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Vitamin D deficiency in women with gestational diabetes mellitus

ABSTRACT

Background. The relationships between vitamin D [25(OH)D] deficiency and gestational diabetes mellitus (GDM) are under investigation. We wanted to assess the relationships between maternal 25(OH)D concentration and metabolic indicators, and blood pressure in women with GDM.

Methods. Prospective study was conducted in northern Poland between September 2012 and February 2013. GDM was diagnosed by 75 g OGTT between 20––29 weeks of pregnancy. Pre-gestational BMI were calculated, weight gain during pregnancy and blood pressure were collected. Fasting glucose, insulin, lipids, 25(OH)D were assessed. HOMA-IR was used to estimate insulin resistance, defined as > 2.5. The women were divided into group A with 25(OH)D deficiency (≤ 20 ng/mL) and group B with 25(OH)D > 20 ng/mL. Statistical analysis was performed.

Results. We analyzed 56 pregnant women with GDM, mean age 30.3 ± 5.1. 25(OH)D deficiency was found in 25 women (44.6%) with its concentration 13.8 ± 3.9 ng/mL. In the group B, the mean 25(OH)D concentration was 30.6 ± 9.3 ng/mL. 25(OH)D deficiency was associated with higher systolic blood pressure (p = = 0.03), insulin resistance (p = 0.38) and with the third and subsequent pregnancies (p = 0.047). 25(OH)D concentration was 22.8 ± 2.0 ng/mL in the first and second pregnancies, comparing to 14.3 ± 3.9 ng/mL in the third and subsequent pregnancies. There was no correlation between 25(OH)D and other parameters.

Conclusions. 1. Low 25(OH)D concentration in the analyzed group of women with GDM was significantly correlated with increased insulin resistance and systolic blood pressure. 2. In multipara the incidence of 25(OH)D deficiency was higher. 3. The results imply necessity of focusing on guidelines implementation for 25(OH)D supplementation for women in childbearing age. (Clin Diabet 2016; 5, 2: 57–61)

Key words: diabetes, gestational, vitamin D, insulin resistance, blood pressure

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Introduction

The relationships between 25 hydroxyvitamin D [25(OH)D] deficiency and occurrence of insulin resistance (IR), and gestational diabetes mellitus (GDM) are not entirely clear. However, several reports have been published drawing attention to the coincidence between a low level of 25 (OH)D and presence of GDM [1–5].

The influence of vitamin D supply to whole human populations gains importance among women in the childbearing age range, including pregnant ones. The main sources of cholecalciferol for the human body are animal food and cutaneous synthesis induced by ultraviolet solar radiation. The food products which provide us with the highest amounts of vitamin D_3 are liver and animal oils, especially fish oil. In some countries, vitamin D is added to such food products as margarine, milk or breakfast cereals [6]. In Poland, manufacturers are legally obliged to fortify margarine, mixture of butter and oil and fat spreads with vitamin D [7].

Detection of the presence of a nuclear receptor for vitamin D and vitamin D activating 1-alpha-hydroxylase in the placenta and decidua supports potential importance of vitamin D during pregnancy. It appears that pregnancy itself does not create a much higher demand

for vitamin D. Another interesting fact is that changes in the calcium metabolism during the gestational period do not depend on vitamin D [8]. On the other hand, research reports have been published which do not show any relationship between the 25(OH)D concentration determined in the second term of pregnancy and GDM [9]. However until now, the association between the role of the vitamin D supply and insulin resistance, GDM and the development of the foetus has not been unequivocally explained. This shows that the problem needs further observations and investigations.

The aim of our study was to evaluate the relationships between 25(OH)D concentration and metabolic indicators, IR and blood pressure in women with GDM.

Material and methods

The study was conducted among women residing in the Province of Varmia and Masuria, in the North of Poland, with GDM diagnosed based on the 75 g oral glucose tolerance test (OGTT) according the WHO criteria, performed between the 20th and 29th week of pregnancy, between September 2012 and February 2013, excluding women with multiple pregnancies. After the diagnosis of GDM the pre-gestational body mass index (BMI) was calculated, weight gain during pregnancy and blood pressure were collected. Fasting plasma glucose, insulin, lipids were assessed using Roche cobas system. IR was assessed using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) > 2.5, derived from the formula: HOMA-IR (mmol/L × μU/mL) = FG (mmol/L)*fasting insulin (μU/mL)/ 22.5. We measured 25(OH)D levels, a combination of 25(OH)D_2 and 25(OH)D_3 in maternal plasma samples which were obtained fasting during the initial visit. We measured 25(OH)D concentration with an automated electrochemillumiscence method. Based on the concentration of 25(OH)D, two groups of women were distinguished: group A with 25(OH)D deficit ≤ 20 ng/mL, and group B with the concentration of 25(OH)D > 20 ng/mL (serum vitamin D deficiency is generally considered to reflect a plasma 25(HO)D concentration < 20 ng/mL) [10].

The results were analysed by statistical software Statistica 6.0 using Mann-Whitney U test and Student's t-test. The differences were considered significant at $p \leq 0.05$.

The research was approved by the bioethics committee.

Results

The study involved 56 women with GDM, with mean age 30.3 ± 5.1; 29 (51.8%) were primagravidae; 78.6% lived in towns. GDM during previous pregnancy was recorded in 6 women (10.7%). Family history concerning diabetes was found in 25 women (44.6%). The pre-gestational BMI for the whole analysed group was 24.2 ± 4.6 kg/m^2, while the average body gain during the current pregnancy before the diagnosis of GDM, was 6.8 ± 3.8 kg (Tab. 1).

Table 1. Characteristics of study population

The group of women with GDM	N = 56
Age (years)	30.3 ± 5.1
Place of residence:	
Town n (%)	44 (78.6)
Village n (%)	12 (21.4)
Primagravidae n (%)	29 (51.8)
BMI before pregnancy [kg/m^2]	24.2 ± 4.6
Body gain during pregnancy [kg]	6.8 ± 3.8
GDM in previous pregnancies n (%)	6 (10.7)
Family history regarding diabetes n (%)	25 (44.6)

BMI — body mass index; GDM — gestational diabetes mellitus

Table 2 shows that women with the pre-gestational BMI > 25 kg/m^2 were characterized by significantly higher values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) and higher levels of triglycerides, 2-h glucose concentration during OGTT and fasting insulin. Also, HOMA-IR was significantly higher in women with pregestational overweight and obesity comparing to women with normal body weight before pregnancy (3.1 ± 1.7 vs. 1.7 ± 0.9, $p < 0.01$).

Table 3 presents the differences in anthropometric and metabolic parameters between groups A and B. 25(OH)D deficiency (group A) was determined in 44.6% of women, with the average concentration of 13.8 ± ± 3.9 ng/mL; in group B the average concentration of 25(OH)D was 30.6 ± 9.3 ng/mL. Women in the group A were characterized by significantly higher values of SBP comparing to women in the group B, respectively 123.1 ± 10.4 mm Hg and 116.5 ± 11.9 mm Hg, $p = 0.03$. Women with 25(OH)D deficiency were characterized by a significantly higher IR estimated by HOMA-IR, $p = 0.38$.

Significantly lower 25 (OH)D concentration in multiparous women comparing to the ones in their first or second pregnancy, $p = 0.047$ (Fig. 1).

Discussion

The data concerning the relationships between 25(OH)D concentration and IR and GDM are inconclusive. They are characterized by various limitations connected with different populations, factors influencing insulin sensitivity, different assays used in studies, and

Table 2. Metabolic parameters of study group according to pre-gestational BMI

Parameters	BMI before gestation > 25 kg/m^2	BMI before gestation ≤ 25 kg/m^2	p value
Age (years)	31.3 ± 4.5	30.0 ± 5.4	0.33
25(OH)D [ng/mL]	22.4 ± 11.9	21.9 ± 7.9	0.88
Body gain during pregnancy [kg]	5.7 ± 4.7	8.1 ± 3.7	0.03
Systolic blood pressure [mm Hg]	128.1 ± 11.1	115.7 ± 9.4	< 0.01
Diastolic blood pressure [mm Hg]	72.9 ± 6.7	67.5 ± 5.9	< 0.01
Cholesterol [mg/dL]	273.1 ± 54.8	269.8 ± 51.1	0.91
HDL-cholesterol [mg/dL]	75.1 ± 13.3	79.0 ± 14.9	0.32
LDL-cholesterol [mg/dL]	154.8 ± 42.4	155.0 ± 47.1	0.99
Triglycerides [mg/dL]	216.5 ± 74.7	179.4 ± 60.2	0.03
Fasting glucose [mg/dL]	83.9 ± 6.4	83.0 ± 10.6	0.67
2-h glucose [mg/dL]	160.3 ± 14.0	152.2 ± 15.3	0.04
Fasting insulin [μU/mL]	14.4 ± 6.8	8.7 ± 4.6	< 0.01
HOMA-IR	3.1 ± 1.7	1.7 ± 0.9	< 0.01

BMI — body mass index; HDL — high-density lipoprotein; LDL — low-density lipoprotein; HOMA-IR — Homeostasis Model Assessment of Insulin Resistance

Table 3. Characteristics of the group of women with GDM depending on 25(OH)D concentrations. Group A with mean concentration 13.8 ± 3.9 ng/mL. Group B with mean concentration 30.6 ± 9.3 ng/mL

Parameters	Group A	Group B	p value
Age (year)	29.5 ± 5.7	30.8 ± 4.2	0.31
Pre-gestational body weight [kg]	66.5 ± 12.5	65.1 ± 15.2	0.68
Pre-gestational BMI [kg/m^2]	24.5 ± 4.7	23.8 ± 5.2	0.57
Weight gain during pregnancy [kg]	7.6 ± 4.1	6.9 ± 4.4	0.56
Systolic blood pressure [mm Hg)	123.1 ± 10.4	116.5 ± 11.9	0.03
Diastolic blood pressure [mm Hg)	70.5 ± 7.0	68.2 ± 6.6	0.24
Cholesterol [mg/dL]	280.3 ± 52.0	259.0 ± 50.3	0.12
HDL-cholesterol [mg/dL]	79.7 ± 13.6	75.6 ± 13.7	0.27
LDL-cholesterol [mg/dL]	161.0 ± 48.5	146.6 ± 47.0	0.25
Triglycerides [mg/dL]	198.1 ± 68.2	181.1 ± 65.3	0.29
Fasting glycaemia [mg/dL]	84.1 ± 7.5	82.1 ± 7.9	0.36
2-h glucose [mg/dL]	154.5 ± 15.8	154.9 ± 12.4	0.92
Fasting insulin [μU/mL]	11.8 ± 6.4	9.1 ± 4.9	0.08
HOMA-IR	2.5 ± 1.5	1.8 ± 1.2	0.38

BMI — body mass index; HDL — high-density lipoprotein; LDL — low-density lipoprotein; HOMA-IR — Homeostasis Model Assessment of Insulin Resistance

furthermore various criteria across the world applied to diagnose GDM.

In this study, over 44% of women with GDM were characterized by a deficit of 25(OH)D between the 20th and 29th week of pregnancy, defined as the concentration < 20 ng/mL. 25(OH)D deficiency was found, despite the fact that the patients were administered multi-vitamin preparations, containing vitamin D (200–800 IU depending on preparation). In one of American studies, the percentage of women with the 25(OH)D concentration ≤ 20 ng/mL was 34%, but was as high as 66% in a population inhabiting the south of India and soared to 90% in the UK in spring and winter seasons [3, 9, 11]. It is worth noticing that the supply of a general population, pregnant women included, with vitamin D depends on several factors. Possible causes of 25(OH)D deficiency are the limited sunlight exposure, staying indoors, use of skin cosmetics with sun filters. It should be added that dietary deficiencies in countries where food is not fortified with vitamin D, also contribute to vitamin deficits. Furthermore, the analysis assessing the content of vitamin D in the daily food rations of female at childbearing age in Poland found it inappropriate (only 48% of recommended daily intakes) [12]. Finally there were no women taking additional vitamin D preparations, as is indicated

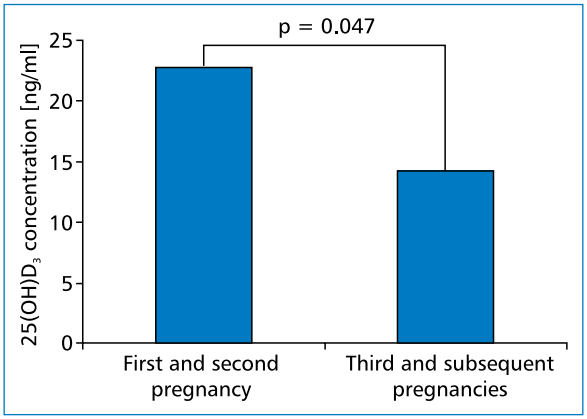

Figure 1. 25(OH)D concentration relative to the number of previous pregnancies in the group of women with GDM

in the new recommendations published in 2013 [12]. Ssupplementation with vitamin D should be recommended for pregnant women soon after pregnancy is confirmed [10].

The results of our study suggest a significant relationship between the 25(OH)D deficiency, detected in the second term of pregnancy, with insulin resistance. At the same time, no significant correlations were found between the deficiency of 25(OH)D and fasting glucose and 2-h glucose concentration during OGTT. Observations carried out globally in women with GDM drew attention to a significantly lower maternal 25(OH)D concentration determined in gestation week 24 to 28 than in pregnant women with normal glycaemia [1]. Studies from US and Iran showed that women with 25(OH)D levels < 25 vs. ≥ 25 nmol/L had significantly increased odds of GDM and higher blood glucose levels after 1-h oral glucose challenge test (OGCT) [3, 13]. Other authors concluded than percentages of women with GDM were similar among women with and without 25(OH)D deficiency. There were no other associations between 25(OH)D levels and maternal outcomes; however among women with 25(OH)D deficiency, 30-minute glucose concentrations were inversely associated with 25(OH)D concentrations [9]. A study completed in Great Britain found a negative correlation between the 25(OH)D concentration measured in the first term of pregnancy and 2-h glucose concentration during OGTT, although the former factor was unrelated to the risk of GDM development [14]. The assessment of the relationship between 25(OH)D and glucose metabolism in the European and South Asian populations showed a weak inverse correlation between 25(OH)D concentration and fasting glucose, as well as lack of correlation with fasting insulin level, glycaemia values in OGCT or GDM [15]. The results do not support the notion that 25(OH)D concentration in the first term of pregnancy will be a good parameter to assess the risk of GDM in later gestation. The published prospective studies contain contrary opinions with respect to the connection between a low 25(OH)D concentration in the first term of gestation and the risk of developing GDM [14–16].

Recently, researchers have been paying attention to the relationship between 25(OH)D deficiency and obesity, a component of metabolic syndrome. Lower 25(OH)D plasma concentration among obese people is connected with its accumulation in adipose tissue. On the other hand, epidemiologic data demonstrating a growing tendency for overweight and obesity in population, including pregnant women, can be said that directly influence the increased risk of GDM. In our group of women, no significant correlation was found between 25(OH)D concentration determined in the second term of pregnancy and the pre-gestational BMI. The women participating in our study with 25(OH)D deficiency had a higher pre-gestational body weight and BMI, and a higher weight gain during the pregnancy, although the differences did not reach the statistical significance. At the same time, we observed a significantly higher 2-h glucose concentration during OGTT, a higher concentration of fasting insulin and a higher HOMA-IR in the group of women with pre-gestational overweight. In one of the studies evaluating the relationship between the 25(OH)D concentration and metabolic syndrome in the Canadian population, the frequency of metabolic syndrome was assessed at 8.9%. The number of medical conditions contributing to metabolic syndrome was inversely proportional to 25(OH)D plasma concentration. People with the highest 25(OH)D concentration presented the lowest risk of metabolic syndrome. An increasing 25(OH)D concentration was inversely proportional to IR measured by HOMA-IR, adjusted for physical activity, smoking, age, sex, ethnic origin, as well as the month when the assays were completed. An increase in the 25(OH)D concentration by another 10 nmol/L was associated with a 14% decrease of the risk of metabolic syndrome [17]. In the NHANES study, 25(OH)D concentration in general population was inversely correlated with the incidence of type 2 diabetes but positively correlated with HOMA-IR [18, 19]. Another study on Iranian women showed that HOMA-IR ≥ 3 was found more frequently in 25(OH)D deficiency than in the control group [20]. In Australian study, carried out in pregnant women, a negative correlation of 25(OH)D versus fasting glucose, insulin and HOMA-IR was found, although when adjusted for the race, age and BMI, only the correlation with fasting glucose remained [2]. A study published in 2013,

assessing the effect of supplementation of vitamin D during pregnancy showed that the HOMA-IR at term, was the lowest in women administered the highest dose of 25(OH)D [21]. A statistically significant decrease in insulin resistance was detected in a randomized study focusing on the effect of a six-week supplementation with vitamin D [22].

The recent years have also shown an increasing interest in the influence of 25(OH)D on blood pressure. Our observations indicate that a low 25(OH)D concentration was associated with higher SBP. No association was found with DBP. The latest reports pay attention to the relationship between low 25(OH)D concentration and a higher risk of pre-eclamptic condition [5, 23–26].

Lower concentrations of 25(OH)D were determined in the multiparous women participating in our study. Similar observations have been reported by American researchers, who concluded that the group with the lowest 25(OH)D concentration (< 10 ng/mL) was especially dominated by multiparae [3]. The Iranian study did not confirm the relationship between 25(OH)D and succession of childbirths [20].

The role of 25(OH)D in pathogenesis of GDM requires further randomized clinical trials. Currently, studies are performed to assess the effect of vitamin D supplementation. So far, there have been no evaluations of the role of 25(OH)D in the prevention of GDM [27].

Conclusions

1. Low 25(OH)D concentration in the analyzed group of women with GDM was correlated significantly with increased IR and SBP.
2. In multipara the incidence of 25(OH)D deficiency was higher.
3. The results imply necessity of focusing on guidelines implementation for 25(OH)D supplementation for women in childbearing age.

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