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A maternal sweet diet is associated with the gut dysbiosis in the first trimester of pregnancy

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Abstract

Background The composition of maternal gut phylum in each trimester of pregnancy has been associated with fetal development, separately. Diet is a main effective factor on the gut composition of phylum. However, associations between dietary glycemic index (GI), load (GL) and total antioxidant capacity (TAC) not studied with the gut population of phylum in mothers at the first trimester of pregnancy.

Materials and methods Ninety healthy pregnant women aged 18–40 yrs, in the first trimester, were participated. Stool samples were gathered in a fasting state. Population of dominant phylum was determined after DNA extraction based on the 16SrRNA expression, as a housekeeping gene. Dietary intake was collected by a validated food frequency questionnaire and dietary indices were computed.

Results The *Proteobacteria* population was significantly higher in the gut of pregnant mothers than the other phylum ($p < 0.001$). Participants in the highest level of dietary GI had lower *Bacteroidetes* ($p < 0.001$) and *Actinobacteria* ($p = 0.04$) in their gut compared to the lowest level. Participants in the lowest level of dietary GL had higher *Bacteroidetes* ($p < 0.001$) and lower *proteobacteria* ($p = 0.04$) in their gut than the highest level. Dietary selenium showed a significant negative effect on the *Firmicutes* ($p = 0.04$) and *Proteobacteria* ($p = 0.04$), however positively affected the *Actinobacteria* ($p = 0.01$) population. Dietary zinc and manganese showed a negative effect on the *Firmicutes* population ($p = 0.01$ and $p = 0.003$). Zinc and vitamin E showed a negative effect on the *Proteobacteria* population ($p = 0.04$ and $p = 0.03$).

Conclusions A maternal diet with high GI and GL have been associated with the gut dysbiosis, however dietary intake of selenium, zinc, manganese and vitamin E act in favor of the intestinal eubiosis in the first trimester of pregnancy.

Keywords Glycemic index, Glycemic load, Selenium, Zinc, Manganese, Gut phyla

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Introduction

Colon is a habitat area for bacteria which have more vital effects on human health including production and absorption of some type of vitamins and bioactive compounds, the synthesis of amino acids, the metabolism of non-digestible carbohydrates [1]. Short chain fatty acids (SCFAs), as the main metabolites produced by the bacterial activity on the undigested food components, have different roles in metabolism by regulating of signaling pathways through the gut-brain axis [1, 2]. Any disturbance in bacterial population lead to metabolic, neurobehavioral and gastrointestinal disorders [3]. In a normal state, more than 80% of the gut phylum belongs to the *Bacteroidetes* and *Firmicutes*, others are *Actinobacteria* and *Proteobacteria* however marked changes occur during pregnancy [4]. Maternal gut phylum effect on fetal health differently, in each trimester. The first trimester is more important due to the development of fetal nervous system however, the most of women didn't know about pregnancy [5–7]. In addition, the gut dysbiosis in the first trimester have been associated with some complications during pregnancy [8–10]. The life cycle, maternal weight, dietary pattern, dietary components including macro and micronutrients, genetic and living geographical area are effective factors on the gut phylum [11, 12]. Hormonal alterations during pregnancy effect on the gut bacterial metabolism, growth, and the host virulence to the pathogenic bacteria [13]. Limited information is available about the factors, especially diet and dietary components that contribute to the maternal bacterial population during pregnancy in different countries. In a previous study, it is reported that the composition of gut is dominated by the *Firmicutes* in obese pregnant mothers [14]. Moreover, it is reported that increase in estrogen and progesterone lead to maternal vulnerability to pathogens such as bacteria belong to the *Proteobacteria* [14]. Regarding the long-lasting and permanent effects of maternal exposures on the gut microbiome and vulnerability of the next generation to chronic diseases [15, 16], it is necessary to identify the nutritional factors affecting intestinal bacterial changes. Herein, we evaluated the population of dominant phylum in the gut of mothers in the first trimester of pregnancy. Moreover, maternal dietary glycemic index, load and total antioxidant capacity focusing on the trace elements with antioxidant effects were assessed. The effects of each dietary parameter were assessed on the gut phyla.

Materials and methods

Study participants and design

All procedure of the present study was performed according to the Helsinki guidelines and ethically approved by the ethics committee of Zanjan University of Medical Sciences under the code of IR.ZUMS.REC.1401.346. After explaining the aims of study, and collecting an informed sign, ninety women, aged 18–40 yrs. with a singleton baby, at the first trimester of pregnancy, living in Zanjan city were participated. Participants who consumed probiotic, prebiotic or symbiotic supplements or products, and antibiotics at the time of sampling or at least six months ago, subjects with any type of liver and kidney disorder, heart and immune system defect, chronic gastrointestinal diseases, preexisting diabetes type 1 or 2, cancer, thyroid and malabsorptive disorders were excluded from the study. Pregnant women with a previous history of GDM, pre-eclampsia, pregnancy induced hypertension, miscarriage, anomalies and diagnosis of glucose intolerance at the time of sampling were omitted. In total, from 300 selected mothers, 90 pregnant met the inclusion criteria. The demographic and anthropometric measures of the participants including education, age, height, pre-pregnancy weight, weight at the time of sampling, and the number of delivery were recorded. Weight was measured using a Seca scale, with minimal clothing and without shoes which was calibrated with a 1 kg weight before each measurement. Height was recorded using an inflexible meter, without shoes in a standing state, look forward. Then, the body mass index (BMI) was calculated by dividing the weight (kilograms) by the square of the height (in meters). The participants were requested to deliver their stool in the fasting state, tomorrow morning to the researcher. Stool samples were stored in a -80 °C refrigerator until the final analysis.

DNA extraction and polymerase chain reaction (PCR)

200 mg of each frozen stool sample was taken and placed in the vicinity of ASL lysing buffer. Then, it was placed in 95 °C for 5 min. Then, the bacterial DNA was extracted using a standard kit according to the instructions provided in its instruction (Qiagen Co., Germany). DNA quality and quantity were examined by running a small amount of the extracted DNA on an agarose gel and a Nano drop spectrophotometer, respectively. The extracted DNA was kept in -20 °C to final analysis. DNA Amplification of each phylum was assessed versus 16SrRNA, as a housekeeping gene, was done by quantitative-PCR method using universal bacterial primers as following (Table 1), and quantitative value was determined. All primers verified in the primer-BLAST database of the National Center for Biotechnology Information (NCBI).

ABI StepOne sequence detection system (Applied Biosystems, California, USA) was used for the real-time PCR. In a 20 µL micro tub, 10 µL of SYBR green master mix (Amplicon, Denmark), 4 µL of DNA template, and 0.5 µL of each forward and reverse primer, and 5 µL purified water free of DNA and RNA were added. 16SrRNA was used as the internal control. A blank (purified water free of DNA and RNA) was added in each run.

Table 1 Forward and reverse primers

Phylum	Forward (5 to 3)	Reverse (5 to 3)
Bacteroidetes	GGARCATGTGGTTTAATTCGATGAT	AGCTGACGACAA CCATGCAG
Firmicutes	GGAGYATGTGGTTTAATTCGAAGCA	AGCTGACGACAA CCATGCAC
Actinobacteria	TACGGCCGCAAGGCTA	TART-CCCCACCTTCCTC-CG
Proteobacteria	CATGACGTTACCCGCAGAAGAA	CTCTACGAGACTC AAGCTTGC
16SrRNA	AAACTCAAAKGAATTGACGG	CTCACRRCAC-GAGCTGAC

The cycle threshold (CT) values were normalized against the internal control (16SrRNA). The initial denaturation included one cycle: 95 °C for 10 min. The amplification profile included 40 three-step cycles, including denaturation, annealing, and extension steps: 95 °C for 30 s, 60 °C for 30 s and 72 °C for 30s. The final extension was provided in one cycle: 72 °C for 30 s. The results were generated and analyzed using the $2^{\wedge-\Delta\Delta Ct}$ method in which was computed as follows:

1. $\Delta CT = (CT_{\text{each bacterial phylum}} - CT_{16SrRNA})$.
2. $\Delta\Delta CT = (\Delta CT_{GDM}^{+} - CT_{GDM}^{-})$.
3. Fold change: $2^{\wedge-\Delta\Delta Ct}$.

Dietary intake, GI and GL calculation

Dietary intake was determined by a validated 168-item food frequency questionnaire [16] that contains everyday dietary intake during the past 12 months (number of daily, weekly, monthly and annual). Data were inserted into the N4 software and converted to gram per day. The nutrients, dietary GI, and dietary GL were energy-adjusted using the residuals method [17]. The calculation of dietary GI and GL has been described previously [18]. We used the published GI values collected in a database [19]. Dietary GI was calculated using the below formula;

$\sum$foods C × F × GI/$\sum$foods C × F, where C represents the grams of carbohydrate in a serving of food, F the frequency of food consumption, and GI the glycemic index using glucose as the reference.

Dietary GL was calculated as;

$\sum$foods C × F × GI/100 or equivalently the product of total carbohydrate and dietary GI expressed as a percentage.

Calculation of Dietary total antioxidant capacity

DAI was calculated based on six dietary antioxidants including vitamins A, C, E, zinc, manganese, and selenium. At the first, intake of each of the above six vitamins/minerals were adjusted to the energy intake and then compared to the daily recommended intake (RDI) for the first trimester of pregnancy [20]. Intake were coded as 0 and 1, if the intake was <2/3 and ≥2/3 of the RDI, respectively [21]. The summed DTAC ranged from 0 (poor quality) to 6 (high quality).

Sample size and statistical analysis

To determine the variations between the gut *Firmicutes* to *Bacteroidetes* ratio using the previous study [22], considering the power of 80% and 95% confidence level, ninety participants were counted. To analyze the data, SPSS software version 18 was used. Quantitative variables have been presented as the mean and standard deviations or errors. Qualitative variables have been described in the form of frequency (percentage). One-Way ANOVA test was used to compare variables among the assessed phylum and dietary indices. Effect of each dietary component on the gut phylum was assessed in a mixed- regression model.

Results

Mean age and BMI of participants were 29.8±4.8 yrs. and 25.7±2.9 kg/m^2. Dietary intake of participants has been described in Table 2. As shown 56%, 13.7%, and 31.3% of total calorie were provided from carbohydrates, proteins and fats, respectively. From total daily fat intake, 28.15%, 29.5%, and 19% were provided from saturated, mono- and poly-unsaturated fatty acids, respectively. Results are comparable with the recommended values in the pregnancy period. Participants had a diet with moderate levels of GI and GL. Other minerals were almost near to the recommended dietary allowance (RDA).

As shown in Fig. 1, *Proteobacteria* population was significantly higher in the gut of pregnant mothers than the other phylum ($p<0.001$). The *Firmicutes* and *Actinobacteria* were lower than the others ($p<0.001$ and $p<0.001$).

Among all participants, 42.2%, 23.3%, and 34.4% of mothers had low, moderate, and high dietary GI levels. However, 51.1%, 23.3%, and 25.6% of participants had low, moderate, and high dietary GL levels, respectively. Participants had moderate score in term of DTAC. A shown in Table 3, a significant difference has been shown in *Bacteroidetes* abundance among various levels of dietary GI ($p<0.001$). Participants with the highest dietary GI had lower *Bacteroidetes* in their gut compared to the lowest level ($p<0.001$). Moreover, *Actinobacteria* population was significantly lower in the gut of pregnant mothers who had the highest dietary GI compared to the lowest level ($p=0.04$).

As shown in Table 4, there was a significant difference among various levels of dietary GL ($p<0.001$). Participants in the lowest level of dietary GL had more *Bacteroidetes* in their gut than the highest level ($p<0.001$). *Proteobacteria* population was significantly different among various levels of dietary GL ($p=0.04$). *Proteobacteria* population was significantly higher in the gut of

Table 2 The mean of dietary intake of participants in the two studied groups

Variables	Means ± SD	RDA [15, 16]
Energy, kcal/day	3062.1 ± 997.8	Based on pre-pregnancy BMI
Carbohydrates, gr/day	437.2 ± 161.8	~ 50% of total calorie
Protein, gr/day	105.1 ± 36.4	60 g/day or 1.2–1.5 g/kg
Total fat, gr/day	106.9 ± 41.6	30–35% of total calorie
Saturated fatty acids, gr/day	30.1 ± 10.6	7% of total fat
Trans-fatty acids, gr/day	0.056 ± 0.52	Near to zero
Mono-unsaturated fatty acids, gr/day	31.6 ± 9.6	Up to 20% of total fat
Poly-unsaturated fatty acids, gr/day	20.4 ± 7.7	Up to 10% of total fat
Total Fiber, gr/day	69 ± 34.6	6 g/1000 kcal
Cholesterol, mg/day	271.9 ± 103.8	250–300 mg/day
Vitamin A, µg/day	734.8 ± 442.6	770 µg/day
Vitamin E, mg/day	14.1 ± 5.1	15 mg/day
Vitamin C, mg/day	174.9 ± 16.1	85 mg/day
Zinc, mg/day	14.7 ± 5.1	11 mg/day
Selenium, µg/day	115.9 ± 51.6	60 µ/day
Manganese, mg/day	64 ± 2.5	360 mg/day
Dietary total antioxidant capacity	3.59 ± 0.7	Low quality: 1–2 Medium quality: 3–4 High quality: 5–6
Glycemic index	60.7 ± 28.9	Low: <55 Moderate: 56–69 High: ≥70
Glycemic load	14.3 ± 10.1	Low: <10 Moderate: 11–19 High: ≥20

RDA: recommended dietary allowance

mothers with moderate dietary GL than the lowest level ($p=0.03$).

As shown in Table 5, there was no significant difference among various levels of DTAC in the assessed phylum. The most of participants were in the moderate level of DTAC.

Adjusted for all parameters, dietary selenium showed a significant negative and positive effects on *Firmicutes* (OR= -0.27, 95% CI= -0.001, -0.004; $p=0.04$), and *Actinobacteria* (OR=0.46, 95% CI=0.07, 0.51; $p=0.01$) abundance in the gut. Moreover, selenium intake negatively affected the *Proteobacteria* abundance in the gut of mothers at the first trimester of pregnancy (OR= -0.74, 95%CI= -0.02, -0.01; $p=0.04$). Dietary manganese showed a negative effect on the *Firmicutes* population (OR= -0.67, -0.07, -0.01; $p=0.003$). Dietary zinc showed a negative effect on the *Firmicutes* and *Proteobacteria* population (OR= -0.24, 95%CI= -0.024, -0.002; $p=0.01$ and OR= -0.3, 95%CI= -0.18,-8.8; $p=0.04$), respectively. Vitamin E showed a negative effect on *Proteobacteria* abundance in the gut (OR= -0.4, 95%CI= -0.22, -0.006; $p=0.03$).

Discussion

The most abundant bacterial phylum in the gut of pregnant women in the first trimester was *Proteobacteria*. A maternal diet with high levels of GI and GL showed a significant association with the gut dysbiosis in the first trimester of pregnancy. Increase in dietary GI, and GL were associated with lower *Bacteroidetes* population in the gut. Moreover, higher dietary GI was associated with lower *Actinobacteria* population in the gut. Mothers with higher dietary GL had more *Proteobacteria* in their gut. None of the assessed phylum showed statistically significant difference in various levels of DTAC because more participants had a diet with moderate levels of antioxidant capacity. However, dietary antioxidant components showed a significant effect on the maternal gut phylum. Dietary selenium and zinc showed a significant negative effect on *Firmicutes* population in the maternal gut. Moreover, dietary selenium positively affected the *Actinobacteria* and negatively affected *Proteobacteria* population in the maternal gut. Dietary manganese and vitamin E negatively affected the *Firmicutes* and *Proteobacteria* abundance in the maternal gut, respectively. A diet rich of selenium, zinc, and manganese put created a eubiosis state in the maternal gut at the first trimester of pregnancy. The intra-uterine period plays an important role on health status and quality of life in future [15]. Maternal dietary pattern, quality and quantity of nutrients effect on neonatal health through change in bacterial community in the gut. The bacterial community effect on maturation of immune and nervous systems [16]. Since maternal dietary components are potential modulators of the maternal-fetal microbiota axis, the impact of diets with high GI, and GL, and nutritional components with antioxidant capacity assessed on the maternal gut phylum during the first trimester of pregnancy. Effects of maternal body composition and diet on fetal programming have been presented in the previous animal-model studies [15, 23, 24]. Dietary micronutrients, regardless of the dietary pattern, alone have been effective in the occurrence of some disorders [25, 26]. However, the association between dietary components, especially vitamins and minerals with antioxidant capacity is not studied on the maternal gut phylum in the pregnancy period. High dietary GI and GL result in the gut dysbiosis by producing the reactive oxygen species and creating oxidative stress [27]. The maternal gut bacterial population plays a critical role in fetal and early postnatal development, shaping fundamental processes such as the immune maturation and brain development. The dietary choices significantly shape this abundance, which diets with high amounts of fats and carbohydrates promote the growth of pathogenic bacteria while reduce the beneficial flora, however limited reviews have been published in this field up to now [28, 29]. Recently, the gut bacteria population

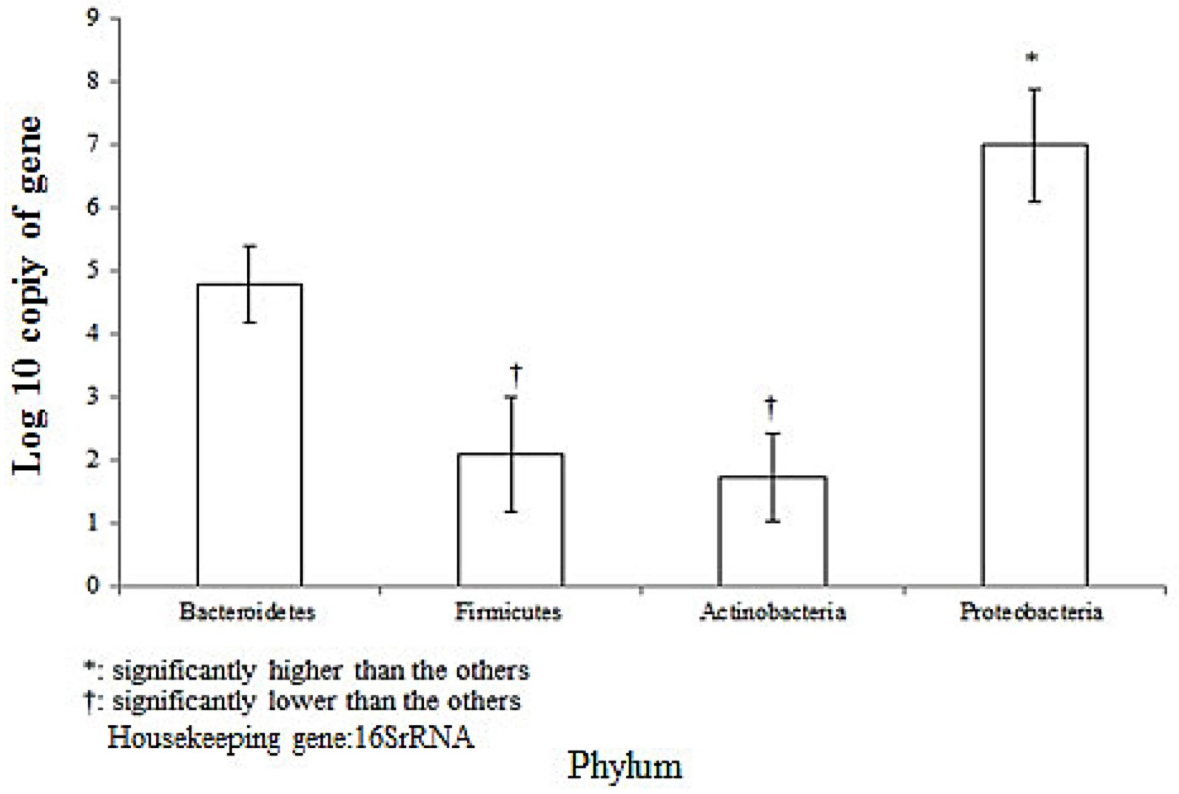

Fig. 1 The main dominant phylum assessed in the gut of mothers at the first trimester of pregnancy

Table 3 Mean population of the gut phylum among various levels of dietary glycemic index

Phylum	GI level	Number	Means ± SE	*p* value†
Bacteroidetes	1	38	5.93 ± 0.43	**< 0.001**
	2	21	5.6 ± 0.99	
	3	31	2.7 ± 0.58	
Firmicutes	1	38	2.2 ± 0.37	0.72
	2	21	2.2 ± 0.29	
	3	31	1.8 ± 0.28	
Actinobacteria	1	38	2.2 ± 0.3	**0.04**
	2	21	1.7 ± 0.4	
	3	31	1.1 ± 0.23	
Proteobacteria	1	38	5.2 ± 1.1	0.17
	2	21	9.3 ± 2.3	
	3	31	7.6 ± 1.5	

†Analyzed by one–way ANOVA test, followed by post–hoc Tukey test; GI: glycemic index; The GI has been categorized as low GI is 55, moderate GI is between 56–69 and high GI is > or = 70

Table 4 Mean population of the gut phylum among various levels of dietary glycemic load

Phylum	GL level	Number	Means ± SE	*p* value†
Bacteroidetes	1	46	6.1 ± 0.4	**< 0.001**
	2	21	4.3 ± 1.1	
	3	23	2.4 ± 0.6	
Firmicutes	1	46	2.3 ± 0.32	0.61
	2	21	1.95 ± 0.32	
	3	23	1.8 ± 0.34	
Actinobacteria	1	46	2.07 ± 0.27	0.09
	2	21	1.6 ± 0.43	
	3	23	1.1 ± 0.22	
Proteobacteria	1	46	5.2 ± 1.04	**0.04**
	2	21	10.6 ± 2.1	
	3	23	7.2 ± 1.9	

†Analyzed by one–way ANOVA test, followed by post–hoc Tukey test; GL: glycemic load; The GL has been categorized as low GL is <10, moderate GI is between 11–19 and high GI is > or = 20

has been proposed as the main regulator of metabolism and insulin signaling which are under the control of dietary GI [30, 31]. In a recent study the effect of high dietary GI was assessed on oral microbiome. Results showed an increase in alpha-diversity of oral microbiome in participants with high carbohydrate intake. Higher carbohydrate intake was associated with increase in *Fusobacteria* and decrease in *Actinomyces* population belongs to *Actinobacteria* phylum, as the beneficial gut flora. Higher dietary GI was significantly associated with more abundance of *Gemella* belong to *Firmicutes* phylum [32]. Our results are in accordance with the mentioned study that women with higher levels of dietary GI had lower *Actinobacteria* population in their gut. However, the mentioned study assessed oral microbiome that is different with us in samples. Moreover, we analyzed the association between dietary GL with the gut phylum and showed that a greater dietary GL was associated with

Table 5 Mean population of the gut phylum among various levels of DTAC

Phylum	DTAC level	Number	Means ± SE	*p* value†
Bacteroidetes	1	3	2.3 ± 1.6	0.46
	2	79	4.88 ± 0.39	
	3	8	4.7 ± 1.7	
Firmicutes	1	3	1.9 ± 1.6	0.92
	2	79	2.1 ± 0.2	
	3	8	1.83 ± 0.63	
Actinobacteria	1	3	1.4 ± 0.79	0.33
	2	79	1.82 ± 0.19	
	3	8	0.87 ± 0.53	
Proteobacteria	1	3	7.6 ± 5.4	0.96
	2	79	7.04 ± 0.97	
	3	8	6.2 ± 2.2	

†Analyzed by one–way ANOVA test, followed by post–hoc Tukey test; DTAC: dietary antioxidant capacity; The DTAC has been categorized as low: 1–2, moderate 3–4 and high 5–6

higher abundance of *Proteobacteria* in the gut, as the pathogenic flora. It is interesting that DTAC showed no significant effect on any bacterial phyla however, its components including selenium, manganese, zinc, and vitamin E have been associated with increase in beneficial flora however, they were correlated with low pathogenic bacteria. One study reported that selenium can decrease potential pathogens under oxidative stress conditions, and promote the growth of gut beneficial bacteria [33]. In the present study, a diet with high level of GI and GL were associated with the gut dysbiosis, may be due to the oxidative stress which may be improved by dietary selenium. Previous studies reported the beneficial effects of zinc and selenium supplementation on oxidative stress and inflammatory pathways which were associated with regression of some disorders [34, 35]. However there is no study on the effect of dietary selenium and zinc intake on the gut bacterial phyla during the pregnancy. The *Bacteroidetes* and *Firmicutes* have been introduced as the dominant phylum in all individuals [36]. However in the present study, the *Proteobacteria*, as the pathogenic phylum, was dominated in the gut of mothers at the first trimester of pregnancy. This means that the gestational period is accompanied by a dysbiosis state that is intensifies with an inappropriate dietary intake. Manganese, zinc, and selenium act as critical cofactors for some bacterial enzymes responsible for DNA replication and transcription, antioxidant action, and cellular respiration [37]. *Escherichia coli*, belong to the *Proteobacteria* phyla, has three selenoprotein in its structure that need selenium for normal metabolism [38]. In our study, higher selenium intake was associated with lower *Proteobacteria* population in the gut of pregnant mothers. In a recent study, selenium supplementation significantly decreased the level of pathogenic and increased the abundance of beneficial bacteria which have protective effects against colitis, and intestinal barrier dysfunction [39]. In a study which was conducted on school-aged children, *Coprobacter* and *Paraprevotella* belong to *Bacteroidetes*, *Acetivibrio* and *Clostridium_XI* belong to *Firmicutes* phyla were significantly higher in the gut of participants with zinc deficiency [40]. In our study, dietary zinc showed a negative effect on *Firmicutes* and *Proteobacteria* population which is similar in term of *Firmicutes* with the mentioned study. Based on our precise literature review, no study was found about the association between dietary manganese intake and the gut bacterial phylum to compare with our results. We concluded that manganese has a negative effect on the gut *Firmicutes* abundance. In a human pilot study, vitamin E supplementation, as the strongest fat-soluble antioxidant, increased *Firmicutes* and *Actinobacteria* population but decreased *Bacteroidetes* population through increasing in production of SCFAs in the gut [41]. Dietary vitamin E has been associated with lower *Proteobacteria* in the gut of pregnant mothers at the first trimester in the present study. Similar to other studies, there are some advantages and limitations. This was the first analytical cross-sectional study on the gut population of phylum in Iranian pregnant at the first trimester considering dietary intake and its association with the abundance of phylum. The sample size was enough with a good power. The present study cannot determine a causal-relationship due to the cross-sectional design. Results are not generalizable to other countries due to the effect of genetic, geographical area and dietary pattern all over the world. Following the pregnant to the second or third trimesters are encouraged to determine the occurrence of metabolic disorders including glucose intolerance, pre-eclampsia, etc. Moreover, infants must be followed to assess the gut bacterial phylum and their association with maternal gut phylum. Evaluating the maternal gut phylum in the species level is more applicable than the phylum, alone. Following the pregnant in each trimester can determine microbiome alterations during this period.

Conclusion

The present study showed that Iranian pregnant have more *Proteobacteria*, as the pathogenic phylum, in the gut which may be associated with their dietary intake. A diet with high levels of GI and GL were associated with more pathogenic bacteria and less beneficial flora in the gut of mothers at the first trimester of pregnancy. Zinc, selenium, manganese and vitamin E were associated with eubiosis. These notions must be educated to pregnant, even before the beginning of this period because these alterations are transmitted to the next generation. Moreover, these changes are related to a healthy pregnancy period to born a well-baby.

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Author contributions
SN.M supervised the study. SN.M and H.Ch conceived and designed the study. N.M collected the data. S.H has been done the laboratory tests. SN.M analyzed the data, interpreted the data and wrote the draft. All the authors approved the final version of the manuscript and critically revised it.

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Data availability
All the data relevant to the manuscript are reported in tables. The raw data can be accessed from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
All methods of the present study were carried out in accordance with Declaration of Helsinki guidelines. Ethic committee of Zanjan University of Medical Sciences ethically approved this project under the code of IR.ZUMS.REC.1401.346. The informed written/verbal consent was obtained from all subjects and/or their legal guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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