Journal of Pregnancy and Child Health
Lessa LRK et al. J Preg Child Health 6: 123.
www.doi.org/10.29011/JPCH-119.100023
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Research Article

Does Maternal Weight Status Influence the Inflammatory Profile of Cord Blood?

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Citation: Lessa LRK, Villar-Delfino PH, Moraes LRB, de Castro LAM, Nogueira-Machado JA, Volpe CMO (2024) Does Maternal Weight Status Influence the Inflammatory Profile of Cord Blood?. J Preg Child Health 6: 123. DOI: https://doi.org/10.29011/JPCH-123.100023

Received Date: 16 April, 2024**; Accepted Date:** 20 April, 2024**; Published Date:** 23 April, 2024

Abstract

Obesity during pregnancy increases the underlying inflammatory state of pregnancy. We aimed to examine the correlation between maternal weight status and inflammatory markers (interleukin-1β, interleukin-6, and malondialdehyde levels) in cord blood among groups categorized by pregnancy BMI. This cross-sectional comparative study included 62 pregnant women divided into four groups based on to pregnancy BMI: underweight, normal, overweight, and obesity. Cord blood collected at birth underwent testing for interleukin (IL)-1β, IL-6, and malondialdehyde (MDA) using ELISA and TBARS Assay Kit. Cord blood levels of IL-1β, IL-6, and MDA showed no significant differences among the pregnancy BMI groups. No correlations were observed between pregnancy BMI and inflammatory markers in cord blood levels. However, gestational weight gain was positively correlated with IL-1β (r=0.78) and IL-6 (r=0.50) in the underweight group, whereas in the overweight group, only IL-6 (r=0.70) showed a positive association. These findings suggest that gestational weight gain correlates with inflammatory markers in cord blood among pregnant women classified as underweight (IL-1β and IL-6) and overweight (IL-6).

Keywords: Obesity; Pregnancy BMI; Gestational weight gain; IL-6; IL-1β; MDA

Introduction

Obesity is commonly characterized as a disease with a rising prevalence, influenced by a combination of various organic, genetic, environmental, cultural, dietary, and emotional factors [1]. Additionally, obesity is associated with a chronic low-grade systemic inflammatory condition [2,3]. Additionally, obesity is associated with a chronic low-grade systemic inflammatory condition. Pregnancy itself is acknowledged as a natural inflammatory state, and appropriate gestational weight gain is crucial for a healthy pregnancy. However, excessive or inadequate weight gain during pregnancy is deemed a risk factor for both pregnant women and the fetus [4].

In gestational obesity, both placenta and adipose tissue contribute to the inflammatory process worsening the underlying inflammatory state of pregnancy. Elevated serum levels of pro-inflammatory cytokines as interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor-α (TNF-α), along with increased oxidative stress, increase the maternal risk of severe complications, including gestational diabetes, preeclampsia, miscarriage, and hemorrhage [5-11].

Studies have shown associations between maternal obesity and fetal overgrowth, high birth weight, as well as an increased risk of childhood obesity [12-17]. Moreover, maternal obesity and overnutrition can lead to permanent changes in the conceptus, including alterations in metabolism, behavior, appetite, and excessive fat accumulation, which may predispose to metabolic problems and obesity in the future [12,13,18-21]. Both excess and deficit of calories intake during the prenatal and perinatal periods appear to be linked to the development of obesity at various life stages [22-24].

The Body Mass Index (BMI), a measure endorsed by the World Health Organization (WHO) to assess nutritional status [22], should be evaluated differently in pregnant women, always considering the gestational age of the fetus as a reference. This is because pregnant women in early pregnancy have different physical conditions compared to those nearing childbirth [14,25,26]. This study investigated the associations between maternal weight status and inflammatory markers (IL-1β, IL-6, and malondialdehyde levels) in cord blood among groups defined by pregnancy BMI.

Material and Methods

Study population

The Ethics Committee of Santa Casa Hospital of Belo Horizonte – Brazil approved this comparative cross-sectional parallel-group study, and all participants provided written informed consent (reference number 05375918.6.0000.5138). Women were recruited from the Gynecology and Obstetrics Service from São José of Avaí Hospital (Itaperuna, Rio de Janeiro, Brazil), including pregnant volunteers (n=62) aged 18-40 years at delivery. Pregnancy BMI was calculated at the time of delivery [14,25,26]. Volunteers were categorized into underweight, normal weight, overweight, and obesity groups based on pregnancy BMI. Table 1 presents the clinical characteristics of the participants. We included pregnant women who received prenatal care and underwent a complete blood count, lipid profile, fasting glycemia, and glycosylated hemoglobin during third trimester of pregnancy. Pregnant women who smoked, had infectious diseases, cancer, dementia, clinically diagnosable inflammatory conditions, fetal distress, premature newborns, post-term infants, or infants with birth asphyxia were excluded from the study.

	Pregnancy BMI category			
	Underweight	Normal	Overweight	Obesity
Clinical characteristics[1]				
Number of patients (n)	10	21	17	14
Age, years	21 ± 2.6[b]	28 ± 6.7[a]	28.1 ± 6.1[a]	28.6 ± 7.6[a]
Height, m	1.60 ± 0.08	1.62 ± 0.07	1.63 ± 0.05	1.62 ± 0.06
Pregnancy BMI, Kg/m^2	23 ± 1.2[a]	26.8 ± 1.3[b]	30.9 ± 1.0[c]	39.3 ± 4.8[d]
Pre-pregnancy Weight, Kg	51.1 ± 6.1[a]	61.2 ± 10.7[a]	65.3 ± 9.1[b]	92.4 ± 19.4[c]
Weight third trimester, Kg	59 ± 4.5[a]	70.8 ± 8.4[b]	82.0 ± 5.6[c]	103.5 ± 15.6[d]
Systolic pressure, mmHg	109.1 ± 9.4[a]	113.8 ± 9.2[a]	122.9 ± 21.7[a,b]	128.7 ± 11[b]
Diastolic pressure, mmHg	71.8 ± 8.7[a]	75.2 ± 8.1[a]	81.2 ± 3.1[a,b]	86 ± 10.6[b]
Metabolic blood measurements[1]				
Serum fasting glucose, mg/dL	71.6 ± 12	72.8 ± 9.5	67 ± 10.7	73.8 ± 9.5
Glycated hemoglobina, %	5 ± 0.3	5.3 ± 0.4	5.4 ± 1.0	5.3 ±0.4
Total cholesterol, mg/dL	238.4 ± 64.9	249.5 ± 55	229.2 ± 29	216.4 ± 52.9
HDL-cholesterol, mg/dL	74.9 ± 19.6	76.8 ± 18.5	76.4 ±26.5	64.4 ± 23.6
LDL-cholesterol, mg/dL	126.1 ± 54	136 ± 44	111.5 ± 28.4	111.5 ± 38.1
VLDL-cholesterol, mg/dL	37.5 ± 12	36.7 ± 12	41.3 ± 13.7	36.6 ± 7.5
Triglycerides, mg/dL	187.1 ± 1	184.2 ± 60	208.5 ± 65.6	181.7 ± 42
Gestational characteristics				
Gestational age at delivery, weeks[1]	38.7 ± 1	38.6 ± 0.8	39.2 ± 1	39.6 ± 1.1

Gestational weight gain, Kg[1]	9 ± 4.4[a]	10.7 ± 4.9[a]	16.7 ± 5.1[b]	11.9 ± 6.7[a]
Mode of delivery, n				
Vaginal	2	5	3	0
Cesarean	8	16	14	14
Newborn characteristics				
Newborn weigth, g[1]	3104 ± 315[a]	3095 ± 381[a]	3521 ± 559[b]	3393 ± 454[a]
Sex, n				
Female	8	13	7	7
Male	2	8	10	7
Apgar score[2]				
1 minute	8 (7 - 9)	8 (7 - 10)	8 (5 - 9)	8 (7 - 9)
5 minutes	9 (8 - 10)	9 (8 - 10)	9 (8 - 10)	9 (9 - 10)
INTERGROWTH-21st classification				
SGA, n	0	1	1	1
AGA, n	10	19	11	12
LGA, n	0	1	5	1

[1]Values expressed in mean ± standard deviation.

[2]Values expressed in median (minimum-maximum).

[a,b,c,d]Values without common notation indicate significant differences (P<0.05), One-Way ANOVA test, Bonferroni post-test.

AGA: appropriate for gestational age; LGA: large for gestational age; SGA: small for gestational age

Table 1: Participant characteristics stratified by pregnancy BMI.

Cord blood collection

At birth, cord blood was collected from the umbilical vein into tubes without anticoagulant. Samples were centrifuged at 200g for 15 minutes, and the serum was aliquoted and stored at -70°C until assayed. Analyses were conducted within three months from the date of storage.

Quantification of inflammatory biomarkers

We quantified Malondialdehyde (MDA) levels using the TBARS Assay Kit (ZeptoMetrix Corp., New York, USA) following the manufacturer's instructions. IL-1β and IL-6 levels were determined using the Enzyme-Linked ImmunoSorbent Assay (ELISA) technique with the "Human IL-β ELISA MAX™ Deluxe-Biolegend" and "Human IL-6 ELISA MAX™ Standard – Biolegend" kits, respectively, according to the manufacturer's instructions.

Statistical analysis

GraphPad Prism 5 (GraphPad Software, Inc) was used for statistical analysis. The D'Agostino-Pearson test was used to assess the normality of the continuous data. Normally distributed data are expressed as mean ± standard deviation (SD) and nonparametric data as median (minimum-maximum). The differences in the samples were compared using the unpaired Student *t*-test or the Mann-Whitney *U*-test or One-Way ANOVA test, Bonferroni post-test. Correlations between pregnancy BMI and inflammatory biomarkers were performed by Spearman's Rho or Pearson's tests [27]. P<0.05 was considered statistically significant.

Results

Maternal characteristics

Table 1 presents the detailed profile of participants categorized by pregnancy BMI. The prevalence of gestational

overweight (n=17) and obesity (n=15) was observed in 51.6% of the 62 women who met the inclusion criteria and were accepted in the study. The age of the underweight group was significantly lower ($p<0.05$) compared to the other groups. There were significant differences in pregnancy BMI and weight at the third trimester between the groups ($p<0.05$). The overweight group exhibited significantly higher gestational weight gain ($p<0.05$) and birth weight of infants ($p<0.05$) compared to the other groups.

Inflammatory markers in pregnancy BMI groups

Figure 1 shows no significant differences in the cord blood levels of IL-1β, IL-6, and MDA among the groups stratified by pregnancy BMI.

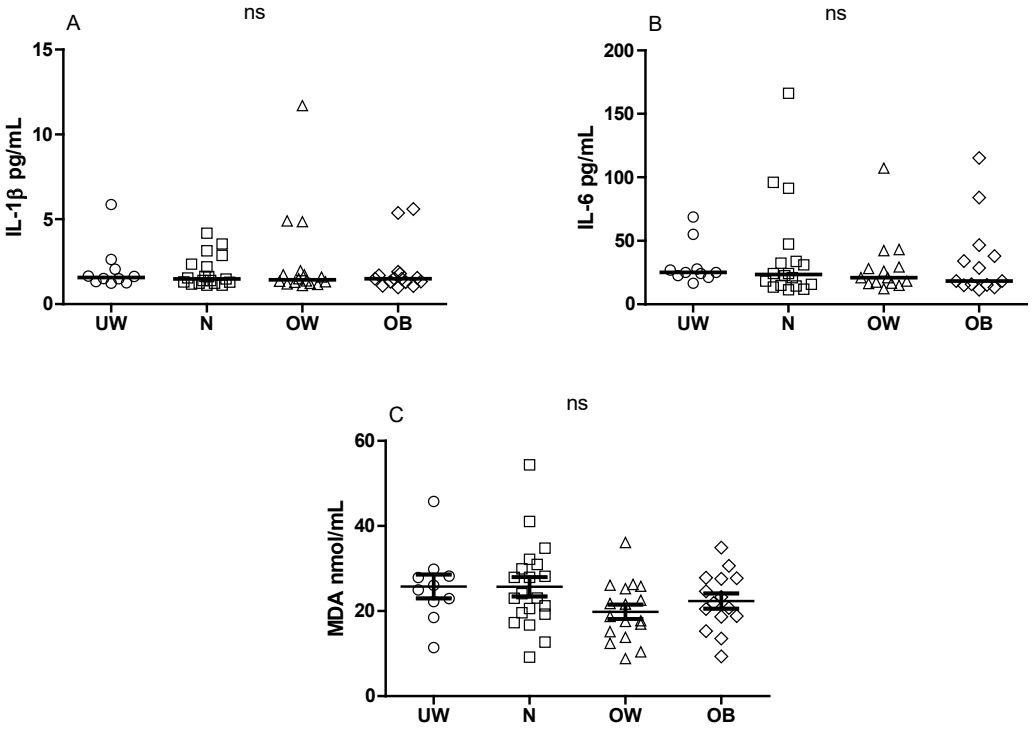

Figure 1: Cord blood levels of IL-1β (A), IL-6 (B), and MDA (C) in studied group stratified by pregnancy BMI.

A and B: values expressed median (minimum - maximum), significant differences between the groups were determined using One-Way ANOVA test. C: values expressed mean and standard error, significant differences between the groups were determined using Student t-test.

IL: Interleukin; MDA: malondialdehyde; N: normal; ns: non-significant; OB: obese; OW: overweight; UW: underweight

Associantions of inflammatory markers with pregnancy BMI and gestational weight gain

Table 2 demonstrates the absence of correlation between pregnancy BMI and inflammatory markers of cord blood levels. Positive correlations were observed between gestational weight gain and inflammatory markers of cord blood levels in the underweight group for IL-1β ($r=0.78$) and IL-6 ($r=0.50$), as well as in the overweight group for IL-6 ($r=0.70$) (Figure 2).

	Underweight	Normal	Overweight	Obesity
MDA nmol/mL[1]	0.21	-0.21	-0.09	0.07
IL-1β pg/mL[2]	-0.10	-0.34	0.16	0.32
IL-6 pg/mL[2]	0.07	-0.08	0.02	0.35

[1]Pearson Correlation coefficient

[2]Spearman Correlation coefficient

IL: Interleukin; MDA: malondialdehyde

Table 2: Correlations between pregnancy BMI and inflammatory markers of cord blood levels.

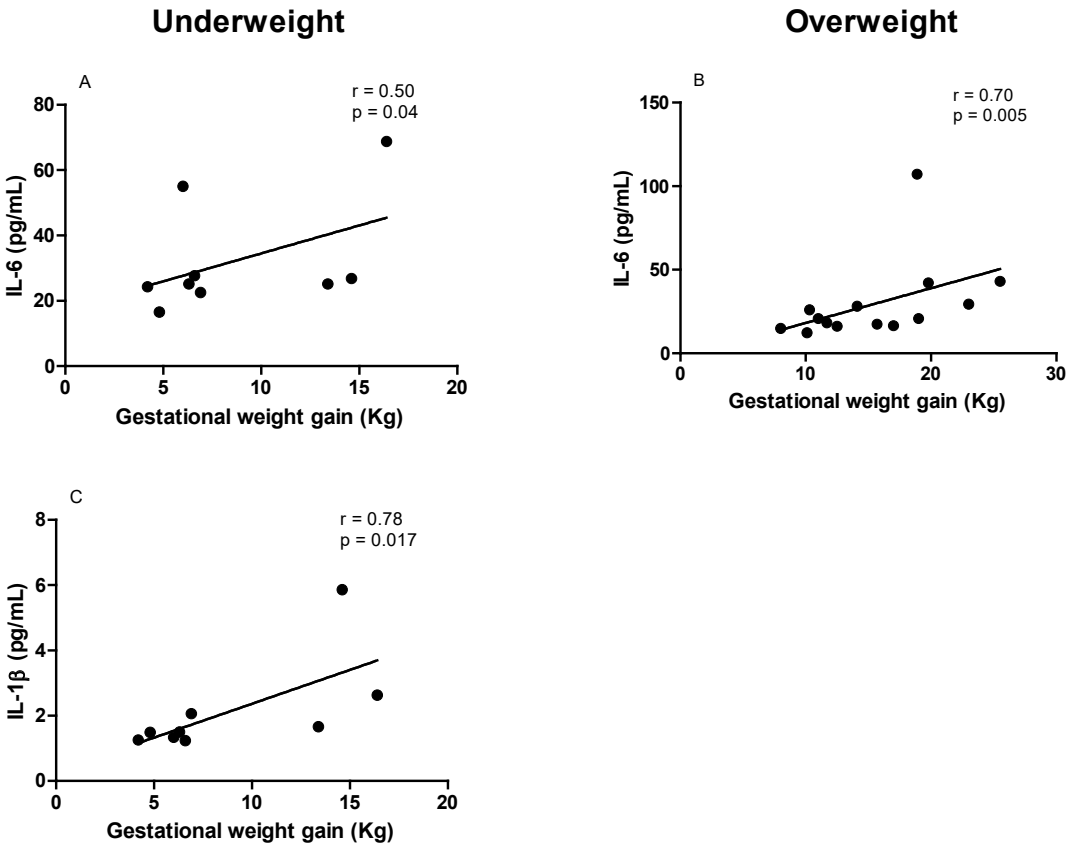

Figure 2: Spearman Correlation coefficient (r) for gestational weight gain and Interleukin(IL)-6 (A,B) and IL-1β (C) of cord blood levels in Underweight and Overweight Pregnancy BMI.

Discussion

In this study, pregnant women were categorized according to gestational BMI, data analyzing inflammation related to gestational BMI are scarce. Most studies typically evaluate inflammatory status in relation to pre-pregnancy BMI. Although the results did not show significant differences in IL-1β, IL-6, and MDA levels in the cord blood of pregnant women classified according to pregnancy BMI, correlations were identified between gestational weight gain and the pro-inflammatory cytokines IL-1β and IL-6. Gestational weight gain in the underweight group showed a positive correlation with IL-1β and IL-6 levels. As for the overweight group, only IL-6 levels were positively associated.

Obesity exacerbates the inflammatory state commonly associated with pregnancy, predisposing newborns to adverse cardiometabolic, endocrine, and neurocognitive events [28-34]. However, reports on the levels of inflammatory biomarkers in pregnant women with obesity are contradictory. While some studies have found increased levels of IL-1, IL-6, and TNF-α in the placenta of obese gestants, as well as higher IL-6 levels in the cord blood of newborns from women with obesity compared to non-obese counterparts [8,31,35], others have shown no significant changes in inflammatory markers, such as leptin, IL-6, and TNF-α, in cord blood in neonates of mothers with obesity compared to controls [36-38]. Additionally, it has been observed that pregnant women with a BMI < 35kg/m^2 at the time of delivery may not induce a fetal inflammatory response, whereas those with a BMI ≥ 35kg/m^2 may exhibit the presence of inflammatory markers such as IL-6 and TNF-α [15]. Alterations in maternal inflammatory markers may not be reflected by similar changes in the fetal circulation, suggesting that the fetal-maternal interface adapts throughout gestation preserving fetal development [36-38].

High pre-pregnancy BMI and excessive weight gain have been linked to inflammatory status in newborns, even though this association is not well understood [38,39]. A pre-pregnancy BMI >35kg/m^2 has been associated with elevated levels of pro-inflammatory cytokines (C-reactive protein, TNF, IL-6) and markers of oxidative stress (MDA and nitric oxide) in placental tissues and cord blood [15,31,40,41]. It is recommended that pregnant women a weight gain of 10 kg, a value associated with lower impacts on obstetric outcomes and weight of postpartum women [42,43]. In this study, only the underweigth group had a gestational weight gain less than 10 kg, but no significant differences in weight gain were observed between underweight, normal weight, and obese groups. The overweight group had significantly higher gestational weight gain compared to the other groups, and this weight gain was positively correlated with IL-6 levels present in cord blood (Figure 2).

The deleterious effects of low pre-gestational weight in mothers on fetal development are well-established. Women with low pre-pregnancy weight are at significantly higher risk for preterm delivery and giving birth to low birth weight newborns [44-47]. While our data did not reveal low birth weight newborns in the underweight group, we did observe a strong positive correlation between weight gain and levels of IL-1β and IL-6 (Figure 2). IL-6 and IL-1β are inflammatory markers commonly found in patients with metabolic diseases. IL-1β production occurs through the activation of inflammasomes, multiprotein platforms present in the cytosol, which are also responsible for IL-18 production and pyroptosis (inflammatory cell death) [48-50]. The NLRP3 (nucleotide-binding oligomerization domain, leucine-rich repeat- and pyrin domain-containing 3) inflammasome is a crucial mediator of sterile inflammation and has been extensively studied in pregnancy [51-54].

While the literature extensively explores the effects of maternal obesity on offspring, there is a notable scarcity of studies dedicated to the underweight population, whether pregnant or not. Our findings suggest a potential association between weight gain in pregnant women classified as underweight and the pro-inflammatory cytokines IL-1β and IL-6. It is important to acknowledge the limitation of our study, namely the small number of pregnant women in the underweight group. Therefore, further investigations are warranted to elucidate how low maternal weight can influence the inflammatory status in newborns, as well as to unravel the underlying pathophysiological mechanisms of this paradoxical phenomenon.

Conclusion

Our results indicated a correlation between gestational weight gain and inflammatory maskers in the cord blood of newborns from mothers with pregnancy BMI classified as underweight (IL-1β and IL-6) and overweight (IL-6). Our results revealed correlations between gestational weight gain and inflammatory markers in the cord blood of newborns from mothers with pregnancy BMI classified as underweight (IL-1β and IL-6) and overweight (IL-6). These findings highlight numerous associations between pregnant women, BMI, newborns, and inflammatory biomarkers, the understanding of which could inform early interventions and potentially influence epigenetic adaptations with lifelong impacts. Further research investigating the associations between underweight patients, maternal weight gain, and maternal and fetal inflammatory status would be valuable. Additionally, longitudinal follow-up of these children is warranted to assess future problems that have thus far been linked primarily to obesity.

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