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Is Mid-trimester Insulin Resistance Predictive of Subsequent Puerperal Infection? A Secondary Analysis of Randomized Trial Data

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Authors' Contribution

Dr. Hughes participated in conception of the secondary analysis study design and contributed to critical aspects of the conduct of this research, including monitoring study implementation, progress, data quality, and data analysis. Dr. Hughes provided significant intellectual contribution to the drafting and revision of this article with regard to scientific content and form, and approved the final article as submitted.

Drs. Hauth, Leveno, Myatt, Varner, Wapner, Mercer, Peaceman, Ramin, Tolosa, Saade, and Sorokin participated in study design and protocol development and contributed to critical aspects of the conduct of this research including assessment of patient recruitment; monitoring center performance; oversight of data quality; and evaluation and analysis of data. They provided significant intellectual contribution to the drafting and revision of this article with regard to scientific content and form, and approved the final article as submitted.

Dr. Clifton participated in conception of the study design and protocol development, and contributed to critical aspects of the conduct of this research including monitoring of recruitment and study progress; data quality evaluation and interpretation; provision of administrative support; and statistical analysis. Dr. Clifton provided significant intellectual contribution to the drafting and revision of this article with regard to scientific content and form, and approved the final article as submitted.

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Disclosure

There are no financial interests, commercial affiliations, or other possible conflicts of interest.

Ethics Approval

IRB approval for secondary analysis of the original trial was from the Women & Infant's Hospital Institutional Review Board, Project number 03–0041.

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Abstract

Objective—The objective of this study was to examine whether there is an association between insulin resistance and subsequent development of puerperal infection by measuring insulin resistance in the mid-trimester using the homeostasis model assessment (HOMA:IR).

Methods—Secondary analysis of low-risk nulliparas enrolled in a multicenter pre-eclampsia prevention trial. HOMA:IR was measured on fasting plasma glucose and insulin concentrations among low-risk nulliparas between 22 and 26 weeks' gestation. Median HOMA:IR was compared between women who did and did not develop puerperal infection using Wilcoxon rank sum test. Logistic regression was used to control for potential confounders.

Results—Of 1,180 women with fasting glucose and insulin available, 121 (10.3%) had a puerperal infection. Median HOMA:IR was higher among those with subsequent puerperal infection (4.3 [interquartile, IQR: 2.2–20.5] vs. 2.6 [IQR: 1.5–6.7], $p < 0.0001$). After controlling for potentially confounding variables HOMA:IR was only marginally associated with an increased risk of development of puerperal infection, adjusted odds ratio: 1.01 (95% confidence interval: 1.00–1.02; $p = 0.04$) per unit increase. Elevated HOMA:IR performed poorly as a predictor of puerperal infection, with a positive predictive value of 15% and a negative predictive value of 92%.

Conclusion—Though associated with an increased risk of puerperal infection, insulin resistance, measured by HOMA:IR, is not a clinically useful predictor of puerperal infection.

Keywords

insulin resistance; puerperal infection; pregnancy; predictor

Puerperal infections are associated with and likely lie in the causative pathway for several adverse perinatal events. Chorioamnionitis is an independent risk factor for both short-term (e.g., sepsis and death) and long-term adverse neonatal outcomes (e.g., cerebral palsy).^{1–3} Postpartum endometritis is associated with maternal sepsis, increased hospital costs, and need for surgical intervention.⁴ As the rate of cesarean delivery continues to rise, the rate of puerperal infection can be expected to increase accordingly.

Diabetes is a well-established risk factor for infectious complications. A large body of literature in nonpregnant populations shows that not only diabetes but also insulin resistance results in a chronic inflammatory state with increased concentrations of proinflammatory cytokines and altered macrophage function.^{5–7} Most of this literature supports the critical role of obesity as the key driving force of insulin resistance. However, some studies have

suggested that markers of insulin resistance are associated with increased infectious complications such as postoperative infections.⁸ In pregnancy, insulin resistance may exist in the absence of obesity or preexisting diabetes due to the presence of placental hormones such as human placental lactogen.⁹ Thus, pregnancy is a unique state in which the independent impact of insulin resistance may be examined as it relates to prediction of potentially devastating infections.

The homeostasis model assessment (HOMA:IR) is a mathematical calculation of insulin resistance that has been shown to correlate highly with the gold standard euglycemic clamp method of assessing insulin resistance ($r = 0.88$).¹⁰ It is used in randomized trials to determine response to therapy for insulin resistance. Hauth et al examined the risk of pregnancy complication association with insulin resistance and found an independent association of elevated HOMA:IR with pre-eclampsia.¹¹ However, to our knowledge, the relationship between insulin resistance and puerperal infection has not been previously examined.

The objective of this study was to use the HOMA:IR to determine whether insulin resistance is independently associated with development of puerperal infection among pregnant women.

Methods

We performed a secondary analysis of a large, multicenter randomized clinical trial of antioxidants (vitamins C and E) for preeclampsia prevention.¹² The trial included more than 10,000 healthy nulliparous women enrolled between 9 and 16 weeks' gestation. As part of this trial, a subset of women provided fasting blood samples between 22 and 26 weeks' gestation, which we used to calculate the HOMA:IR for women with and without puerperal infection at delivery.

The study population included women from 16 clinical centers across the United States as part of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Pregnant women with a singleton gestation were included if they had not had a prior pregnancy lasting beyond 19 weeks 6 days of gestation. They were excluded if they had underlying hypertension, proteinuria, preexisting diabetes, serious medical conditions, or fetal complications. Gestational age was determined with the use of a previously described algorithm that takes into account the date of the last menstrual period and the earliest ultrasound examination.¹³

Women with fasting (12 hours) blood samples as well as complete data available were included in this analysis. Study groups were those with and without puerperal infection. Puerperal infection was defined as either a clinical diagnosis of maternal chorioamnionitis before delivery or postpartum endometritis. Chorioamnionitis was coded if a patient had a clinical diagnosis of chorioamnionitis noted in the chart or if antibiotics were administered during labor due to an elevated body temperature or uterine tenderness with no other defined infection. Postpartum endometritis was coded if there was a clinical diagnosis of postpartum endometritis in the chart or if a patient received intravenous antibiotics initiated during the

postpartum period for fever elevation in the absence of another specified infection such as pyelonephritis or pneumonia. The HOMA:IR was calculated as follows: fasting insulin multiplied by fasting glucose divided by 22.¹⁰

Categorical variables were compared using the chi-square test and continuous variables using the Wilcoxon rank sum test. Median HOMA:IR values were compared between women with and without infection. We also examined the HOMA:IR as a dichotomous variable such that values at or above the 75th percentile (defined using women without puerperal infection) were considered elevated. We examined positive and negative predictive values of elevated HOMA:IR in the mid-trimester for infection at the time of delivery. Multivariable logistic regression analysis was used to calculate odds ratios (ORs) and included gestational age at collection, study treatment group (vitamins, placebo), race or ethnic group, obesity defined as a body mass index (BMI) ≥ 30 , tobacco use, antenatal infections such as sexually transmitted infections or urinary infections, prolonged rupture of membranes > 18 hours, and cesarean delivery. Analyses were performed using SAS software (Cary, NC).

Results

A total of 10,154 women were randomized within the parent trial. Of these, 1,180 women had fasting glucose and insulin values available for inclusion in this analysis of whom 121 (10.3%) had puerperal infection: 96 (8.1%) had chorioamnionitis, 21 (1.8%) had endometritis, and 4 (0.3%) had both. Demographic characteristics of women in the infected and uninfected groups are shown in ►Table 1. BMI was measured for enrolled women at the time of study entry (9–16 weeks' gestation) and was similar between groups. Women experiencing puerperal infections were more likely to be of younger age, Hispanic have lower education level, have had a prior pregnancy < 20 weeks, and have experienced an infection earlier in the index pregnancy. There was no difference in the frequency of receipt of vitamins versus placebo between the groups. Gestational diabetes was not significantly more common among the women in the infection group, 8 (6.6%) versus 36 (3.4%), $p = 0.12$.

As was demonstrated in a prior publication from this cohort, the median HOMA:IR increased with increasing gestational age and increasing BMI, $p < 0.0001$ (►Tables 2 and 3, respectively).¹¹ The sharpest rise appeared to occur between gestational weeks' 24 and 25. Although HOMA:IR was relatively similar between underweight and normal weight women, there was a clear increase in the values among overweight and obese women. HOMA:IR varied by race, with Hispanic women having the highest values, median 6.80 (interquartile [IQR]: 2.6–20.2), then African American women, median 3.12 (IQR: 1.6–7.8), followed by Caucasians, median 2.04 (IQR: 1.3–4.0), $p < 0.001$.¹¹ HOMA:IR did not vary by receipt of therapy compared with placebo, $p = 0.5$.¹¹

The median HOMA:IR was higher among women with puerperal infection, 4.3 (IQR: 2.2–20.5) versus 2.6 (IQR: 1.5–6.7) ($p < 0.0001$). After adjustment for the numerous potential confounders in the logistic regression model, this association remained only marginally statistically significant (►Table 4). We chose the 75th percentile (6.71) to examine

HOMA:IR as a dichotomous variable with regard to association with puerperal infection based on the prior association with preeclampsia above this level.¹¹ Elevated HOMA:IR was associated with puerperal infection, 40 versus 25%, $p < 0.001$. This association did not persist after controlling for potentially confounding variables in a logistic regression model, adjusted OR: 1.34, (95% confidence interval [CI]: 0.85–2.14). To investigate the clinical utility of using elevated HOMA:IR as a predictor of puerperal infection, we created a receiver operating characteristic curve (►Fig. 1), which demonstrated weak predictive capability with an area under the curve of 0.63 (95% CI: 0.57–0.68). The test characteristics of HOMA:IR above the 75th percentile in predicting infectious complications were notable for a sensitivity of only 40% (►Table 5).

Discussion

Main Findings

Insulin resistance as measured by the HOMA:IR at mid-pregnancy, while weakly associated with the subsequent development of puerperal infection after adjustment for other risk factors, is not a clinically useful predictor. In this study of nulliparas, those intrapartum risk factors previously shown to be associated with puerperal infection, such as prolonged rupture of membranes and cesarean delivery, were more strongly associated with infection than was insulin resistance. Hispanic and African American ethnic backgrounds were both also significantly associated with development of puerperal infection. The mechanism for these associations is unclear, but the differences in HOMA:IR values by ethnicity have been previously reported.¹¹

Outside of pregnancy, HOMA:IR is used to diagnose insulin resistance with much lower cutoff values than those seen in our pregnant subjects. Among nonpregnant individuals, normal values appear to vary by ethnicity, consistent with our observations,¹⁴ but a commonly quoted cutoff is 2.8. By 25 weeks' gestation, the median values in this study exceeded 2.8, supporting the notion that pregnancy is a state of relative insulin resistance. Similar to Qu et al and as reported by Hauth et al in a prior analysis of this cohort,¹¹ we found that the values varied by ethnicity, with values being highest among women reporting Hispanic ethnicity.

Hauth et al also found that in this cohort, HOMA:IR was positively correlated with BMI.¹¹ Other investigators have similarly reported positive correlation between BMI and HOMA:IR^{15,16} outside of pregnancy. Ferraro et al recently reported a small study investigating this correlation in pregnancy. They studied 12 obese pregnant women at full-term gestation and found a positive linear correlation between log-transformed HOMA:IR and maternal BMI.¹⁷

Interpretation

Prediction of puerperal infection is an important goal for obstetric research to develop preventive strategies in the future. Chorioamnionitis at term and near term is associated with increased odds of developing cerebral palsy after controlling for other risk factors.^{1,2,18} Despite a vast body of research aimed at prevention of cerebral palsy, there has been very

little progress in decreasing the rate of its occurrence over time. It is vitally important to develop measures to predict and subsequently to prevent puerperal infections in an effort to decrease this risk. Prevention of maternal risk of infections in the peripartum period including sepsis, prolonged hospitalization, and decreased bonding with the new infant is also important. Moreover, prevention of puerperal infection is desirable from a cost perspective given the changes in reimbursement related to hospital-associated infections. Some health care payers are beginning to withhold reimbursement for treatment of infections deemed to be preventable. Despite the importance of peripartum clinical infection, little work has been done to identify a predictive model to develop prevention strategies.

New research must be directed toward developing an accurate predictor of puerperal infection. HOMA:IR is promising because it can be measured before the occurrence of infection. To date, most of the research aimed at early diagnosis focuses on predicting infection in the setting of preterm premature rupture of the membranes. The serum marker of systemic inflammation, C-reactive protein (CRP) has been most extensively studied,^{19,20} although several cytokines and chemokines have been candidate predictors as well.^{21–25} These have focused on prediction of either chorioamnionitis or neonatal sepsis. The meta-analyses that have been published on the topic suggest that the data are not supportive of the use of CRP as a clinically useful predictor, leaving the field devoid of useful markers.^{19,20}

Insulin resistance, as measured by HOMA:IR, has been associated with infectious risk in several clinical settings. Demmer et al showed that elevated HOMA:IR in nondiabetic people was associated with severe periodontal infection using National Health and Nutrition Examination Survey (NHANES) data.²⁶ Increased insulin resistance has been found in other clinical settings as well, including sepsis and *Helicobacter pylori* infection.^{27,28} The existing literature on the topic fails to establish whether insulin resistance is causal or an effect of the infection. This analysis was designed to evaluate whether insulin resistance, present many weeks before the development of infection, was associated with the subsequent development of infection. Although it appears that such an association does exist, causality cannot be determined, nor does it appear to be clinically useful to measure as a predictor given the poor positive predictive value of 15%. Recently, a study examining the risk of postoperative infections following colorectal surgery suggested that increased markers of insulin resistance were associated with a risk of surgical site infections.⁸

Strengths and Limitations

HOMA:IR has particular appeal as a potential predictive test because it can be improved with the use of insulin-sensitizing agents. In theory, one could identify patients at risk and research could focus on whether treatment improves outcomes. For example, metformin use has been studied in women with polycystic ovary syndrome and shown to decrease HOMA:IR values significantly.²⁹ Unfortunately, while HOMA:IR is frequently used as an outcome in trials of antidiabetic agents, it has not reliably been shown to predict adverse outcome. A recent study examining its association with development of venous thromboembolism did not find it clinically useful.³⁰ A strength of our study is the prospective nature of the collection of the cohort and the laboratory testing. The standardized timing of blood collection avoids any biases in the decision of timing of

obtaining insulin and glucose measurements. In addition, the results of the laboratory tests were not available to the study personnel abstracting the outcome data, so any biases regarding the outcome assignment were eliminated by our study design.

In the current study, HOMA:IR did not accurately predict puerperal infection after controlling for confounding variables. A study by Hauth et al examined data from this same cohort of women and found that HOMA:IR remained significantly associated with subsequent development of pre-eclampsia after controlling for potential confounding variables (adjusted OR: 1.9; 95% CI: 1.1–3.2).¹¹ However, they demonstrated similar test characteristics to the current study. The positive predictive value of HOMA:IR in predicting preeclampsia was only 19%, with a negative predictive value of 90%. In the setting of preeclampsia, this association is likely to become manifest only after the altered vascular reactivity of preeclampsia has already begun. In the setting of puerperal infection, it may be that insulin resistance is actually a contributor to the development of puerperal infection by altering appropriate maternal immune response to events of labor and delivery.

A limitation of our study was that the definition of puerperal infection was obtained by chart review diagnosis of clinical chorioamnionitis or postpartum endometritis. Because infection was not a primary outcome of the parent trial, rigorous confirmation of these diagnoses was not prospectively conducted. This may have underestimated the outcome and thus the power of HOMA:IR at prediction. Although this study was a secondary analysis of an interventional trial using multivitamins, there is no reason to believe that the receipt of study drug would necessarily alter either the exposure of HOMA:IR value or the outcome of puerperal infection. To confirm this, we included treatment group in our regression model and did not find any association with infection.

Conclusion

In summary, although insulin resistance, as measured by the HOMA:IR, is weakly associated with the development of puerperal infection, it is not useful as a clinical predictor. Further investigations should focus on pathogenesis to identify a useful marker and develop interventions to prevent puerperal infection.

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References

1. Wu YW, Escobar GJ, Grether JK, Croen LA, Greene JD, Newman TB. Chorioamnionitis and cerebral palsy in term and near-term infants. *JAMA*. 2003; 290(20):2677–2684. [PubMed: 14645309]
2. Neufeld MD, Frigon C, Graham AS, Mueller BA. Maternal infection and risk of cerebral palsy in term and preterm infants. *J Perinatol*. 2005; 25(2):108–113. [PubMed: 15538398]
3. Winter S, Autry A, Boyle C, Yeargin-Allsopp M. Trends in the prevalence of cerebral palsy in a population-based study. *Pediatrics*. 2002; 110(6):1220–1225. [PubMed: 12456922]

4. Maharaj D. Puerperal pyrexia: a review. Part I. *Obstet Gynecol Surv.* 2007; 62(6):393–399. [PubMed: 17511893]
5. Harford KA, Reynolds CM, McGillicuddy FC, Roche HM. Fats, inflammation and insulin resistance: insights to the role of macrophage and T-cell accumulation in adipose tissue. *Proc Nutr Soc.* 2011; 70(4):408–417. [PubMed: 21835098]
6. Hardy OT, Czech MP, Corvera S. What causes the insulin resistance underlying obesity? *Curr Opin Endocrinol Diabetes Obes.* 2012; 19(2):81–87. [PubMed: 22327367]
7. Stienstra R, Tack CJ, Kanneganti TD, Joosten LA, Netea MG. The inflammasome puts obesity in the danger zone. *Cell Metab.* 2012; 15(1):10–18. [PubMed: 22225872]
8. Ortega-Deballon P, Duvillard L, Scherrer ML, et al. AGARIC Study group. Preoperative adipocytokines as a predictor of surgical infection after colorectal surgery: a prospective survey. *Int J Colorectal Dis.* 2014; 29(1):23–29. [PubMed: 24132530]
9. Newbern D, Freemark M. Placental hormones and the control of maternal metabolism and fetal growth. *Curr Opin Endocrinol Diabetes Obes.* 2011; 18(6):409–416. [PubMed: 21986512]
10. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985; 28(7):412–419. [PubMed: 3899825]
11. Hauth JC, Clifton RG, Roberts JM, et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Maternal insulin resistance and preeclampsia. *Am J Obstet Gynecol.* 2011; 204(4):327.e1–327.e6. [PubMed: 21458622]
12. Roberts JM, Myatt L, Spong CY, et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Vitamins C and E to prevent complications of pregnancy-associated hypertension. *N Engl J Med.* 2010; 362(14):1282–1291. [PubMed: 20375405]
13. Carey JC, Klebanoff MA, Hauth JC, et al. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. *N Engl J Med.* 2000; 342(8):534–540. [PubMed: 10684911]
14. Qu HQ, Li Q, Rentfro AR, Fisher-Hoch SP, McCormick JB. The definition of insulin resistance using HOMA-IR for Americans of Mexican descent using machine learning. *PLoS ONE.* 2011; 6(6):e21041. [PubMed: 21695082]
15. Xia C, Li R, Zhang S, et al. Lipid accumulation product is a powerful index for recognizing insulin resistance in non-diabetic individuals. *Eur J Clin Nutr.* 2012; 66(9):1035–1038. [PubMed: 22781025]
16. Sayin NC, Gücer F, Balkanli-Kaplan P, et al. Elevated serum TNF-alpha levels in normal-weight women with polycystic ovaries or the polycystic ovary syndrome. *J Reprod Med.* 2003; 48(3):165–170. [PubMed: 12698773]
17. Ferraro ZM, Qiu Q, Gruslin A, Adamo KB. Characterization of the insulin-like growth factor axis in term pregnancies complicated by maternal obesity. *Hum Reprod.* 2012; 27(8):2467–2475. [PubMed: 22674202]
18. Redline RW. Severe fetal placental vascular lesions in term infants with neurologic impairment. *Am J Obstet Gynecol.* 2005; 192(2):452–457. [PubMed: 15695986]
19. van de Laar R, van der Ham DP, Oei SG, Willekes C, Weiner CP, Mol BW. Accuracy of C-reactive protein determination in predicting chorioamnionitis and neonatal infection in pregnant women with premature rupture of membranes: a systematic review. *Eur J Obstet Gynecol Reprod Biol.* 2009; 147(2):124–129. [PubMed: 19819609]
20. Trochez-Martinez RD, Smith P, Lamont RF. Use of C-reactive protein as a predictor of chorioamnionitis in preterm prelabour rupture of membranes: a systematic review. *BJOG.* 2007; 114(7):796–801. [PubMed: 17567416]
21. Cobo T, Kacerovsky M, Palacio M, et al. A prediction model of histological chorioamnionitis and funisitis in preterm prelabor rupture of membranes: analyses of multiple proteins in the amniotic fluid. *J Matern Fetal Neonatal Med.* 2012; 25(10):1995–2001. [PubMed: 22372866]

22. Gulati S, Bhatnagar S, Raghunandan C, Bhattacharjee J. Interleukin-6 as a predictor of subclinical chorioamnionitis in preterm premature rupture of membranes. *Am J Reprod Immunol.* 2012; 67(3):235–240. [PubMed: 22023383]
23. Miura H, Ogawa M, Hirano H, et al. Neutrophil elastase and interleukin-6 in amniotic fluid as indicators of chorioamnionitis and funisitis. *Eur J Obstet Gynecol Reprod Biol.* 2011; 158(2):209–213. [PubMed: 21645958]
24. Holst RM, Laurini R, Jacobsson B, et al. Expression of cytokines and chemokines in cervical and amniotic fluid: relationship to histological chorioamnionitis. *J Matern Fetal Neonatal Med.* 2007; 20(12):885–893. [PubMed: 18050018]
25. Kim KW, Romero R, Park HS, et al. A rapid matrix metalloproteinase-8 bedside test for the detection of intraamniotic inflammation in women with preterm premature rupture of membranes. *Am J Obstet Gynecol.* 2007; 197(3):292.e1–292.e5. [PubMed: 17826425]
26. Demmer RT, Squillaro A, Papapanou PN, et al. Periodontal infection, systemic inflammation, and insulin resistance: results from the continuous National Health and Nutrition Examination Survey (NHANES) 1999-2004. *Diabetes Care.* 2012; 35(11):2235–2242. [PubMed: 22837370]
27. Polyzos SA, Kountouras J, Zavos C, Deretzi G. The association between *Helicobacter pylori* infection and insulin resistance: a systematic review. *Helicobacter.* 2011; 16(2):79–88. [PubMed: 21435084]
28. Hogan BK, Wolf SE, Hospenthal DR, et al. Correlation of American Burn Association sepsis criteria with the presence of bacteremia in burned patients admitted to the intensive care unit. *J Burn Care Res.* 2012; 33(3):371–378. [PubMed: 22210056]
29. Jensterle M, Sebestjen M, Janez A, et al. Improvement of endothelial function with metformin and rosiglitazone treatment in women with polycystic ovary syndrome. *Eur J Endocrinol.* 2008; 159(4):399–406. [PubMed: 18653546]
30. Van Schouwenburg IM, Mahmoodi BK, Veeger NJ, et al. Insulin resistance and risk of venous thromboembolism: results of a population-based cohort study. *J Thromb Haemost.* 2012; 10(6):1012–1018. [PubMed: 22443091]

Fig. 1.

A receiver operating characteristic curve of HOMA:IR as a predictor of puerperal infection, which demonstrated weak predictive capability. AUC, area under the curve; CI, confidence interval; HOMA:IR, homeostasis model assessment measuring insulin resistance.

Table 1

Demographic characteristics of women with and without puerperal infection

Characteristic	Puerperal infection (<i>N</i> = 121)	No infection (<i>N</i> = 1,059)	<i>p</i> -Value
Maternal age	22.1 ± 4.7	23.8 ± 4.8	< 0.001
Race/ethnicity			
Hispanic	60 (49.6)	246 (23.2)	< 0.001
Caucasian/other	28 (23.1)	589 (55.6)	
African American	33 (27.3)	224 (21.2)	
BMI at enrollment (9–16 wk)			
< 18.5 (underweight)	3 (2.5)	36 (3.4)	0.53
18.5–24.9 (normal)	54 (44.6)	523 (49.4)	
25.0–29.9 (overweight)	35 (28.9)	247 (23.3)	
30.0 (obese)	29 (24.0)	253 (23.9)	
Education (total y)	12.0 ± 3.0	13.2 ± 2.5	< 0.001
Previous pregnancy < 20 wk	40 (33.1)	253 (23.9)	0.027
Smoked during pregnancy	20 (16.5)	181 (17.1)	0.88
Infections during pregnancy	64 (52.9)	420 (39.7)	0.005
Treatment group			
Vitamins	61 (50.4)	517 (48.8)	0.74
Placebo	60 (49.6)	542 (51.2)	

Abbreviation: BMI, body mass index.

Note: Data presented as *N*(%) or mean ± standard deviation.

Table 2

Median HOMA:IR values across weeks of gestation at fasting blood draw

GA	N	Median	Interquartile range
22	97	2.02	1.42–3.92
23	242	2.20	1.30–4.45
24	424	2.59	1.54–5.80
25	249	4.02	1.73–12.67
26	168	4.49	1.83–20.40

Abbreviations: GA, gestational age; HOMA:IR, homeostasis model assessment measuring insulin resistance.

Table 3

Median HOMA:IR values across categories of BMI

BMI	N	Median	Interquartile range
< 18.5 (underweight)	39	1.72	0.84–3.43
18.5–24.9 (normal)	577	1.88	1.26–4.88
25.0–29.9 (overweight)	282	3.39	1.79–7.45
≥ 30 (obese)	282	4.74	2.98–11.15

Abbreviations: BMI, body mass index; HOMA:IR, homeostasis model assessment measuring insulin resistance.

Table 4

Puerperal infection regression model

	Adjusted odds ratio	95% confidence Interval
HOMA:IR	1.01	1.00–1.02
Gestational age at sample collection	1.14	0.94–1.36
Treatment group	0.95	0.63–1.43
African American race	2.46	1.38–4.37
Hispanic ethnicity	4.34	2.56–7.33
Obesity	0.73	0.44–1.21
Smoking	1.43	0.81–2.51
Prior infection	1.58	1.03–2.42
Prolonged rupture > 18 h	4.49	2.69–7.50
Cesarean	2.14	1.40–3.28

Abbreviation: HOMA:IR, homeostasis model assessment measuring insulin resistance.

Table 5

Test characteristics of elevated HOMA:IR (above the 75th percentile) at predicting puerperal infection

Diagnostic performance	Rate (%)	95% confidence Interval
Sensitivity	40	31–49
Specificity	75	72–78
Positive predictive value	15	12–20
Negative predictive value	92	90–93

Abbreviation: HOMA:IR, homeostasis model assessment measuring insulin resistance.