Gestational diabetes as a risk factor for preeclampsia

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Abstract

Aim: Gestational diabetes (GDM) and preeclampsia (PE) are associated with an increased risk of maternal and perinatal short-term and long-term complications. Despite the available evidence, there is no definitive information about the association of GDM and PE, particularly in developing countries. In this context, we aimed to determine whether GDM is associated with an increased risk for subsequent preeclampsia in transitional Albania.
Methods: This was a retrospective cohort study including all pregnant women being hospitalized for different reasons in the two public tertiary obstetric-gynecologic university hospitals in Tirana, the capital of Albania, during 2005-2012. Diagnosis of GDM was based on a fasting plasma glucose level higher than 120 mg/dl, or postprandial glucose levels higher than 180 mg/dl (exposed group). The non-GDM control group comprised hospitalized pregnant women who did not develop GDM during the same time interval. Pregnant women with previously known diabetes, chronic hypertension, chronic renal disease and prior hepatic disease were excluded from both study groups. Incidence of PE was measured in both groups and results were compared.
Results: GDM occurred in 89 (2.8%) patients among all pregnant women meeting study criteria (N=3218). The incidence of preeclampsia was significantly higher in the exposed group (GDM pregnant women) than in the non-exposed group (non-GDM pregnant women) (27% and 13.5%, respectively, P=0.039). GDM pregnant women were 2.37 times more likely to develop PE compared to non-GDM pregnant women.
Conclusion: GDM is a significant risk factor for preeclampsia in pregnant women in Albania. Special attention should be paid to the association between GDM and PE in order to improve the treatment quality of these patients. Future studies are needed in order to support our findings.

Keywords: Albania, diabetes mellitus, gestational diabetes, incidence, preeclampsia.

Introduction

Gestational Diabetes Mellitus (GDM) and preeclampsia (PE) are leading causes of complications during pregnancy with serious negative effects on the health of both the mother and her unborn child (1,2). GDM is associated with an increased risk of maternal and perinatal short-term and long-term complications (3,4) and together with PE they constitute two of the main complications of pregnancy.

Evidence suggests that gestational diabetes and preeclampsia might have several mechanisms in common. For example, altered carbohydrate metabolism as a result of gestational diabetes causes vascular changes such as arteriosclerosis and a glomerular filtration dysfunction, which can result in a predisposition for preeclampsia (5).

Based on these findings, the control and treatment of GDM would be an effective way to prevent preeclampsia. Previous research has also suggested that various dysfunctions such as increased insulin resistance could be a cause to both illnesses (7,8). International literature offers robust evidence in support of the fact that, while these two conditions have quite distinctive clinical and pathophysiologic characteristics, they also share some important similarities since many risk factors such as obesity, elevated blood pressure, dyslipidemia, insulin resistance, and hyperglycemia are associated with both PE and GDM (9,10).

Recent studies show that PE is associated with altered levels of angiogenic factors, including increased levels of soluble fms-like tyrosine kinase-1 (sFlt1) and reduced levels of placental growth factor (PlGF). PlGF is a placenta-derived angiogenic factor, and sFlt1 is an alternatively spliced circulating form of the VEGF receptor that binds and reduces bioactivity of PlGF. Abnormalities in these circulating factors that regulate angiogenesis have been reported in PE (11,12). It is not clear if this is true for women with GDM who develop PE as well (11,12), but the altered anti-angiogenic state in diabetic pregnancies may be one mechanism for the increased risk for PE. In this context, the objective of this study was to determine whether GDM is associated with increased risk for subsequent preeclampsia independently of other risk factors in Albania.

Methods

Study population

The study was designed as a retrospective cohort study based on the review of all obstetric-gynecologic hospital medical charts between 2005 and 2012. These two public obstetric-gynecologic hospitals are the only tertiary university hospitals of this kind in Albania. Therefore, they attract the overwhelming majority of pregnant women from Tirana and other districts. Furthermore, the complicated cases are referred to these two hospitals from all over Albania.

The target study population comprised all pregnant women presented and hospitalized for different causes requiring treatment between 2005 and 2012 in both hospitals. Diagnosis of GDM was based on the findings of fasting plasma glucose levels higher than 120 mg/dl or postprandial glucose levels higher than 180 mg/dl (exposed group). Pregnant women with previously known diabetes were not included in the exposed group since their disease has not been induced by pregnancy. For comparison purposes, we selected randomly a group of hospitalized pregnant women who did not develop gestational diabetes during the same time interval (non-exposed group). Pregnant women with chronic HTA, chronic renal disease and prior hepatic disease were excluded from both study groups. For every pregnant woman diagnosed with gestational diabetes, a pregnant woman without gestational diabetes and complying with exclusion criteria was selected. In total, 89 pregnant women with gestational diabetes were detected and further 89 controls were randomly selected.

Data collection

The following information was retrieved from the observed clinical medical charts: maternal age, place of residence, education level, parity, gestational age, blood glucose level, HbA1c levels, personal history of diabetes, fetal birth weight, presence of polyhydramnios, and previous history of stillbirth. In addition, the clinical charts were scrutinized in order to detect the occurrence of preeclampsia in both exposed and non-exposed groups during pregnancy timeline. Since women were free of preeclampsia at the start of their observation and free of most common risk factors for preeclampsia, any detected case was consequently considered a new case, or an incidence case.

Statistical analysis

Data were assessed using univariate and bivariate analysis. In bivariate analysis, the chi-square and Fisher's exact test were used to check whether the associations between two categorical variables were statistically significant. Differences between the mean values of continuous variables according to the categories of independent variables were analyzed using the student's T-test. Confidence intervals were calculated based on the binominal distribution.

To take into consideration the effect of potential confounding factors (parity, maternal age and maternal birth weight) on the association of diabetes with preeclampsia we used multivariable-adjusted binary logistic regression procedures. Statistical analysis was performed using Intercooled STATA, version 9.1.

Results

During the study period, 3218 pregnant women showed up and were admitted at the gynecologic service of both tertiary hospitals included in the study. GDM occurred in 89 (2.8%) of these patients.

The overwhelming majority of the GDM cases resided in urban areas (89%). Significantly higher proportions of women with GDM had secondary school education compared to non-GDM patients (53% vs. 28%). There was no statistically significant difference of the parity between the two groups. Approximately 87% of the GDM cases have a plasma glucose level higher than normal. HbA1c levels, which are considered a very important indicator of the glucose metabolism, were not available in the medical records for the majority of the subjects (70%). The average birth weight was 3,715 g for GDM patients and 3,242 g for non GDM cases (P<0.05). Polyhydramnios is encountered at 14% of non GDM cases and 11% of GDM cases. The total incidence of preeclampsia was 20.2% (Table 1). In the exposed group the incidence of preeclampsia was 27% compared to an incidence of 13.5% in the non-exposed group. This difference was statistically significant (P=0.039).

Table 1. Occurrence of preeclampsia in relation to gestational diabetes mellitus cases

Study Group	Total	Occurrence of preeclampsia		P-value
		No	Yes	
Exposed (GDM)	89 (100.0%)	65 (73.0%)	24 (27.0%)	0.039
Not exposed (no GDM)	89 (100.0%)	77 (86.5%)	12 (13.5%)	
Total	178 (100.0%)	142 (79.8%)	36 (20.2%)	

Diabetic pregnant women are 2.37 times more likely to develop preeclampsia compared with non-diabetic pregnant women (95% confidence interval: 1.1-3.7). Subjects with preeclampsia belonged to the age-group younger than 35 years (79%).

All subjects with preeclampsia were at a gestational age of more than 20 weeks, 21% in the second trimester and 79% in the third trimester.

Stillbirths were reported more often in diabetic subjects with preeclampsia (55%) compared with non-diabetic subjects with preeclampsia (29%).
From the parity point of view, among non-GDM patients, preeclampsia was more frequent in their first or second pregnancy. Among GDM patients, preeclampsia was more frequent in their first pregnancy (42%).
Controlling for parity, age and fetal birth weight, we didn't detect any significant effect on the magnitude of the association between gestational diabetes mellitus and preeclampsia.

Discussion

The results from this retrospective cohort study of 3218 pregnant women demonstrated that GDM is independently associated with a higher risk for preeclampsia (RR=2.37). Therefore, this study makes a fine contribution to the literature, as evidence from Albania regarding this association is scarce in the perspective of using robust study designs able to clarify temporal relationships between exposure and outcomes.
The relation between gestational diabetes and preeclampsia is not well understood, however, several studies suggest an association between these diseases. In a study in Finland, Suhonen and Teramo found a combined rate of pregnancy-induced hypertension and preeclampsia that was twice as high in their GDM women compared to women without GDM (13,14). Women with GDM are characterized by increased insulin resistance and/or defective insulin secretion. Studies also support an association between preeclampsia and increased insulin resistance (8,15,16). The clinical syndrome of insulin resistance and essential hypertension has been termed as the Syndrome X by Reaven (17), whereas an abnormal maternal vascular endothelial function has also been found in gestational-diabetic mothers during pregnancy (18). As a result abnormalities of the vascular endothelium and increased insulin resistance are associated with both preeclampsia and gestational diabetes. Epidemiological studies have suggested an increased risk of preeclampsia in pregnancies complicated by insulin resistance, such as those with gestational diabetes mellitus (19). There is evidence that sodium retention (20) and insulin resistance (12,21,22) could result in hypertension and preeclampsia.
The placenta plays a central role in the pathogenesis of PE. In animal models, hyperglycemia increases feto-placental angiogenesis and regulates glucose transporters since the first trimester. Furthermore, hyperglycemia increases capillary permeability through an increased production of nitric oxide and reactive oxygen species. These mechanisms may explain the increased placental and fetal growth observed in pregnant women with diabetes. The increased angiogenesis and endothelial permeability observed in the placenta of pregnant diabetic animals are similar to what is observed in human diabetic retinopathy and nephropathy (23,24).
This study showed that there is an association between preeclampsia and parity. Preeclampsia rate was higher among women without GDM at their first pregnancy or second pregnancy, but in patients with GDM, preeclampsia rate is higher only at their first pregnancy.
It is evident that women with GDM differ from the background population in factors such as age, parity, and pre-existing hypertension. Most of the subjects with preeclampsia belong to the age-group younger than 35 years (79%). Age and obesity are the well-known factors that influence glucose tolerance.
Goldman et al. found a doubled rate of preeclampsia in GDM women that approached but did not reach statistical significance (25). They also reported a relation between preeclampsia and maternal overweight.
In the literature there are discussions on the threshold values of the plasma glucose levels that are used for diagnosing of diabetes during pregnancy. There are, of course, variations of the criteria for performing OGTT, which means that there must be some women with undiagnosed GDM in the non-

GDM group. In the current study this has resulted in an underestimate level of the presented excess risk of preeclampsia in GDM pregnancies.

Since GDM mothers are characterized by obesity, it is important to consider obesity as a risk factor for preeclampsia in the analysis. A recently published study of risk factors for preeclampsia in quiet a different population of Latin American and Caribbean women supports the finding of GDM as an independent risk factor for preeclampsia (26).

HbA1c levels, which are considered a very important indicator of the glucose metabolism, were not available in the medical records for the majority of the subjects under study as explained earlier in this paper. Therefore, this parameter could not be used in order to better judge about glycemic control of study participants. Several studies have reported an association between poor glycemic control early in pregnancy and the risk of preeclampsia (27-29). The American Diabetes Association recommends that HbA1c levels should be as close to normal as possible (<7%) in an individual patient before conception is attempted (30).

Further large-scale cohort studies are needed to vigorously establish the association between diabetes during pregnancy and preeclampsia, as well as other factors that play a role.

Conclusion

The present study found that gestational diabetes mellitus is a risk factor for preeclampsia among pregnant women in Albania. On the face of it, this was not a spurious finding and, therefore, special attention should be devoted in order to provide at-risk pregnant women with the appropriate treatment options.

Conflicts of interest: None declared.

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