Cytokine 70 (2014) 134–140

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

Longitudinal changes in serum proinflammatory markers across pregnancy and postpartum: Effects of maternal body mass index

Lisa M. Christian [a,b,c,d,*], Kyle Porter [e]

[a] Department of Psychiatry, The Ohio State University Wexner Medical Center, United States
[b] The Institute for Behavioral Medicine Research, The Ohio State University Wexner Medical Center, United States
[c] Department of Obstetrics and Gynecology, The Ohio State University Wexner Medical Center, United States
[d] Psychology, The Ohio State University Wexner Medical Center, United States
[e] Center for Biostatistics, The Ohio State University Wexner Medical Center, United States

ARTICLE INFO

Article history:
Received 9 January 2014
Received in revised form 12 June 2014
Accepted 27 June 2014
Available online 28 July 2014

Keywords:
Inflammation
Pregnancy
Postpartum
Cytokines
Obesity

ABSTRACT

Background: The maternal immune system undergoes substantial changes to support healthy pregnancy. Although obesity is a primary driver of inflammation and predictive of perinatal complications, additive effects of pregnancy and obesity on changes in inflammatory processes are not well delineated.
Methods: This study examined serum proinflammatory markers interleukin(IL)-6, IL-8, tumor necrosis factor (TNF)-α, IL-1β, and C-reactive protein (CRP) during each trimester of pregnancy and 4–6 weeks postpartum among 57 women.
Results: Overall, IL-6 showed an increasing trend across pregnancy and significant increase at postpartum. Similarly, TNF-α increased significantly across gestation, with a further increase at postpartum. Both IL-8 and IL-1β showed a U-shaped curve, decreasing from early to later pregnancy, and increasing at postpartum. Finally, serum CRP decreased significantly across pregnancy, with further decreases at postpartum. Maternal obesity predicted higher IL-6 at each study visit. Obese women showed a trend toward elevated serum CRP during pregnancy, and significantly higher levels at postpartum.
Discussion: The course of pregnancy and postpartum is characterized by significant changes in serum proinflammatory mediators. Obese women show elevations in serum proinflammatory markers relative to normal weight women during pregnancy and postpartum. Further research is needed to determine the extent to which obesity-induced inflammation affects maternal and fetal health.

1. Introduction

The maternal immune system undergoes substantial changes to support healthy pregnancy. Compared to nonpregnancy, normal pregnancy is characterized by mild elevations in both serum pro- and antiinflammatory cytokine levels [1–8]. It has been proposed that at the local uterine/placental level, early pregnancy (i.e., implantation) and late pregnancy (i.e., approaching delivery) are inflammatory states while mid-pregnancy is an anti-inflammatory state [9]. However, few studies have examined longitudinal changes in circulating serum cytokines as pregnancy progresses or during the postpartum transition. Moreover, the majority of existing studies on this topic are small, cross-sectional in design, and/or do not include assessment at every trimester or at postpartum. Thus, the typical course of change in serum inflammatory markers in normal pregnancy and postpartum is not fully delineated.

While available evidence suggests that healthy pregnancy is typified by an enhanced inflammatory state, studies also show that *excessive* inflammation is incompatible with healthy pregnancy. Elevations in proinflammatory cytokines in maternal serum and amniotic fluid are causally implicated in risk of preterm delivery in the context of infection as well as idiopathic cases [10–14]. Proinflammatory cytokines can promote preterm labor by triggering preterm contractions, encouraging cervical ripening, and causing rupture of the membranes [15,16]. Inflammatory pathways are also implicated in the development of gestational hypertension [17–23] and gestational diabetes [24]. Moreover, maternal inflammation has been associated with effects on fetal development including risk for neurobehavioral disorders and adverse metabolic changes [25–27].

Because adipocytes secrete proinflammatory cytokines, obesity is a primary promoter of inflammation. Obesity in pregnancy is linked to risk of gestational hypertension and gestational diabetes with

* Corresponding author. Address: Institute for Behavioral Medicine Research Room 112, 460 Medical Center Drive, The Ohio State University Wexner Medical Center, Columbus, OH 43210, United States. Tel.: +1 614 293 0936; fax: +1 614 293 4200.
E-mail address: Lisa.Christian@osumc.edu (L.M. Christian).

http://dx.doi.org/10.1016/j.cyto.2014.06.018
1043-4666/

inflammatory mechanisms serving as clear drivers [24,28]. Moreover, maternal obesity has been linked to adverse perinatal outcomes including fetal death and premature birth as well as increased risk of metabolic syndrome, diabetes, obesity, and neurodevelopmental disorders in offspring [29,30]. Despite clear health relevance, limited data are available regarding the potential synergistic relationship between pregnancy and obesity in affecting inflammatory processes.

The current study examined longitudinal changes in the serum proinflammatory markers interleukin(IL)-6, IL-8, tumor necrosis factor (TNF)-α, IL-1β, and C-reactive protein (CRP) during each trimester of pregnancy and at 4–6 weeks postpartum in a racially diverse sample of predominately lower income women. These markers were selected based on their relevance to pregnancy-related health outcomes including preterm birth, gestational hypertension/preeclampsia, and fetal brain injury [31–34] as well as obesity [35–37]. It was hypothesized that, in the sample overall, there would be significant changes in inflammatory markers across the course of pregnancy and postpartum. It was also hypothesized that greater maternal body mass index (BMI) would be associated with elevated inflammatory markers across the study period.

2. Methods

2.1. Study design

Sixty pregnant women were recruited from the Ohio State University Medical Center (OSUMC) Prenatal Clinic. Study visits were conducted during the 1st trimester (Mean = 11.1 ± 2.3 weeks gestation), 2nd trimester (Mean = 22.9 ± 2.3 weeks gestation), 3rd trimester (Mean = 31.4 ± 1.8 weeks gestation) and at 4–6 weeks postpartum (Mean = 4.1 ± 2.1 weeks). At each visit, women provided a blood sample. Underweight women (BMI < 18.5) were excluded from the current analyses due to low representation ($n = 3$), resulting in a final sample of 57.

2.2. Participants

All women were born and raised in the United States. Women were not eligible if they had current hypertension, diabetes, chronic conditions with implications for immune function (e.g., rheumatoid arthritis, multiple sclerosis, or human immunodeficiency virus), fetal anomaly, illicit drug use or more than two alcoholic drinks per week during pregnancy (per self-report or medical record). Women reporting acute illness (e.g., cold or flu-like symptoms) or antibiotic use within 10 days of a study visit were rescheduled. Each completed informed consent and received modest compensation. The study was approved by the OSU Biomedical Institutional Review Board.

2.3. Demographics

Age, race/ethnicity, marital status, education, annual family income, and number of prior pregnancies (parity) were collected by self-report.

2.4. Body mass index

Pre-pregnancy body mass index (BMI; kg/m^2) was calculated using self-reported pre-pregnancy weight and height measured at the first visit.

2.5. Health behaviors

At the initial study visit, information on current and past smoking as well as frequency of participation in vigorous physical activity was collected.

2.6. Statistical analysis

Women were categorized based on BMI categories using the following standard ranges: 18.5–24.9 = normal weight, 25–29.9 = overweight, and ⩾30 = obese. To evaluate demographic similarity between groups, participant characteristics were compared between groups by ANOVA for continuous variables and chi-square tests for categorical variables. The primary endpoints were serum levels of IL-6, TNF-α, IL-1β, IL-8, and CRP at each trimester of pregnancy and postpartum. Each endpoint was log transformed for analysis to meet normality assumptions. For descriptive purposes, Pearson's correlations were conducted to determine associations between cytokines at each study visit. A linear mixed model was fit to each endpoint across the four visits. The model included main effects for BMI group and study visit, the interaction between BMI group and study visit, and a random effect for subject with a compound symmetry covariance structure to account for correlation among measures from the same subject. Parameter estimate contrasts were constructed to test for differences over pregnancy for all subjects (comparing each pair of visits) and differences between BMI groups at each study visit. Each comparison was performed at the $\alpha = 0.05$ significance level. With this testing approach, the expected number of false positives for each endpoint was 0.9. All analyses were performed using SAS® software, version 9.2.

3. Results

3.1. Demographics and health behaviors

Participant characteristics for each BMI group are reported in Table 1. As shown, the BMI groups did not differ significantly in age, race, parity, marital status, income, education, smoking history, or exercise ($ps \geqslant 0.07$).

3.2. Correlations between biomarkers

To determine associations between biomarkers at each study visit, Pearson's correlations were conducted. As shown in Table 2, inflammatory markers were highly correlated with each other at each study visit. These patterns of association were highly similar at each stage of assessment.

3.3. Longitudinal changes in biomarkers overall

Trajectories of change for each inflammatory marker are presented in Fig. 1. In the sample overall, a non-significant trend was observed for increases in IL-6 across pregnancy (1st versus 3rd trimester $p = 0.12$). In addition, IL-6 increased significantly from the 3rd trimester to postpartum ($p = 0.01$). Similarly, TNF-α increased significantly from early ($p = 0.001$) and middle to later pregnancy ($p = 0.01$), with a further increase at postpartum relative to the 3rd trimester ($p = 0.03$). In contrast, IL-8 showed a U-shaped curve, decreasing in the 2nd trimester relative to the 1st trimester ($p = 0.03$) and increasing significantly at postpartum follow-up ($p < 0.001$). Similarly, IL-1β showed a U-shaped curve, decreasing from early to late pregnancy and increasing significantly at postpartum ($p = 0.01$). CRP decreased from the 1st to 3rd trimester ($p = 0.02$), and decreased further at postpartum ($p = 0.01$).

3.4. Longitudinal Changes in Biomarkers by BMI

Next, analyses examined the moderating effect of BMI on changes in biomarkers across pregnancy and postpartum. Both obese and overweight women had significantly higher serum IL-6

Table 1
Subject characteristics by body mass index (BMI).

Characteristic	Normal Weight (n=17)	Overweight (n=16)	Obese (n=24)	p-value
Age				0.99
mean (SD)	24.3 (3.9)	24.1 (3.5)	24.3 (3.7)	
Race				0.16
African-American	11 (65%)	8 (50%)	19 (79%)	
White	6 (35%)	8 (50%)	5 (21%)	
Parity				0.72
0	1 (6%)	1 (6%)	3 (13%)	
1	9 (53%)	7 (44%)	8 (33%)	
≥ 2	7 (41%)	8 (50%)	13 (54%)	
Marital Status				0.47
Married	2 (12%)	3 (19%)	2 (8%)	
In a relationship (unmarried)	13 (76%)	10 (63%)	14 (58%)	
Single	2 (12%)	3 (19%)	8 (33%)	
Income				0.26
< $15,000	12 (71%)	8 (50%)	17 (81%)	
$15,000 - $30,000	4 (24%)	4 (25%)	6 (25%)	
≥ $30,000	1 (6%)	4 (25%)	1 (4%)	
Education				0.88
Some high school or less	5 (29%)	5 (31%)	7 (29%)	
High School Graduate	7 (41%)	4 (25%)	6 (25%)	
Some college or college degree	5 (29%)	7 (44%)	11 (46%)	
Smoking				0.07
Current	5 (29%)	4 (25%)	2 (8%)	
Past	6 (35%)	1 (6%)	10 (42%)	
Never	6 (35%)	11 (69%)	12 (50%)	
Vigorous activity				0.87
≥ 1 hour/ week	8 (47%)	8 (50%)	10 (42%)	

Table 2
Pearson's correlation coefficient for log-transformed cytokines at each study visit.

	IL-6	IL-8	TNF-α	IL-1β	CRP
1st Trimester					
IL-6	1	0.49***	0.59***	0.48***	0.46***
IL-8		1	0.52***	0.39**	0.25
TNF-α			1	0.49***	0.13
IL-1β				1	0.10
CRP					1
2nd Trimester					
IL-6	1	0.50***	0.62***	0.40**	0.46***
IL-8		1	0.39**	0.16	0.25
TNF-α			1	0.33*	0.15
IL-1β				1	0.21
CRP					1
3rd Trimester					
IL-6	1	0.45***	0.57***	0.34**	0.47***
IL-8		1	0.37**	0.13	0.13
TNF-α			1	0.40**	0.24
IL-1β				1	0.29*
CRP					1
Postpartum					
IL-6	1	0.30*	0.53***	0.25	0.36**
IL-8		1	0.49***	0.26*	−0.08
TNF-α			1	0.32*	0.20
IL-1β				1	0.15
CRP					1

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

than normal weight women at all three pregnancy study visits (*ps* < 0.04). At postpartum IL-6 was higher in obese women than in normal weight women ($p = 0.004$). For TNF-α, overweight women showed elevations at each pregnancy study visit relative to normal weight women (*ps* < 0.04).

During pregnancy, there was a trend toward higher CRP in obese women relative to normal weight women at each pregnancy study visit (*ps* ⩾ 0.052). Obese women had significantly elevated CRP at postpartum as compared to overweight ($p = 0.04$) or normal weight women ($p = 0.045$). No significant differences were observed in IL-1β or IL-8 based on BMI category.

4. Discussion

The role of inflammation in pregnancy has been a topic of debate; the allograft paradigm forwards that in order to prevent rejection of the fetus, the maternal immune system must acquire an anti-inflammatory state during pregnancy. More recently, it has been suggested that, at least at the local level, each stage of pregnancy is characterized by a unique inflammatory environment with the first and third trimesters typified by a proinflammatory state and the second trimester an antiinflammatory state [9]. However, the typical course of changes in inflammatory markers at the peripheral level has not been well-delineated. Moreover, the extent to which obesity, a known promoter of chronic low-grade inflammation, may alter such trajectories is not known. Thus, delineating the course of immune change across the perinatal period in relation to maternal weight is of clinical importance.

IL-6 is a key cytokine associated with adverse perinatal health outcomes [38–42]. Notably, IL-6 is secreted by adipose tissue [35]. In this study, IL-6 showed a non-significant trend toward increases across the course of pregnancy with significant increases at postpartum relative to the 3rd trimester. As hypothesized, both overweight and obese women showed elevated IL-6 relative to normal weight women at each pregnancy visit. A similar pattern at postpartum was statistically significant for obese women only. These findings are consistent with prior evidence that IL-6 is elevated during pregnancy as compared to non-pregnancy, with greater elevations in women with higher body mass [1,43]. The current data replicate and extend prior findings to the postpartum period.

TNF-α is also secreted by adipose tissue. In this study, serum TNF-α increased significantly from early to late pregnancy, with further increases at postpartum. This is consistent with prior studies

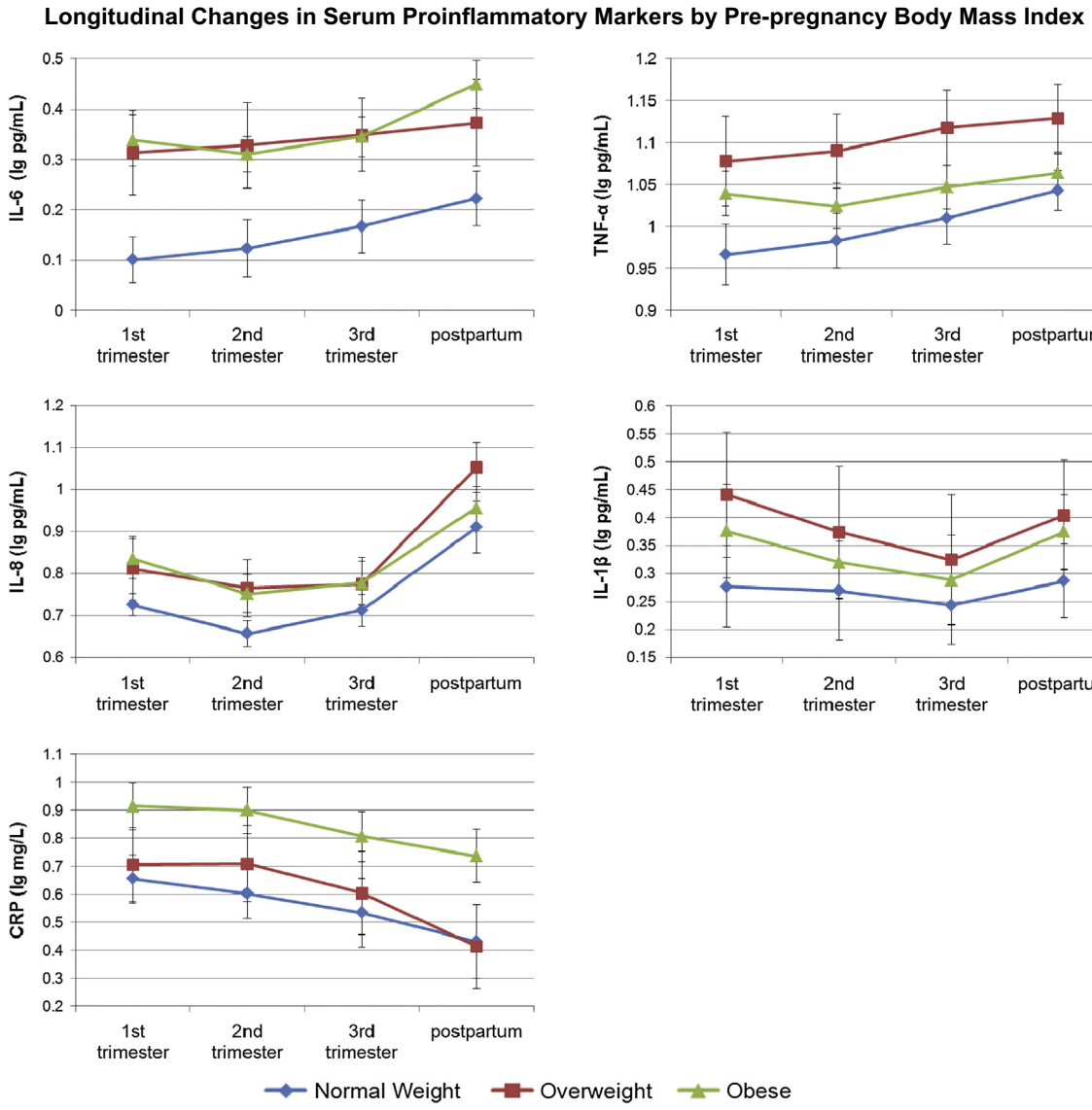

Fig. 1. Key findings in relation to obesity: Compared to normal weight women, obese women had significantly higher serum IL-6 at each assessment timepoint. There was a similar, non-significant trend for CRP during pregnancy. Obese women showed significantly higher CRP than normal weight women at postpartum. Error bars ±1 SE.

showing increasing TNF-α across gestation [44,45]. Overweight women showed elevations in TNF-α at each pregnancy visit. However, serum TNF-α values in obese women were between normal weight and overweight women; thus, an incremental increase in TNF-α based on BMI was not observed.

Both IL-8 and IL-1β showed a U-shaped curve, with decreases in mid or late pregnancy compared to early pregnancy, and subsequent increases at postpartum. This pattern of response could indicate an initial inflammatory response in early pregnancy that is down-regulated over time. Contrary to prediction, no differences in IL-1β or IL-8 were observed based on maternal body mass. As adipokines, both IL-1β and IL-8 tend to be increased in obesity [36,46,47], however central adiposity may be a more sensitive predictor of inflammatory status than BMI [48]. Thus, although difficult to accurately quantify in pregnant women, future studies should include other measures of adiposity in addition to BMI; in particular, waist-hip ratio measured in early pregnancy should be reasonably valid as limited weight gain occurs during the first trimester.

C-reactive protein (CRP) is an acute-phase protein synthesized by the liver in response to inflammatory mediators, particularly IL-6. In the current study, serum CRP decreased significantly from early to late pregnancy in the overall sample, with further decreases at postpartum. This is consistent with prior longitudinal studies showing decreases in CRP across gestation [49,50]. However, other studies have found increasing levels [51] or no significant changes in serum CRP across pregnancy [8]. Thus, findings in relation to CRP are inconsistent. In the hypothesized direction, obese women showed a trend toward higher CRP during pregnancy as well as significantly higher CRP at postpartum than normal weight women.

IL-6 is a potent inducer of the acute-phase response which is characterized by hepatic release of CRP [52]. Thus, as expected, IL-6 and CRP levels were highly correlated at each study visit. Despite these correlations, different patterns of change in IL-6 versus CRP across time were observed. IL-6 release does not result in concomitant CRP production in certain circumstances. For example, in response to acute exercise, substantial increases in serum IL-6 do not result in corresponding increases in CRP [53]. In addition to instigating the acute phase response, IL-6 serves multiple functions including effects on metabolism, regulation of bone homeostasis, and pain regulation [54]. The functional roles for

inflammatory markers and the relative importance of given roles at different stages of gestation remain to be fully explicated.

Notably, with the exception of CRP, all inflammatory mediators assessed (IL-6, TNF-α, IL-8, and IL-1β) increased at 4–6 weeks postpartum relative to the 3rd trimester. This may be related to the substantial neuroendocrine changes occurring at postpartum, particularly the considerable drop in cortisol. In addition, regardless of mode of delivery, healing processes occur following delivery which may instigate inflammatory responses [55]. In addition to affecting the healing process, functioning of the immune system following childbirth may have clinical implications for risk of postpartum mood disorders [56,57]. Moreover, certain autoimmune diseases including rheumatoid arthritis and multiple sclerosis tend to remit during pregnancy, but become exacerbated at postpartum [58,59]. Thus, propensity toward inflammatory responses following childbirth also has clinical relevance in this context.

A strength of this study is utilization of a longitudinal rather than cross-sectional design. In addition, inclusion of a postpartum timepoint extends prior findings. However, this study did not include a pre-pregnancy assessment or a non-pregnant comparison group. Thus, we were unable to determine the extent to which first trimester values may be altered relative to the non-pregnant state. Although we assessed women at postpartum, this does not represent a typical non-pregnant state since substantial neuroendocrine changes and healing processes occur following childbirth, as described. However, based on prior studies which have included a non-pregnant control group or women assessed several months postpartum [6–8], we expect that women in this study had elevations in inflammatory markers during each trimester as compared to a non-pregnant state, including markers such as IL-8 and CRP which showed a decreasing course from earlier to later pregnancy.

This study was observational and did not address possible mechanisms behind the observed changes. Changes in cytokine levels during pregnancy likely reflect a combination of (1) responses to the changing neuroendocrine environment, (2) functional changes to support pregnancy (which may be mechanistically supported by neuroendocrine changes) and (3) a reflection of the physiological stress of pregnancy. This study did not examine the extent to which concomitant changes in neuroendocrine function (e.g., cortisol, progesterone) correspond to the observed changes. However, even with such data, delineating causal relationships between neuroendocrine and immune parameters in human pregnancy within an observational design is not possible because numerous complex changes occur relatively simultaneously within short time periods. With regard to functional changes, many cytokines, including IL-6 as described above, are pleiotropic – having multiple effects [60]. Moreover, the ultimate effects of cytokines are affected by cytokine receptor function and related sensitivity of immune cells. Future studies should aim to identify the functional effects of specific cytokines during each stage of gestation, both at the peripheral and local level, as these functions should provide insight into mechanisms underlying observed changes. Finally, pregnancy is a considerable physical stressor on the body; it is marked by nearly 50% increase in blood volume, changes in lung volume and kidney function, as well as weight increases that reflect the developing baby as well as placental growth, blood volume, and fat stores. These considerable physical stressors of pregnancy likely affect inflammatory processes.

This study examined serum proinflammatory proteins, but did not examine inflammatory responses to a stimulus. Such data would be highly informative, as prior studies show that conditions with an inflammatory component including depression and coronary artery disease as well as obesity are associated with dysregulation of inflammatory responses [61–64]. Moreover, despite elevations in serum proinflammatory markers during pregnancy versus non-pregnancy, available evidence from both human and animal studies indicates that inflammatory *responses* are attenuated [65–69]. Because responses to *in vivo* as well as *in vitro* stimuli provide greater variability across individuals than serum levels, examination of responses to challenges may ultimately provide greater ability to differentiate women showing typical versus atypical (i.e., dysregulated) immune function during pregnancy. This should be considered in future studies.

In conclusion, these data demonstrate that pregnancy and postpartum are characterized by different trajectories of change for specific inflammatory markers. In addition, women with higher body mass show elevations in inflammatory markers across pregnancy and postpartum, but similar trajectories of change in these markers as do normal weight women. As reviewed, excessive inflammation has been associated with a variety of adverse perinatal health outcomes, including preterm delivery, effects on fetal development, and risk of serious maternal health conditions including gestational diabetes and gestational hypertension [70,71]. Given such associations, there is growing interest in describing typical changes in immune parameters across pregnancy, identifying deviations with health relevance, and determining risk factors for such deviations. The current investigation advances our knowledge in this regard. Further research is needed to determine the extent to which obesity-induced inflammation during pregnancy and postpartum may mediate the association between maternal obesity and adverse perinatal health outcomes.

Role of the funding sources

This study was supported by NINR (R01 NR013661, LMC) and NICHD (R21 HD067670, LMC). The project described was supported by Award Number Grant UL1TR000090 from the National Center for Advancing Translational Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institutes of Health. NIH had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflicts of Interest

The authors report no conflicts of interest.

Acknowledgments

We appreciate the contributions of Clinical Research Assistants Colleen Sagrilla, Kelly Marceau, and Rebecca Long to data collection and Research Associate Hui Xu for conducting the cytokine assays. We thank Jay Iams, MD, for his support in participant recruitment. We would like to thank our study participants and the staff at the OSU Clinical Research Center and Wexner Medical Center Prenatal Clinic.

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