

## Relation between total Iron intake and gestational diabetes: a cohort study

Seyed Abdolvahab Taghavi<sup>1</sup> Najmeh Tehranian<sup>2</sup> Reza Jamhiri<sup>3</sup> Shahintaj Aramesh<sup>4</sup> Mina Mosadegh<sup>5</sup> Zahra Rezaee<sup>5</sup> Hedyeh Bahraini<sup>5</sup> Nasibeh Rozbeh<sup>6</sup> Fatemeh Bazarganipour<sup>6</sup>

<sup>1</sup> Fertility and Infertility Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

<sup>2</sup> Department of Reproductive Health and Midwifery, Tarbiat Modares University, Tehran, Iran.

<sup>3</sup> Department of Nursing, Faculty of Nursing and Midwifery, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

<sup>4</sup> Department of Gynecology and Obstetrics, Faculty of Medicine, Yasuj University of Medical Sciences, Yasuj, Iran.

<sup>5</sup> Student Research Committee, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

<sup>6</sup> Mother and Child Welfare Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

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### Original Article

### Abstract

**Introduction:** Gestational diabetes is a common problem in pregnancy that affects about 7% of pregnancies. The high intake of iron intake is associated with an increased risk of type 2 diabetes in the general population. The purpose of this study was to determine the association between total iron intake (diet and supplement) and gestational diabetes.

**Methods:** This is a one-year prospective cohort study. 120 pregnant women referred to rural health centers in Bandar Abbas, Hormozgan, Iran were enrolled in the study. The data were collected using a checklist, food frequency questionnaire (FFQ) questionnaire for measurement of iron intake through food. Demographic data was presented as mean±SD or number (%) and final results were presented with Odds Ratio (OR) with 95% confidence interval.

**Results:** The findings showed that hemoglobin level in 6-10 (OR: 2.62 CI: 1.42-4.39) and 24 to 28 weeks (OR: 2.9 CI: 1.43-4.02), the amount of iron intake from the beginning of the pregnancy from 6 to 10 (OR: 2.81 CI: 1.28-3.98) and 16-20 weeks of pregnancy (OR: 2.94 CI: 1.35-5.43) as well as, the amount of iron supplemental ingestion (OR: 2.83 CI: 1.39-4.54) are the most important predictors of GDM.

**Conclusion:** According to the findings of this study and the current national guidelines for the administration of routine iron to all pregnant women, increasing the level of iron by supplement and subsequent increased risk of GDM should be more considered.

**Key words:** Hemoglobin, Iron, Gestational diabetes, Cohort

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### Introduction:

Gestational diabetes mellitus (GDM), which is defined as glucose intolerance in the onset or early diagnosis of pregnancy (1). A common pregnancy problem that affects about 7% of pregnancies (2).

Over the past 20 years, its prevalence has increased significantly throughout the world, and it is expected to increase as obesity increases (3,4).

GDM has a significant impact on maternal and neonatal outcomes during pregnancy - childbirth and beyond that. Progression to type 2 diabetes is

possible in over 50% of women with GDM during 5 to 10 years after pregnancy (5). Children born from mothers with GDM are also at high risk for obesity and early onset of type 2 diabetes (6). Also, girls of GDM mothers are at increased risk of developing GDM in the future. This leads to a defective cycle in the development of diabetes (4,7).

Therefore, identifying the corrected risk factors can lead to strategies and prevention programs.

Iron is considered as a double-edged sword for human (8). Iron is a basic micronutrient that plays a vital role in oxygen transfer, electron transfer, gene expression, growth, and differentiation (9). Iron deficiency is the most common food shortage in the world (9). Also, the increase in iron is potentially harmful and leads to oxidative stress because of its pro-oxidative properties (10). Pancreatic B cells are susceptible to oxidative stress because their antioxidant defense mechanisms are very weak (11).

Previous studies have shown that high levels of iron administration lead to diabetes in animals. Also, iron restriction of diet can be countered by the spread of diabetes (12). Excessive iron intake is associated with increased risk of type 2 diabetes in the general population (13-16). According to previous studies, most studies have been conducted in the Jewish population, and there is a need for more information from other races and countries. In Iran, there is only one study in this field that merely examines the relationship between iron parameters and GDM. The results of previous study has shown that ferritin concentration, serum iron, transferrin saturation, hemoglobin concentration in the gestational diabetes group were significantly higher than the control group (17). On the one hand, according to the instructions of the Iranian Ministry of Health and Medical Education, iron tablets routinely prescribed to all pregnant women, on the other hand iron supplements are required high cost and sometimes it is associated with gastrointestinal complications including abdominal cramps, nausea, diarrhea, and heart burn. Therefore the aim of this study is to assess the relationship between the total intake of iron (from food and supplements) and GDM.

## Methods:

The present study was conducted as a one-year-old prospective cohort in the year 2014-16. All pregnant women who referred to rural health centers of Bandar Abbas, Iran included in this study for one year. The inclusion criteria were the desire to participate in the study, gestational age less than 10 weeks, ages 15 to 40 years, Iranian, the absence of underlying disease (diabetes, high blood pressure, known anemia, and other diseases requiring a diet Specific), non-consumption of coffee, cigarettes, alcohol, drugs, married, first pregnancy, single pregnancy. Exclusion criteria were the unwillingness of the study unit during sampling.

Data collection was done by a questionnaire. After the introduction and disclosure of research goals and remembering confidentiality of data, the signed consent form of pregnant women were obtained before the completion of the questionnaire. The questionnaire was completed by trained experts. All eligible pregnant women were included in the study by easy sampling. The referral intervals were according to the national guidelines (6 to 10 weeks, 16 to 20 weeks, and 26 to 30 weeks).

### Data Collection Tool

1. Checklist: it was included basic information such as age, education level of women and their husbands.
2. Socio economic status: the formal education of women was considered as an indicator of social status (18).
3. BMI: weight in kilograms was divided by the square of height in meters and calculated for all subjects.
4. Food frequency questionnaire: dietary intake was measured using a modified food frequency questionnaire (FFQ) based on Iranian dietary questionnaire which contains 168 items. The reliability and validity of the questionnaire are approved in Iran (19). FFQ included a list of foods with a standard size of a food. Subjects were asked to report the frequency of consumption of each food during the past month on a daily, weekly or monthly basis. The amount of nutritional item consumed was converted to grams using household scales. This dietary information was analyzed using

the software Nutrition4 which calculated the amount of energy, macronutrients (carbohydrates, lipid, and protein) and micronutrients (at least 30 micronutrients) including fat soluble vitamins, water soluble vitamins and minerals (20,21).

For each woman, two FFQ questionnaires (6 to 10 weeks and the beginning of the second trimester 16-20 weeks) were completed. It should be noted that in all of the study units, a routine 400 µg folic acid pill and iron pill (depending on HB) were administered routinely from 16 weeks to the end of pregnancy in accordance with the national guidelines. In order to calculate the intake dose through iron supplementation, the amount of iron was multiplied by iron supplement. Intake iron by supplementation was added to dietary iron for total iron measurement.

Diagnosis of diabetes was based on the national guidelines, all women aged 24 to 28 weeks underwent OGTT screening for 75g glucose. 75g glucose anhydride was dissolved in 300mg of water and was fed in 5 minutes. The test was considered positive if fasting sugar was more than 92 and one hour more than 180 and two hours sugar more than 153. Sampling was carried out early in the morning and after at least 8 hours of fasting.

#### Data analysis

Demographic data is presented as mean±SD or number (percent). Multivariable logistic regression was used where the response was binary and explanatory two or more i.e. continuous and categorical or ranked. Univariate and stepwise

multiple logistic regression analysis were used to evaluate risk factors associated with gestational diabetes. The analysis of risk factors was concluded in two steps. All the socioeconomic and characteristics of patients presented in Table 1,2,3 were tested one by one in separate, univariate analysis. Secondly, all statistically significant variables in the univariate analysis were tested using multivariable logistic regression analysis. Significant variables were entered in a stepwise manner. Results from the final model are presented as odd ratio with 95% confidence interval. The significance level was 0.05.

#### Ethical considerations

The Ethics Committee of Hormozgan University of Medical Sciences approved the study. After presenting the research objectives, eligible individuals signed the consent form. They were asked to complete the relevant questionnaires.

#### Results:

Over a one-year period, 120 patients were enrolled in the study. The social, economic, clinical, and reproductive features of the study units are listed in Table 1-3.

The incidence of gestational diabetes in participants was 9 (7%). There was no significant difference between the socio-economic characteristics of the study units in the women with GDM and without GDM.

**Table 1. Basic and demographic characteristics of participants**

Variable	Diabetic	Non-diabetic	P-value	
Age	24.55±5.92	24.25±7.27	0.86	
Age of husband	28.35±6.78	24.16±7.86	0.74	
Education	8.63±4.43	8.25±4.02	0.77	
BMI	22.73±5.63	21.57±5.33	0.47	
BP baseline	Systole	79.07±4.93	75.83±6.4	0.82
	Diastole	51.01±7.65	59.16±8.63	0.78
BP 6-10 weeks	Systole	80.64±2.53	99.16±9.01	0.13
	Diastole	59.16±0.65	51.01±0.65	0.31
BP 16-20 weeks	Systole	78.79±2.98	92.45±8.13	0.28
	Diastole	49.16±7.33	60±20.06	0.17
BP 26-30 weeks	Systole	93.33±0.25	10.84±0.83	0.17
	Diastole	74.38±0.83	76.78±0.2	0.44

**Table 2. Biochemical test of participants**

Variable	Diabetic	Non-diabetic	P-value
FBS first trimester	68.87±33.16	67.53±52.62	0.89
HB first trimester	11.05±3.63	10.11±5.71	0.05
HCT first trimester	32.62±10.70	27.30±16.71	0.28
HB 24-28 week	13.28±7.29	10.91±5.18	0.001
HCT	43.79±0.16	31.76±6.81	0.05
FBS 24-28 week	83.91±8.32	77.93±9.29	<0.001
OGTT: 24-28 week	189.75±7.97	133.03±0.64	<0.001
OGTT: 24-28 week	172.58±2.96	140.13±0.57	<0.001
OGTT: 24-28 week	82.91±4.71	52.62±0.96	<0.001

**Table 3. Iron level of participants**

Variable	Diabetic	Non-diabetic	P-value
Iron from food 6-10 weeks	61.83±0.33	55±0.32	0.05
Iron from food 16-20 weeks	68.94±0.42	53.9±0.19	0.05
Supplementary iron 16-20 weeks	61.83±0.33	55±0.33	0.05
Total iron 16-20 weeks	569.68±61.89	447.31±36.25	0.04

The findings of this study showed that patients with GDM had higher levels of hemoglobin for weeks 6-10 and 24-28, higher dietary iron from 6-10 weeks and 16-20 weeks, and they were received more iron from supplementation than non-GDM women ( $P < 0.05$ ).

### Predictive factors affect GDM

After evaluating social, economic and clinical variables using univariable analysis, the remaining significant variables were entered into the logistic regression. Logistic regression results showed that hemoglobin level in 6-10 weeks ( $OR=2.62$ ), and 24-28 weeks ( $OR=2.9$ ), dietary iron intake in the beginning of pregnancy 6 to 10 weeks ( $OR=2.81$ ) and 16-20 weeks ( $OR=2.94$ ), the amount of intake iron from supplementation ( $s=2.83$ ) is the most important predictor of GDM. It should be noted that BMI and maternal age were studied as confounder

### Conclusion:

According to our knowledge, the present study is the first study on the relationship between intake iron and GDM in Iran. The results of this study showed that there was a significant positive correlation between total iron intake, dietary and iron supplementation in the first and second trimester, as well as our study has shown that the level of HB in the first and second trimester of

pregnancy was correlated to gestational diabetes. This correlation remained even after the adjustment of other confounders.

The increasing evidence suggests that the most important deficiency in the pathogenesis of GDM is the reduction of insulin secretion along with insulin resistance during pregnancy (21). Receiving higher total iron, dietary iron and iron supplementation significantly increase the iron content (22-24). Iron is a potent pro-oxidant that results in oxidative stress (25). Several mechanisms have been proposed in this regard. Increasing Iron can attack to pancreatic B cells through increased oxidative stress, which is leading to cell-apoptosis and reduce glucose-induced insulin secretion (25). Increasing iron also interacts with glucose in muscle tissue which is leading to a shift from glucose oxidation to fatty acids and reducing glucose transfer in adipose tissue (26). Finally this may damage insulin function and increase insulin resistance.

Previous studies on the relationship between iron status in pregnancy and the risk of GDM are few and contradictory. Some studies have shown that there was a positive and significant correlation between serum iron level and risk of GDM, while another study has shown an inverse correlation. A study from Turkey has shown that there is no correlation between the level of ferritin, Hb concentration, and the risk of GDM (27-31).

Some animal studies have shown that the administration of additional iron may create diabetic

animal model (32). Also, dietary iron restriction can prevent progression of diabetes in animal models. Iron supplementation administration in mothers with adequate iron exacerbates free radicals and causes to the lipid membrane damage and delayed cell growth and carcinogenesis (33).

On the other hand, previous studies have shown that women who intake iron supplementation had more dietary iron than they receive no iron supplementation. About 7% of these consumers are receiving more than the recommended dose of iron (45mg total Fe/d) (34).

Although today, few guidelines such as the American Congress on Obstetrics and Gynecology (ACOG), recommend screening and treating iron deficiency in pregnancy but other organizations including WHO and centers for disease control and prevention are recommend the routine supplement therapy in pregnancy (35).

Therefore, with regard to the above mentioned, the risks of increasing the body's iron in pregnant women by iron supplements should be given more attention. Although iron administration can improve the outcomes of pregnancy in women with iron deficiency anemia, it can increase the risk of pregnancy complications such as gestational diabetes but when the maternal reserves are normal increased iron stores can increase oxidative stress and produce free radicals during pregnancy then leads to diabetes. Although the present study has several strengths, there are some limitations. Due to the observational nature of our study, we cannot evaluate the likelihood of uncertain and unmeasured confounders. Iron absorption may also be influenced by lifestyle variables that increase the risk of GDM, although we have been attempted to control the major variables such as mother' age and BMI.

According to the findings of this study and the current national guidelines for the administration of routine iron to all pregnant women, increasing the level of iron by supplement and subsequent increased risk of GDM should be more considered.

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