Relation of maternal vitamin D status with gestational diabetes mellitus and perinatal outcome

Niyazoglu Mutlu¹, Hatipoglu Esra¹, Aydogan Begum², Dellal Fatma³, Yavuz Arzu⁴, Hacioglu Yalcin⁵, Kaya Fatih⁶, Kumru Selahattin⁶

1. Division of Endocrinology and Metabolism, Department of Internal Medicine, Cerrahpasa Medical School, Istanbul University, Istanbul, Turkey
2. Department of Obstetrics and Gynecology, Cerrahpasa Medical School, Istanbul University, Istanbul, Turkey
3. Department of Endocrinology and Metabolism, Ministry of Health’s Ankara Ataturk Education and Research Hospital, Ankara, Turkey
4. Department of Obstetrics and Gynecology, Ministry of Health’s Ankara Ataturk Education and Research Hospital, Ankara, Turkey
5. Department of Internal Medicine, Ministry of Health’s Istanbul Education and Research Hospital, Istanbul, Turkey
6. Department of Obstetrics and Gynecology, Ministry of Health’s Antalya Education and Research Hospital, Antalya, Turkey

Abstract

Objective: To investigate the relationship between maternal vitamin D status and glucose intolerance, and its impact on pregnant women and their newborns.

Methods: A cohort of pregnant women were divided into three groups: women with gestational diabetes mellitus, ones with normal results both after the 50 gr and 100 gr OGTT (CG-1) and ones having a positive result after the 50 gr OGTT screening but negative results for gestational diabetes mellitus (GDM) after the 100 gr OGTT (CG-2)

Results: The newborn length in CG-1 was greater than in GDM and CG-2 (p= 0.002 and p= 0.02). Fasting blood glucose and insulin resistance (IR) were negatively correlated with length of the newborns (r=-0.3, p=0.03 and r=-0.3, p=0.01). The newborns of women with GDM had lower APGAR-1 and 5 scores than those of CG-1 and CG-2 (APGAR-1 p= 0.001 and p= 0.004, APGAR-5 p=0.005 and p=0.007, respectively). APGAR scores were correlated negatively with IR (APGAR-1 r=-0.32, p=0.01, APGAR-5 r=-0.3, p=0.03) and positively with 25OHD levels (APGAR-1 r=0.3, p=0.01, APGAR-5 r=0.3, p=0.02).

Conclusion: Vitamin D deficiency, gestational diabetes and insulin resistance are interrelated. Severe vitamin D deficiency during pregnancy is associated with poor pregnancy and neonatal outcome.

Keywords: Vitamin D deficiency, gestational diabetes, insulin resistance, pregnancy and neonatal outcome.

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Introduction

Vitamin D deficiency is common all around the world and has a prevalence of 26-98% in pregnancy, bringing concerns about its consequences and need for supplementation1-4. As vitamin D receptor is expressed widely in nucleated cells, it does not only have a role in calcium and bone homeostasis but also in various organs and system functions.

Vitamin D has a wide spectrum of extraskeletal effects and its deficiency has various consequences including muscle weakness, impairment of immune system, increase in cardiovascular disease and hypertension, disturbance of neuropsychiatric function and even increased mortality5-8. Taking this wide range of actions into consideration, it is not surprising that Vitamin D also has a role in insulin homeostasis and resistance. It may improve beta-cell activity and increase insulin
sensitivity. Poor Vitamin D status has also been linked with type-2 diabetes, obesity and other elements of metabolic syndrome.

Pregnancy is another condition associated with insulin resistance and hyperinsulinaemia. During pregnancy, the effects of diabetogenic hormones cannot be handled in women with insufficient pancreatic reserve, thus gestational diabetes occurs. Gestational diabetes is an important health issue since it has serious consequences involving increased risks of preeclampsia, macrosomia, cesarean delivery, and their associated morbidities. There have been several reports that tried to ascertain the link between diabetes in pregnancy and maternal vitamin D status. To date, the connection between vitamin D status and gestational diabetes mellitus and/or insulin resistance is not clear. Given what is known in existing literature, the current study aimed to investigate the relationship between maternal vitamin D status with glucose intolerance and its consequences in pregnant women.

Materials and methods

A total of 21 consecutive women with gestational diabetes mellitus (GDM) were included in the study. Age and body mass index-matched 43 healthy pregnant subjects constituted the control group. There were no racial/ethnic or socioeconomic differences between the groups. The method used for diagnosing gestational diabetes had two parts. First, a 50 gr oral glucose tolerance test (OGTT) for screening was performed at 24 to 28 weeks of gestation. Plasma glucose, measured one hour later, had two parts. First, a 50 gr oral glucose tolerance test (OGTT) for screening was performed at 24 to 28 weeks of gestation. Plasma glucose, measured one hour later, was considered elevated if it was ≥ 7.8 mmol/L (140 mg/dL) or ≥ 11.1 mmol/L (200 mg/dL) two hours after the test. The mean BMIs of patients with GDM and in CG-1 and CG-2 were 27.2±4.9, 25.2±4.6 and 24.9±4.5 kg/m², respectively (p=0.22).

Table 1. Mode of delivery, complications and fetal status in each group

<table>
<thead>
<tr>
<th>Classification</th>
<th>GDM (n=21)</th>
<th>CG-1 (n=15)</th>
<th>CG-2 (n=28)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>Vaginal</td>
<td>8 (38%)</td>
<td>5 (33%)</td>
<td>7 (25%)</td>
<td></td>
</tr>
<tr>
<td>C/S</td>
<td>13 (62%)</td>
<td>10 (67%)</td>
<td>21 (75%)</td>
<td></td>
</tr>
<tr>
<td><strong>Preeclampsia</strong></td>
<td>4 (19%)</td>
<td>1 (7%)</td>
<td>2 (7%)</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Early membrane rupture</strong></td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>3 (10%)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Preterm labor (spontaneous)</strong></td>
<td>8 (38%)</td>
<td>1 (7%)</td>
<td>5 (18%)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Newborn-Birth weight (gr)</strong></td>
<td>3180</td>
<td>3370</td>
<td>3230</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>[2700-3480]</td>
<td>[3150-3729]</td>
<td>[2960-3505]</td>
<td></td>
</tr>
<tr>
<td><strong>Classification-</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>Normal SGA</td>
<td>18 (85%)</td>
<td>14 (93%)</td>
<td>24 (86%)</td>
<td></td>
</tr>
<tr>
<td>LGA</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>3 (10%)</td>
<td></td>
</tr>
<tr>
<td><strong>Newborn-Length (cm)</strong> †</td>
<td>50[48.5-51]</td>
<td>52[51-52]</td>
<td>50 [50-51]</td>
<td>0.006*</td>
</tr>
<tr>
<td></td>
<td>7 [6-8]</td>
<td>8 [8-8]</td>
<td>8 [7-8]</td>
<td>0.002*</td>
</tr>
<tr>
<td><strong>Newborn-APGAR-1</strong> †</td>
<td>8 [8-9]</td>
<td>9 [9-9]</td>
<td>9 [8-9]</td>
<td>0.006*</td>
</tr>
<tr>
<td><strong>Newborn-APGAR-5</strong> †</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C /S cesarean section, IUGR intrauterine growth retardation, TTN transient tachypnea of newborn, SGA small for gestational age, LGA large for gestational age. *The results are presented as median and interquartile range [IQR]
There was a tendency towards a difference between the three groups in terms of presence of preterm labor, although the difference was not statistically significant (p=0.06). The newborn length in CG-1 was higher than in GDM and CG-2 (p= 0.002 and p= 0.02, respectively). There was no difference between GDM and CG-2 in terms of median newborn length (p=0.3).

The newborns of the GDM group recorded lower of APGAR-1 and 5 scores than the newborns of CG-1 and CG-2 (for APGAR-1 p= 0.001 and p= 0.004, for APGAR-5 p=0.005 and p=0.007, respectively). The median scores of APGAR-1 and 5 were not different between the newborns of CG-1 and CG-2 (p=0.5 and p=0.3, respectively).

FBG levels were higher in cases with GDM than in CG-1 and CG-2 (p< 0.001 and p=0.004). Cases with higher glucose levels after the 50 gr OGTT (CG-2) also had higher FBG levels than the cases that had normal glucose levels after the 50 gr OGTT (CG-1) (p=0.001).

HOMA-IR was significantly higher in patients with GDM compared to the cases in CG-1 (p=0.01). Cases in CG-2 did not have significantly different levels of HOMA-IR than the patients with GDM and the cases in CG-1 (p=0.2 and p=0.1, respectively) (Table II).

FBG levels were also negatively correlated with BMI (r=-0.3, p=0.02, n=63) whereas it was negatively correlated with length of the newborns (r=-0.3, p=0.03, n=62) (Figure 2). 25OHD levels were also negatively correlated with HOMA-IR and BMI (r=-0.5, p< 0.001, n=64 and r=- 0.3, p=0.04, n= 63, respectively) (Figure 3).

**Table 2. Comparison of HOMA-IR and laboratory values between the three groups**

<table>
<thead>
<tr>
<th></th>
<th>GDM (n=21)</th>
<th>CG-1 (n=15)</th>
<th>CG-2 (n=28)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG (mg/dl)</td>
<td>95</td>
<td>78</td>
<td>87</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>[88.5-105]</td>
<td>[75-87]</td>
<td>[81-90]</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.3</td>
<td>1.4</td>
<td>1.8</td>
<td>0.04*</td>
</tr>
<tr>
<td></td>
<td>[1.7-3.5]</td>
<td>[1.2-1.9]</td>
<td>[1.4-2.9]</td>
<td></td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.2</td>
<td>9.2</td>
<td>9.4</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>[8.9-9.6]</td>
<td>[9-9.5]</td>
<td>[9-9.5]</td>
<td></td>
</tr>
<tr>
<td>25(OH) Dvit (ug/l)</td>
<td>7.4</td>
<td>11.71</td>
<td>8.4</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>[6.1-9.9]</td>
<td>[4.5-24.9]</td>
<td>[5-15.8]</td>
<td></td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>34</td>
<td>34.6</td>
<td>31</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>[27.9-49.4]</td>
<td>[30.5-43.9]</td>
<td>[28-40.9]</td>
<td></td>
</tr>
</tbody>
</table>

FBG fasting blood glucose, PTH parathyroid hormone. Data was expressed as median and IQR.

When the whole cohort was taken into consideration, FBG was positively correlated with age of the cases (r=0.3, p=0.02, n=60), BMI (r=0.4, p=0.001, n=61), HOMA-IR (r=0.5, p< 0.001, n=62), and was negatively correlated with length of the newborns (r=-0.3, p=0.03, n=62) (Figure 1). HOMA-IR was positively correlated with BMI (r=0.3, p=0.02, n=63) whereas it was negatively correlated with length of the newborns (r=-0.3, p=0.01, n=64), APGAR-1 (r=-0.32, p=0.01, n=62) and APGAR-5 (r=-0.3, p=0.03, n=62) (Figure 1 and Figure 2).
Maternal levels of 25OHD showed a positive correlation with APGAR-1 and APGAR-5 scores of the newborns (r=0.3, p=0.01, n=62 and r=0.3, p=0.02, n=62) (Figure 2). Multiple regression analysis was used to test if BMI, 252Dvit levels and FBG predicted HOMA-IR, APGAR score and neonatal length. In the regression analysis for HOMA-IR (adjustedR2= 0.20, F(3,57)=4.71, p=0.005), it was found that 25OHDvit levels significantly predicted HOMA-IR (β=-0.3, p=0.02). In the regression analysis for APGAR score (adjustedR2= 0.10, F(3,55)=3.2, p=0.03) APGAR-1 was associated with neonatal length. Maternal levels of 25OHD showed a positive correlation with increased frequency of preterm labor. Additionally, increased maternal fast- ing blood glucose, presence of gestational diabetes and insulin resistance contributed to lower APGAR scores. These results indicate that metabolic condition of the mother is closely associated with health of the newborn and vitamin D deficiency not only contributes to metabolic impairment in the mother but also is related with birth related complications and poor health of the newborn. Both fasting blood glucose and insulin resistance had a negative impact on length of the newborn. Women with gestational diabetes also tended to have preterm labor more frequently than the women without diabetes, although the difference was not statistically significant.

GDM is the onset or first recognition of impaired glucose tolerance during pregnancy. Since insulin resistance is a major contributing factor for GDM, in the present study, as expected, HOMA-IR was found to be significantly higher in cases with GDM. There are several well-known risk factors for developing GDM, including increased maternal age and body mass index. In the current study FBG increased with advanced age. Women with GDM tended to be older, but this was not statistically significant.

GDM has various adverse outcomes which tend to increase with higher maternal FBG levels and these outcomes also influence the newborn. Rates of preterm labor increase when pre-gestational diabetes is present. Likewise, in the present study, women with GDM tended to have higher incidences of preterm labor, but did not reach a statistically significant level of association. In addition, newborns of the women with GDM had lower scores of APGAR in comparison to newborns of women without diabetes. Nevertheless, the median scores were at levels calling for urgent medical attention. Moreover, increased levels of maternal FBG and insulin resistance were associated with lower APGAR scores. Since APGAR reflects general well-being of the newborn, these results suggest that maternal glucose metabolism may influence health status of the newborn. Interestingly, the median length of the newborns of women without diabetes was significantly higher than those of women with positive results only after the 50 gr OGTT and GDM. The reason why infants of women without diabetes have hypocalcemia and this proportion may reach up to 50%.

In our study, maternal HOMA-IR was negatively correlated with maternal Ca levels. Thus, increase in insulin resistance was also associated with a decrease in Ca levels. Theoretically, maternal serum Ca levels may have some impact on fetal bone maturation and fetal growth. Accordingly, increased glucose levels and insulin resistance in pregnant women may indirectly affect length of the newborns. Although statistically insignificant, lower levels of 25OHD in women with GDM may be responsible for lower newborn length in the present study since vitamin D inadequacy may alter fetal skeletal development. However, further studies are necessary for a certain explanation.

The relationship between Vitamin D deficiency and GDM is controversial. While a number of previous studies have found an association between decreased levels of 25OHD and GDM, others have failed to show such an association. In the current study, 25OHD levels were 36.7% and 28% lower in the groups of GDM and CG-2, respectively. However, this decrease was not statistically significant. A distinctive characteristic and one of the limitations of our study was the overwhelmingly lower levels 25OHD than found in previous studies. Ethnicity may be a major contributing factor since 25OHD levels may vary between different ethnic groups. All cases in our cohort were of the same ethnic origin. In the whole cohort, lower levels of 25OHD were associated with higher HOMA-IR and increased BMI, suggesting vitamin D deficiency during pregnancy may be related to the components of metabolic syndrome, namely insulin resistance and higher BMI. Also in regression analysis vitamin D levels were predictive of insulin resistance. Additionally, both human and animal studies show maternal Vitamin D deficiency also has adverse perinatal outcomes. Although the exact mechanism has not been found, in the light of this data, it was not surprising that in our study, lower levels of 25OHD were associated with lower APGAR scores.
Most striking examples for impact of low maternal vitamin D levels on maternal and fetal outcomes were revealed when the whole cohort was grouped based on presence and absence of severe vitamin D deficiency, with a cut-off of 10 ug/l. Severe vitamin D deficiency was associated with maternal insulin resistance, increased frequencies of preterm labor and preeclampsia, and with decreased Apgar scores of the newborns. This means extra caution both for the mother and the newborn should be taken when physicians deal with pregnancies especially in the presence of severe vitamin D deficiency.

Limitations
This study was not without certain limitations. First the method for screening GDM is still controversial. Although certain organizations recommend one step approach with 75-gram OGTT others recommend two step approach or any of them. With one step approach more women are labeled with GDM and it is uncertain whether there will be any benefit from treating them all, rendering this approach not cost effective. Therefore we preferred to use the two-step approach. Moreover in addition to extremely low levels of 25OHD, other limitations include the measurement of the levels once during whole pregnancy and uncertainty of the contributing factors to the low levels including diet, lifestyle and medications. Further studies are needed to demonstrate the relation between maternal serum 25OHD concentration and fetal deviation and perinatal outcome.

Conclusion
Lower maternal serum vitamin D is related with both maternal insulin resistance and adverse perinatal outcomes of newborns. Particularly severe vitamin D deficiency during pregnancy may have detrimental effects. Infants of the women with vitamin D deficiency and/or gestational diabetes mellitus should be carefully evaluated. During pregnancy, insulin resistance and vitamin D status are interrelated, so while dealing with one of them the other should also be taken into consideration.

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References