The effect of gestational weight gain on serum total oxidative stress, total antioxidant capacity and gut microbiota

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INTRODUCTION

Pregnancy is a critical period for both the mother and fetus. During this period, diet and lifestyle of the mother affect the health of both the mother and fetus. Maternal nutrition can alter the epigenetic status of the fetal genome and pave the way for several chronic diseases in adulthood [1]. It is important to ensure optimal nutrition in the preconception period, evaluate eating disorders, follow-up on vegan or vegetarian diets, and evaluate malabsorption diseases (e.g., celiac disease) in women of childbearing age to improve maternal and infant health during pregnancy and postpartum [2].

Due to the risks of gestational diabetes, preeclampsia, preterm birth, fetal growth retardation, fetal macrosomia, neonatal hypoglycemia, and childhood obesity, it has been reported that underweight, overweight, or obese individuals should receive nutritional counseling and achieve ideal body weights during the prepregnancy period [3–7]. It has been shown that the risks of macrosomia, hypertensive disease, gestational diabetes, and cesarean delivery are 2-fold, 2.5-fold, 4-fold, and 2-fold higher, respectively, in women who were obese during pregnancy when compared with women with normal body mass index [8–10].

Obesity is a metabolic disorder characterized by the simultaneous deterioration of fat metabolism and the inflammatory and hormonal processes caused by insulin resistance. The pathogenesis of obesity is complex. It involves metabolic and hormonal dysregulation, low-grade chronic inflammation, and endoplasmic reticulum stress. Oxidative stress has been the focus of research as a central mechanism that can ameliorate the negative effects of obesity [11].

The presence of oxidative stress during a healthy pregnancy has been established in previous research. Trophoblast proliferation,
invasion, and angiogenesis, which are necessary for a healthy pregnancy, are not affected by the absence of other risk factors that contribute to oxidative stress. However, in pregnant women with obesity, increased oxidative stress levels lead to the development of several reproductive and pregnancy-related disorders and high-risk pregnancies [12]. Notably, the consumption of antioxidant-rich foods decreases the level of oxidative stress by increasing the serum antioxidant capacity [13].

Recent studies have shown that the gut microbiome affects energy metabolism and plays a role in the pathogenesis of obesity, which has emerged as an important public health problem. It has been reported that the diversity of the gut microbiome decreases in people with obesity [14]. Glucose and lipid metabolism are primarily affected, and the pathophysiological process of obesity begins through inflammation and increases levels of oxidative stress. The gut microbiome has also been shown to be directly associated with body weight and weight gain during pregnancy, and the diversity of the microbiome is lower in overweight and obese pregnant women [15].

In addition to the importance of receiving optimal nutrition during pregnancy, studies have shown that many adverse maternal and fetal conditions can be prevented by supplementing the diets of pregnant women with probiotics that help achieve optimum gut microbiome levels [16, 17]. Furthermore, probiotic supplements have positive effects on oxidative stress and inflammation in pregnant women [18, 19]. However, no studies have evaluated the relationship between oxidative stress and the gut microbiome in pregnant women who do not take probiotic supplements.

Additionally, although the relationship between oxidative stress and antioxidant capacity has been evaluated in high-risk pregnancies [20], no studies have evaluated the relationships among maternal obesity, oxidative stress, the gut microbiome, and antioxidant capacity. Although vitamin E and C supplementation has been shown to produce positive results due to increased oxidative stress, especially in high-risk pregnancies [20], there are no data on the relationship between vitamin E and C supplementation and the gut microbiome in pregnant women.

In light of these findings, this study aimed to evaluate the relationships among body weight gain, oxidative stress, the gut microbiome, and antioxidant capacity in pregnant women and reveal those among oxidative stress, antioxidant levels, and the gut microbiome.

**MATERIALS AND METHODS**

The study was conducted between January and November 2021 and included 40 pregnant women aged 18–28 years old. Women with high-risk pregnancies (such as those with gestational diabetes, preeclampsia, multiple births, or chronic diseases), prepregnancy body mass index (BMI) of $<18.5$ kg/m$^2$ or $\geq 40$ kg/m$^2$, smokers, and those with a history of previous cesarean birth were excluded from the study.

All the pregnant women provided written informed consent at the beginning of the study. Body weight and height measurements were taken during third trimester hospital visits. Prepregnancy body weight measurements were obtained from the electronic database of the hospital.

To evaluate the effect of body weight gain on various parameters, the pregnant women were divided into four study groups: a) normal prepregnancy body weight and normal gestational weight gain (NN) b) normal prepregnancy body weight and body weight gain above the recommended values during pregnancy (NO) c) obese before pregnancy and gestational weight gain according to the recommended values (ON) and d) obese before pregnancy and gestational weight gain above the recommended values (OO).

The sample size was calculated to be 40 pregnant women (10 per group) using Student’s $t$ test, with a power of 0.80 and a significance level of 0.05, as described by Collado et al. [21].

A survey form was then used by the researchers to collect general characteristics of the participants, blood samples were collected by a specialist nurse, and stool samples were taken.

**Ethical considerations**

Ethics committee approval (number 11/2020, January 22, 2020) for this study was obtained from the Ankara Etlik Zübeyde Hanım Women’s Health Training and Research Hospital Clinical Research Ethics Committee. The purpose and methods of the study were explained to each participant prior to starting the study. Informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association.

**Data collection tools**

**Survey form**

The general characteristics of the participants were collected with a questionnaire during face-to-face interviews.

**Anthropometric measurements**

Body weight and height were measured during the first hospital visits at the gestational age of 8–12 weeks and the gestational age of 30–35 weeks in the third trimester. All measurements were performed in accordance with the recommendations of the World Health Organization [22, 23].

According to the World Health Organization recommendations [24], individuals with a BMI of 18.50–24.99 kg/m$^2$ are classified as having a healthy weight, those with a BMI of 25.0–29.9 kg/m$^2$ are classified as having mild obesity, those with a BMI of 30.00–34.99 kg/m$^2$ are classified as having type I obesity, and those with a BMI of 35.00–39.99 kg/m$^2$ are classified as having type II obesity. Based on the Institute of Medicine criteria [25], the recommended values for gestational weight gain based on prepregnancy BMI are 12.5–18 kg for women who are underweight, 11.5–16 kg for women who have a healthy weight, 7–11.5 kg for women who are overweight, and 5–9 kg for women who are obese before pregnancy.

**Dietary antioxidant intake**

The frequency of food consumption was recorded in the third trimester (30–35 weeks of pregnancy), and the antioxidant contents of the foods were evaluated using the database created by Carlsen et al. in 2010 based on the ferric antioxidant power method [26].

**Evaluation of total oxidant status (TOS) and total antioxidant capacity (TAC)**

Blood samples were collected during the third trimester of pregnancy. Venous blood samples were collected by a nurse in the morning after the participants had fasted for 8 hr, and the samples...
were stored at −80°C until analysis. Serum TOS and TAC levels were analyzed using a commercial enzyme-linked immunosorbent assay kit (Rel Assay, Turkey). To calculate the oxidative stress index (OSI), the TAC value was converted to μmol/L using the following equation: OSI (arbitrary units) = TOS (μmol H₂O₂ equivalent/L)/TAC [(Trolox equivalent) μmol/L] [27, 28].

**Fecal samples**

Fecal samples from the participants were collected in the third trimester at the same time as serum samples were collected. Sterile containers were provided for stool sample collection, and the collected samples were stored at −80°C until microbiome analyses were performed using the 16S rRNA gene.

**Genomic DNA extraction**

For DNA extraction, QuickGene DNA tissue kit S was used according to the instructions of the manufacturer (https://www.kurabo.co.jp/bio/English/product/tableTemplatePdf.php?f=23&r=3&c=4&t=2). The quality and quantity of DNA were measured by a Colibri spectrophotometer (Tittertek-Berthold) and Qubit 2.0 fluorometer with a dsDNA HS Assay Kit (Thermo Fisher Scientific).

**Amplification and sequencing of the 16S rRNA gene**

Polymerase chain reaction (PCR) was performed with primers specific for the V3 and V4 regions in the 16S rRNA gene according to the amplification conditions recommended in the Illumina MiSeq 16S metagenomic sequencing library preparation kit protocol (https://support.illumina.com/documents/chemistry_documentation/16s/16s-metagenomic-library-prep-guide-15044223-b.pdf). After checking the PCR product by agarose gel electrophoresis, the amplification product was purified using a QIAquick Gel Extraction Kit (Qiagen, Germany). A Qubit dsDNA HS Assay Kit (Thermo Fisher Scientific, Warrington, England) was used to measure the DNA concentration, and then index PCR was performed using a Nextera XT Index Kit (Illumina, San Diego, CA, USA). The index PCR product was cleaned using AMPure XP beads and quantified. It was then multiplexed equally and sequenced using MiSeq Reagent Kit v3 on an Illumina MiSeq Sequencing platform (Illumina, San Diego, CA, USA) as recommended by the manufacturer’s instructions (https://support.illumina.com/documents/chemistry_documentation/16s/16s-metagenomic-library-prep-guide-15044223-b.pdf).

**Analysis of sequence results**

Paired-end Illumina reads (2*150 bp) were imported into the QIIME 2 (2019.10) environment [29]. Quality trimming, chimera detection, and cleaning of the reads were implemented through the QIIME2 using the DADA2 pipeline. Amplicon sequence variants (ASVs) generated by DADA2were mapped to the Greengenes database (http://greengenes.lbl.gov). Phylloseq [30] objects were created from QIIME 2 artifacts in the R4.1 environment. Alpha diversity assessments, which were used to evaluate the diversity of related taxonomic units in individual samples, were made using Chao1, and Shannon indices [29, 31]. The Kruskal–Wallis statistical test was used to reveal differences in distribution between groups. Beta diversity, which was used to assess taxonomic differences between groups, was calculated based on weighted and unweighted UniFrac. Specific taxonomic differences between groups were determined by differential abundance analysis using DESeq2 (R package) [31].

**Statistical analysis**

All statistical analyses were performed using IBM SPSS Statistics for Macintosh (Version 22.0; IBM Corp., Armonk, NY, USA). The normality of the data was evaluated using the Kolmogorov–Smirnov test. Independent samples t tests and analysis of variance were used to evaluate differences between groups. Differences in the parameters examined between the groups classified according to recommended body weight gain based on prepregnancy BMI were evaluated using the Kruskal–Wallis test for independent samples. Correlations between numerical data were evaluated using Pearson’s correlation coefficient. Statistical significance was set at p<0.05. As a nonparametric method, the Mann–Whitney U test was used to determine statistically significant differences between study groups in terms of the phylum, genus, and species levels of OTUs with relative abundances of ≥1%.

**RESULTS**

The mean age of the participants was 26.70 ± 5.35 years and mean age at the time of marriage was 20.60 ± 3.46 years. Furthermore, the mean BMI, serum TAC level, serum TOS level, and OSI were 30.37 ± 2.73 kg/m², 1.75 ± 0.31 mmol/L, 14.91 ± 9.02 mmol/L, and 0.85 ± 0.51, respectively.

Significant differences in serum TAC and TOS levels, OSI, and dietary antioxidant intake in the third trimester were found among the study groups classified according to the Institute of Medicine criteria (p<0.05). A significant difference in serum TOS level was observed among the NN and NO, OO groups and among the ON and OO, NO groups. Furthermore, there was a significant difference in OSI among the NN and NO, OO groups and among the ON and NO, OO groups (p<0.05; Table 1).

A significant difference was also observed in the serum antioxidant level between the NO and OO groups in dietary antioxidant intake (mmol/day) among the ON and NO, OO groups (p<0.05; Table 1).

A significant positive correlation was found between the BMI in the third trimester and the serum TOS and OSI levels (p<0.05). A negative correlation was found between the serum TOS level and alpha diversity indices (Shannon and Chao1 indices). Furthermore, a negative correlation was found between the OSI and Shannon index (p<0.05), and a positive correlation was found between dietary antioxidant intake and the alpha diversity indices (p<0.05; Table 2).

According to the alpha diversity analysis, there were no significant differences in terms of microbiome richness or relative abundance of taxa between the NN and NO groups or between the ON and OO groups (p>0.05). Beta diversity UniFrac distance matrix results did not show differences among the study groups (p>0.05). There were no unique microbiome structures that were specific to any of the four study groups. Six different phyla with mean relative abundances of ≥1% were detected in all tested samples. Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria were the most common phyla among all the groups. Comparison of the NN and NO groups revealed that Firmicutes and Proteobacteria phyla were more abundant...
The relationships among the mean relative abundances of some bacterial phyla in the gut microbiome of pregnant women and the serum levels of TAC and TOS, OSI, and dietary antioxidant intake are presented in Table 4. A positive correlation was found between the serum levels of TAC and the relative abundance of Proteobacteria. Negative correlations were found between the serum level of TAC and the relative abundances of Bacteroidetes, Firmicutes, and Firmicutes/Bacteroidetes. The serum level of TOS and the OSI were found to be negatively correlated with the relative abundance of Proteobacteria and to be positively correlated with the relative abundances of Bacteroidetes, Firmicutes, and Firmicutes/Bacteroidetes (p<0.05).

(p=0.003) and Bacteroidetes and Actinobacteria phyla were less abundant in the NO group (p=0.019). Comparison of the ON and OO groups revealed that only the Bacteroidetes phylum was more abundant in the OO group (p=0.002) while the Firmicutes and Actinobacteria phyla were less abundant (p=0.004, p=0.019, respectively; Fig. 1).

There were significant differences in the mean relative abundances of some genera and species among the study groups. For instance, the genera Prevotella and Bacteroides were more abundant in the NN group than in the NO group, whereas Lactobacillus was more abundant in the NO group than in the NN group. The genus Dialister was significantly more abundant in the OO group. Only the species Prevotella copri had a significantly different relative abundance among the species detected in the four groups (Table 3).
DISCUSSION

This is the first study to evaluate the relationships between gestational weight gain and the gut microbiome, serum levels of TAC and TOS, and dietary antioxidant intake in pregnant women. Gestational weight gain has been shown to increase serum TOS levels and decrease serum TAC levels, which are associated with some bacterial phyla in the maternal gut microbiome.

An increase in oxidative stress levels, which normally occurs at 8–12 weeks of pregnancy, has been shown to be an exacerbating factor for maternal obesity, which is a risk factor for pregnancy failure in spontaneous and ovulation induction pregnancies [32, 33]. This was also confirmed in the present study; body weight gain above the recommended values resulted in higher serum TOS levels in women with obesity or normal prepregnancy body weights. However, the increase in TOS level was lower in the NO group than in the obese groups during the prepregnancy period.

Oxidative damage to the placenta in obese pregnant women results in inflammation and apoptosis, which is accompanied by a decrease in antioxidant capacity [34]. The results of the present study also showed that the serum TAC level decreased as the serum TOS level increased due to body weight gain above the recommended values. Furthermore, the serum TAC level and dietary antioxidant intake were found to be lower, especially in the OO group, than in the groups of women with normal prepregnancy body weights. The results clearly show that prepregnancy weight is an important predictor of the serum TAC level and dietary antioxidant intake.

Studies have reported that the gut microbiome is not only involved in nutrient absorption, digestion, and metabolic activities but is also associated with energy balance. There is an influx of recent evidence on the effect of obesity on the microbiome composition during pregnancy [21, 35, 36]. It has been confirmed that obesity-related reductions in microbial diversity and dysbiosis also occur during pregnancy [37]. The Shannon index, which is an indicator of gut microbiome alpha diversity, was also investigated in this study. Negative correlations were found between the Shannon index and BMI, OSI, and the serum TOS level in the third trimester, while there was a positive correlation between the Shannon index and dietary antioxidant intake. Furthermore, a positive correlation was found between dietary antioxidant intake and the Chaol index, which is another indicator of microbiome alpha diversity.

A diet rich in antioxidants protects people from obesity. In addition, antioxidant-rich diets provide the prebiotics necessary for the gut microbiome and improve microbial composition, with a positive effect on richness and diversity [38].

Antioxidants play a vital role in maintaining health and are necessary for the prevention and treatment of inflammation and dysbiosis associated with obesity or overweight. The best way to provide the body with a wide variety of antioxidants is to consume foods of animal origin while also eating adequate plant-based foods according to the Mediterranean diet [39].

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Fig. 1. Changes in the relative abundances of the gut microbiome at the phyla level.

NN: women with normal prepregnancy body weight and normal gestational weight gain; NO: women with normal prepregnancy body weight and body weight gain above the recommended values during pregnancy; ON: women with obese before pregnancy and gestational weight gain according to the recommended values; OO: women with obese before pregnancy and gestational weight gain above the recommended values.
It has been reported that gestational weight gain is associated with gut microbiome composition and that changes in maternal weight before and during pregnancy may offer new insights, leading to the discovery of possible preventive and therapeutic applications aimed at risk reduction [21]. A previous study reported that the relative abundance of *Firmicutes* was higher in overweight and obese mothers and did not change during pregnancy [40]. In the present study, when the relative abundances of the gut microbiomes of the study groups were compared, it was found that excessive body weight gain led to an increase in the phylum *Firmicutes* in pregnant women with normal prepregnancy weights.

Collado *et al.* [21] found a positive correlation between the genus *Bacteroides* and gestational weight gain. In the present study, a decrease in the relative abundance of the genus *Bacteroides* was observed with gestational weight gain in both the NO and OO groups.

In a previous study investigating the relationship between maternal obesity and the gut microbiome, a positive correlation was found between BMI at the 16th week of pregnancy and the abundance of the family *Lachnospiraceae* [37]. In the present study, a decrease in the relative abundance of the family *Lachnospiraceae* was found in both the NO and OO groups. Furthermore, a high BMI and body weight gain above the

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**Table 3.** Mean relative abundances of bacterial taxa at various taxonomic levels according to recommended body weight gain status based on prepregnancy BMI values

| Taxa (family)         | NN   | NO   | p value | ON   | OO   | p value |
|-----------------------|------|------|---------|------|------|---------|
| *Prevotellaceae*      | 29.58| 26.93| 0.003*  | 18.50| 27.91| 0.010*  |
| *Ruminococcaceae*     | 15.19| 14.38| 0.051   | 19.08| 17.56| 0.004*  |
| *Lachnospiraceae*     | 13.57| 13.48| 0.025*  | 14.81| 10.17| 0.002*  |
| *Veillonellaceae*     | 4.82 | 5.67 | 0.006*  | 5.06 | 5.16 | 0.050   |
| *Lactobacillaceae*    | 1.91 | 4.79 | 0.012*  | 3.13 | 2.06 | 0.020*  |
| *Bacteroidaceae*      | 3.65 | 2.70 | 0.041*  | 3.84 | 2.17 | 0.034*  |
| *Bifidobacteriaceae*  | 2.51 | 2.47 | 0.928   | 3.61 | 1.67 | 0.025*  |
| *Succinivibrionaceae* | 1.57 | 1.80 | 0.474   | 2.27 | 1.92 | 0.380   |
| *Paraprevotellaceae*  | 2.54 | 1.61 | 0.316   | 2.14 | 1.40 | 0.307   |
| *Erysipelotrichaceae* | 2.01 | 1.41 | 0.175   | 1.22 | 3.41 | 0.356   |

| Taxa (genus)          | NN  | NO  | p value | ON  | OO  | p value |
|-----------------------|-----|-----|---------|-----|-----|---------|
| *Prevotella*          | 29.58| 26.93| 0.003*  | 18.50| 27.91| 0.010*  |
| *Faecalibacterium*    | 7.36 | 7.59 | 0.994   | 11.90| 11.30| 0.766   |
| *Lactobacillus*       | 1.91 | 4.79 | 0.012*  | 3.13 | 2.06 | 0.090   |
| *Dialister*           | 3.30 | 3.60 | 0.973   | 2.97 | 4.79 | 0.004*  |
| *Bacteroides*         | 3.63 | 2.70 | 0.041*  | 3.81 | 2.17 | 0.002*  |
| *Bifidobacterium*     | 2.47 | 2.47 | 0.311   | 3.60 | 1.66 | 0.025   |
| *Oscillospira*        | 2.43 | 1.86 | 0.477   | 1.83 | 1.91 | 0.844   |
| *Pseudobutyribrio*    | 1.74 | 1.57 | 0.929   | 1.61 | 1.07 | 0.288   |
| *Succinivibrio*       | 1.57 | 1.80 | 0.457   | 2.27 | 1.92 | 0.380   |
| *Blautia*             | 1.46 | 1.68 | 0.946   | 2.41 | 1.55 | 0.249   |

| Taxa (species)        | NN | NO | p value | ON | OO | p value |
|-----------------------|----|----|---------|----|----|---------|
| *Prevotella copri*    | 23.78| 22.99| 0.070   | 14.74| 25.94| 0.010*  |
| *Faecalibacterium prausnitzii* | 7.24 | 7.45 | 0.740 | 11.79 | 11.15 | 0.187 |
| *Lactobacillus helveticus* | 1.17 | 1.85 | 0.702 | 1.03 | 0.62 | 0.640 |
| *Bifidobacterium adolescentis* | 1.62 | 1.65 | 0.542 | 2.8  | 1.24 | 0.124 |

| *Significant at the 0.05 level.**Significant at the 0.01 level. |

BMI: body mass index; NN: women with normal prepregnancy body weight and normal gestational weight gain; NO: women with normal prepregnancy body weight and body weight gain above the recommended values during pregnancy; ON: women with obese before pregnancy and gestational weight gain according to the recommended values; OO: women with obese before pregnancy and gestational weight gain above the recommended values.

**Table 4.** Correlations between the relative abundances of bacterial taxa and maternal biomarkers

| Variables       | TAC (mmol/L) | TOS (mmol/L) | OSI | DTAC (mmol/day) |
|-----------------|--------------|--------------|-----|-----------------|
| Proteobacteria  | 0.408*       | −0.633**     | −0.641** | 0.137           |
| *Bacteroides*   | −0.461**     | 0.581**      | 0.570** | −0.250          |
| *Firmicutes*    | −0.438*      | 0.374**      | 0.441** | 0.232           |
| *Firmicutes/Bacteroides* | −0.508** | 0.453**   | 0.403*   | −0.348*         |

*Significant at the 0.05 level. **Significant at the 0.01 level.*

TAC: serum total antioxidant capacity; TOS: serum total oxidative stress; OSI: oxidative stress index; DTAC: dietary antioxidant intake.
recommended values during pregnancy were associated with a decrease in the relative abundance of the family Lachnospiraceae. A previous study evaluating the effects of nutrition on the gut microbiome also investigated the effects of antioxidants on gut microbial composition and showed that anthocyanins had positive effects on the genera Lactobacillus, Enterococcus, and Bifidobacterium and that resveratrol had positive effects on the genera Bifidobacterium and Lactobacillus [41]. The results of the present study showed that dietary antioxidant intake was associated with the Firmicutes/Bacteroidetes ratio.

In addition to studies that evaluate the relationship between obesity and the gut microbiome, recent evidence is available on the effect of the gut microbiome on biochemical findings. In a previous study evaluating the relationship between alpha diversity and inflammatory indicators, the Shannon index was determined to be associated with high levels of high-sensitivity C-reactive protein and haptoglobin [40]. In this study, a significant correlation was found between the serum TAC level and the Shannon index, TOS level, OSI, and Shannon and Chaol indices. When we examined the relationship between biochemical indicators and bacterial taxa, the results revealed that the phyla Proteobacteria, Bacteroidetes, and Firmicutes were associated with serum TAC, TOS, and OSI.

This study has certain limitations. Data on the frequency of food consumption by the pregnant women were collected only once during the third trimester. These data should be collected and evaluated during all trimesters, which would provide a more comprehensive picture of the effects of dietary antioxidant intake on the gut microbiome. Furthermore, the analysis of food consumption focused only on dietary antioxidant intake, and other micro- and macronutrients were not evaluated. More comprehensive data covering the three trimesters would enable a more detailed assessment of the gut microbiome and nutrition.

In conclusion, our results show that gestational weight gain is associated with the serum TAC and TOS levels, dietary antioxidant intake, and gut microbiome composition. Gestational weight gain above the recommended values in women with normal prepregnancy weights results in high serum total oxidative stress. Furthermore, microbiome diversity is adversely affected by a high serum oxidative stress level and is positively affected by dietary antioxidant intake.

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