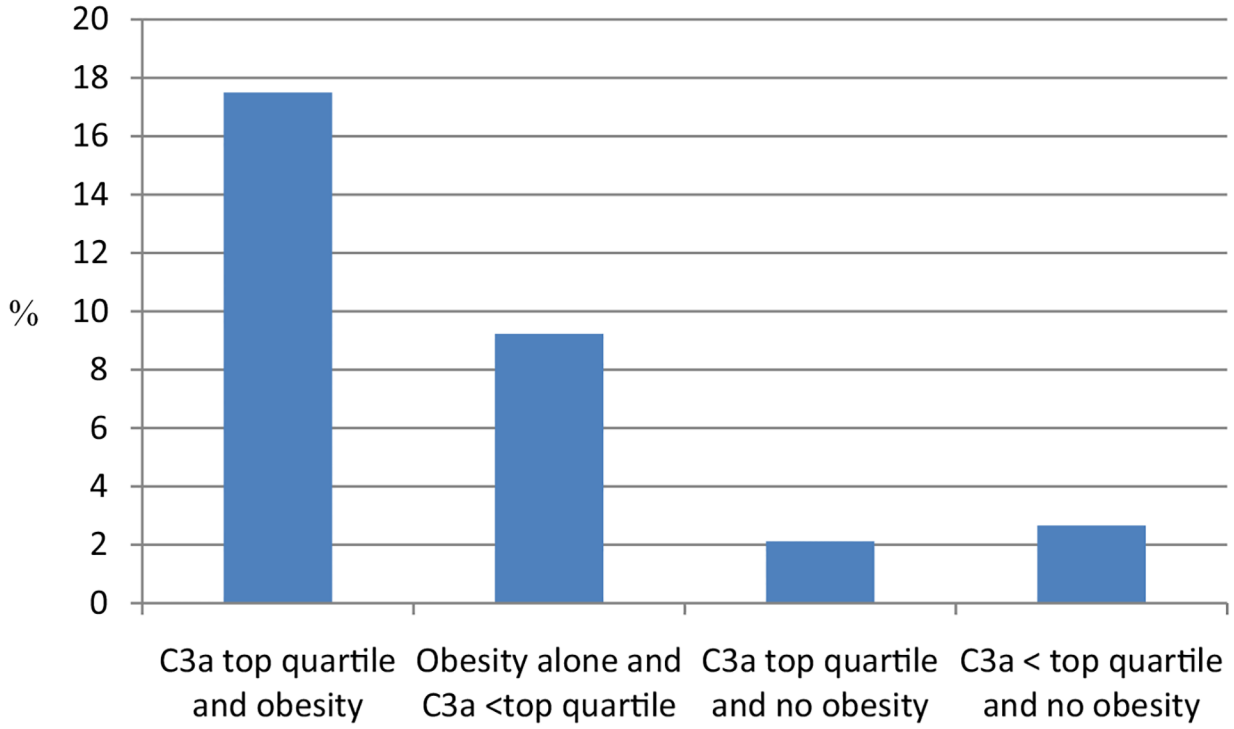

FIGURE 5.

Incidence of preeclampsia across categories of complement C3a

The incidence of preeclampsia across categories of complement C3a inflammatory metabolic risk categories.

TABLE

Relationship of complement metabolic/inflammatory categories with preeclampsia[a]

Category, entire cohort (n = 932)	Unadjusted, OR	Adjusted[b]		
		OR	95% CI	*P* value
Complement metabolic/inflammatory categories[c]				
Bb top quartile and obesity	8.3	10	3.3–30	< .0001
Obesity alone and Bb less than top quartile	5.0	5.3	1.9–15	.002
Bb top quartile and no obesity	1.8	1.8	0.7–4.6	.200
Bb less than top quartile and no obesity	1.0	1.0		
C3a top quartile and obesity	7.7	8.8	3–24	< .0001
Obesity alone and C3a less than top quartile	3.7	3.7	1.3–10	.01
C3a top quartile and no obesity	0.8	0.8	0.3–2.5	.80
C3a less than top quartile and no obesity	1.0	1.0	—	—
Nulliparous women (n = 399)				
Bb top quartile and obesity	8.3	8.3	1.4–49	.02
Obesity alone and Bb less than top quartile	6.8	5.2	1.4–19	.01
Bb top quartile and no obesity	1.8	1.3	0.4–4.6	.70
Bb less than top quartile and no obesity	1.0	1.0		
C3a top quartile and obesity	9.7	8.3	1.9–36	.005
Obesity alone and C3a less than top quartile	4.8	4.1	0.99–17	.051
C3a top quartile and no obesity	1.1	0.9	0.2–3.4	.90
C3a less than top quartile and no obesity	1.0	1.0	—	—
Multiparous women (n = 533)[d]				
Bb top quartile and obesity	13.8	7.7	1.7–36	.009
Obesity alone and Bb less than top quartile	4.6	3.3	0.5–20	.2
Bb top quartile and no obesity	2.3	2.2	0.5–10	.3
Bb less than top quartile and no obesity	1.0	1.0		
C3a top quartile and obesity	9.0	6.8	1.6–29	.0097
Obesity alone and C3a less than top quartile	3.9	1.7	0.3–8.8	.5
C3a top quartile and no obesity	0.5	0.4	0.05–3.6	.4
C3a less than top quartile and no obesity	1.0	1.0	—	—

CI, confidence interval; *OR*, odds ratio.

[a] Deliveries less than 20 weeks' gestation and cases of gestational hypertension were removed from the analysis;

[b] Adjusted for maternal race, parity, age, and cigarette smoking at conception;

[c] The categories are mutually exclusive;

[d] The multivariable logistic regression model also included adjustment for a history of preeclampsia in a previous pregnancy (n = 41; 7%).