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# THE INFLUENCE OF FIRST TRIMESTER MATERNAL GLUCOSE ON FETAL GROWTH AND POSSIBLE IMPLICATIONS IN PREGNANCY EVOLUTION

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## Abstract

***Background and Aims**: Maternal hyperglycemia during the first trimester of pregnancy is frequently associated with the appearance of maternal and fetal complications. The aim of our study was to analyze the influence of the first trimester blood glucose on the glycemic values from the second and third trimester and on fetal birth weight. **Material and method**: We performed an observational study on a group of 46 pregnant women who finally delivered on due date. We determined glycemia values in the first and third trimester of pregnancy while an Oral Glucose Tolerance Test (OGTT) was performed during the second trimester (24 – 28 weeks of pregnancy). We divided the pregnancies in two groups: with normal glucose or hyperglycemia during the first trimester. Finally we analyzed the influence of first trimester hyperglycemia on different maternal characteristics and on fetal birth weight. **Results**: Third trimester glycemia was significantly increased in women with first trimester hyperglycemia in comparison with the control group (p= 0.04) but no effect of the last on OGTT values was recorded. The ROC curve for the influence of first trimester glycemia on fetal macrosomia had an Area Under the Curve (AUC) of 0.551. **Conclusions**: First-trimester glycemia has a low diagnostic accuracy in the appreciation of fetal macrosomia risk.*

**key words**: *hyperglycemia, gestational diabetes, macrosomia.*

## Background and Aims

It was reported that hyperglycemia during the first trimester of pregnancy increases the risk of miscarriage [1], of perinatal morbidity and mortality (three times), and of congenital anomalies (two times) [2-6]. In the year 2008, the HAPO study reported an association between maternal glycemia and the high frequency of perinatal complications (macrosomia, increase in caesarean section rate, neonatal hypoglycemia) [7].

Though the association between maternal hyperglycemia and perinatal complications is already established, few studies have analyzed the importance of first-trimester hypergly-

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cemia as a predictable factor in the appearance of different fetal complications.

The aim of our study was to analyze the influence of the first-trimester blood glucose over the glycemic values from the second and third trimester and on fetal birth weight, aiming to identify some potential predictive factors which may place the pregnant women in a high risk group for developing gestational diabetes.

## Material and methods

We performed a prospective study on a group of 46 pregnant women who finally gave birth on due date (37 – 41 weeks of gestation) in Oradea Clinic Hospital for Obstetrics and Gynecology between January 2009 and June 2011. The subjects were taken into evidence in their first half of pregnancy (up to 20 weeks of gestation). For each woman we registered age, height and weight, body mass index (BMI), gestational age when registered, personal physiological and pathological along with obstetric history, blood pressure, medicine and intoxicants consumption. We also registered the presence of risk factors for gestational diabetes including family history of diabetes and obesity, parity, history of gestational diabetes or previous macrosomic fetus deliveries and the presence of glycosuria when taken under observation.

Inclusion criteria were: pregnant women with monofetal pregnancy and known first trimester glycemic value.

Exclusion criteria were: age younger than 18 years, maternal chronic diseases, pregnancy associated pathology, twin pregnancy, conception after ovarian stimulation treatment or in vitro fertilization, chronic use of medication or intoxicants.

Blood glucose was measured from maternal venous blood during the first and third trimester of pregnancy (in the period just before giving birth). In addition, between 24 – 28 weeks of gestation (±2 weeks) we performed an oral glucose tolerance test (OGTT). OGTT consisted in the determination of glucose level in venous plasma, after ingesting 100 g of glucose powder diluted in 300 ml of water in an interval of 5 – 10 minutes. Glycemia was determined in fasting state and after one, two and three hours after glucose ingestion.

We separated the pregnant women in two groups: group I with normal glucose values and group two with hyperglycemia in the first trimester of pregnancy. The grouping was done according to the recommendations of The International Association of Diabetes and Pregnancy Study Groups (IADPSG) according to which glucose values over 92 mg/dl in the case of prime trimester pregnancies are considered to be diagnostic for gestational diabetes [8]. The diagnosis of gestational diabetes in the second trimester of pregnancy was set using Carpenter and Coustan's criteria for OGTT's using 100 g glucose [9].

### *Statistical analysis*

Quantitative data are expressed as average ± standard deviation. The statistic comparison of the data was done using the Student t test to compare the average values of the different characteristics of the groups and Pearson correlation test to compare two characteristics of a group. The P value was considered significant at $\alpha = 0.05$. The diagnostic relevance of glucose values achieved during pregnancy for fetal birth weight was investigated with the help of the area under the

ROC curve (AUC). The confidence interval (95%), diagnostic level, sensitivity and specificity were determined. For statistical analysis we used the SPSS 19 and MedCalc 12.2.1 software.

**Results**

The social-demographic and anthropometric maternal parameters (BMI at the moment of taking into evidence) as well as predisposing factors for gestational diabetes are given in Table 1.

**Table 1.** Social- demographic and anthropometric parameters, predisposing factors.

| | WHOLE GROUP (N= 46) | GROUP I with normal glucose values (N= 34) | GROUP II with hyperglycemia in the first trimester of pregnancy (N= 12) | p |
|---|---|---|---|---|
| Age (years) | 28.32±5,07<br>Min: 20<br>Max: 43 | 28.82±-5.29<br>Min: 20<br>Max: 43 | 26.91±4.27<br>Min: 21<br>Max: 35 | 0.13 |
| BMI (kg/m$^2$) | 25.06±4.17<br>Min: 18.42<br>Max: 38.6 | 25.51±4.25<br>Min: 18.42<br>Max: 38.6 | 23.78±3.82<br>Min: 19.5<br>Max: 31.74 | 0.11 |
| Parity | 1.67±1.30<br>Min: 1<br>Max: 7 | 1.64±1.15<br>Min: 1<br>Max: 6 | 1.75±1.71<br>Min: 1<br>Max: 7 | 0.40 |
| Risk factors | 2 macrosomia<br>2 multiparous<br>1 father with diabetes | 2 macrosomia<br>1 multiparous<br>1 father with diabetes | 1 multiparous | |

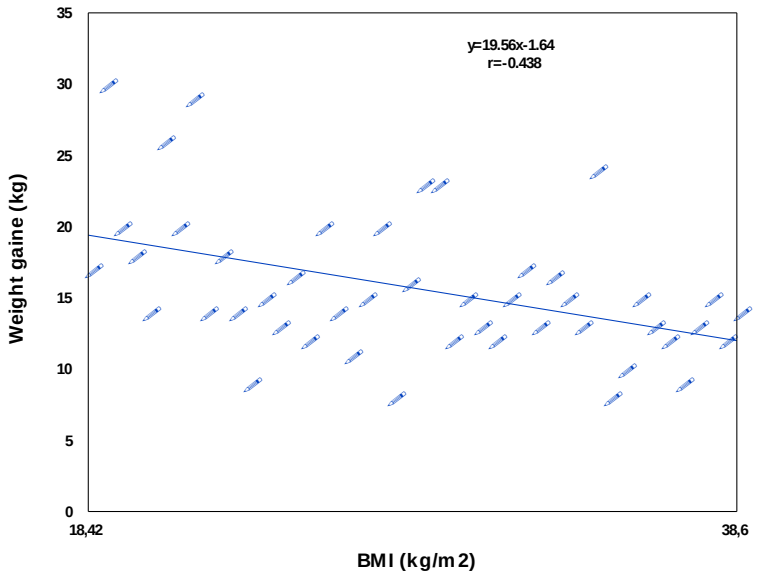


**Figure. 1:** The correlation between BMI when taken under observation and weight gain during pregnancy.

The average age for group II was lower than in the control group, but without statistic signification. Average parity of the two studied groups was similar.

An increased percent of pregnant women from the group with first trimester hyperglycemia had BMI values including these women in the group of overweight

pregnant: 25% up against 20.59% for the group with normal first trimester glucose values. In the group with normal first trimester glucose values, a percent of 14.70% of the women had first degree obesity (BMI 30-35), in contrast to only 8.33% of the women from the hyperglycemia group. Instead, only pregnant women from the group with normal first trimester glucose values (2.94%) had second degree obesity.

In the hyperglycemia group we found only one pregnant women with risk factors towards for gestational diabetes - multiparity.

Correlation between BMI when taken under observation and weight gain during pregnancy is given in Figure 1.

As can be noticed, we found a negative correlation between BMI when taken under observation and weight gain during pregnancy ($p< 0.01$).

Blood glucose (BG) values in the first trimester of pregnancy, during the second trimester OGTT and from the third trimester (the period close to due date) are given in Table 2.

**Table 2.** Blood glucose levels during pregnancy.

| Biological parameteres | WHOLE GROUP (N= 46) | GROUP I with normal glucose values (N= 34) | GROUP II with hyperglycemia in the first trimester of pregnancy (N= 12) | p |
|---|---|---|---|---|
| Glycemia in the first trimester (mg/dl) | 86.12±14.84<br>Min: 65<br>Max: 140.2 | 79.61±8.25<br>Min: 65<br>Max: 91.5 | 104.55±14.01<br>Min: 92.7<br>Max: 140.2 | 0.0001 |
| OGTT fasting BG (mg/dl) | 80.81±20.95<br>Min: 49.3<br>Max: 130.9 | 77.96±20.23<br>Min: 49.3<br>Max: 129.8 | 88.9±21.69<br>Min: 56.5<br>Max: 130.9 | 0.06 |
| OGTT 1 h BG (mg/dl) | 133.40±36.41<br>Min: 82.7<br>Max: 229.8 | 133.74±32.87<br>Min: 83.9<br>Max: 229.8 | 132.45±40.03<br>Min: 82.7<br>Max: 219.3 | 0.45 |
| OGTT 2 h BG (mg/dl) | 115.71±34.03<br>Min: 69.8<br>Max: 250.4 | 113.75±29.93<br>Min: 69.8<br>Max: 187 | 121.28±44.76<br>Min: 82.7<br>Max: 250.4 | 0.25 |
| OGTT 3 h BG (mg/dl) | 85.27±20.51<br>Min: 67.2<br>Max: 139.2 | 82.16±13.52<br>Min: 67.2<br>Max: 121.9 | 93.36±21.57<br>Min: 72.1<br>Max: 139.2 | 0.33 |
| Glycemia in third trimester (mg/dl) | 87.41±-23.96<br>Min: 49.5<br>Max: 163 | 82.59±18.78<br>Min: 49.5<br>Max: 116.3 | 98.66±31.57<br>Min: 61.4<br>Max: 163 | 0.04 |
| OGTT + | 5 | 4 (80%) | 1 (20%) | |
| OGTT 2+ out of 4 | 4 | 2 | 2 | |
| OGTT 3+ out of 4 | 1 | 1 | 0 | |
| OGTT 4+ out of 4 | 0 | 0 | 0 | |

From the pregnant women included in the study 12 (26.08%) had increased BG values during the first trimester of pregnancy accordindg to IADPSG criteria.

New borns' birth weight, the method of giving birth and the eventual complications appeared during pregnancy or labour are presented in Table 3.

In order to assess the clinic utility of maternal BG from the first trimester of pregnancy in predicting macrosomia risk, we used the ROC curve method. Two ROC

curves were drawn in order to obtain Sensitivity (Sn), Specificity (Sp) and the cut-off values of glucose in detecting macrosomia risk (newborns with a weight over 4000 g); utility performance as a diagnostic test was appreciated according to the positive predictive value (PPV), negative predictive value (NPV) and the area under the ROC curve.

Using BG value from the first trimester of pregnancy for the appreciation of macrosomia risk, we found an AUC of 0.551 (CI 95%= 0.398- 0.698) (Figure 2).

**Table 3.** Type of birth and newborns' weight.

| | WHOLE GROUP (N= 46) | GROUP I with normal glucose values (N= 34) | GROUP II with hyperglycemia in the first trimester of pregnancy (N= 12) | p |
|---|---|---|---|---|
| Birth weight | 3517.39±488.21<br>Min: 2600<br>Max: 4800 | 3564.70±497.19<br>Min: 2800<br>Max: 4800 | 3383.33±454.93<br>Min: 2600<br>Max: 4200 | 0.2 |
| Type of delivery | Natural: 30 (65.22%)<br>Cesarean Section: 16 (34.78%) | Natural: 22 (64.70%)<br>Cesarean Section: 12 (35.30%) | Natural: 8 (66.67%)<br>Cesarean Section: 4 (33.33%) | |

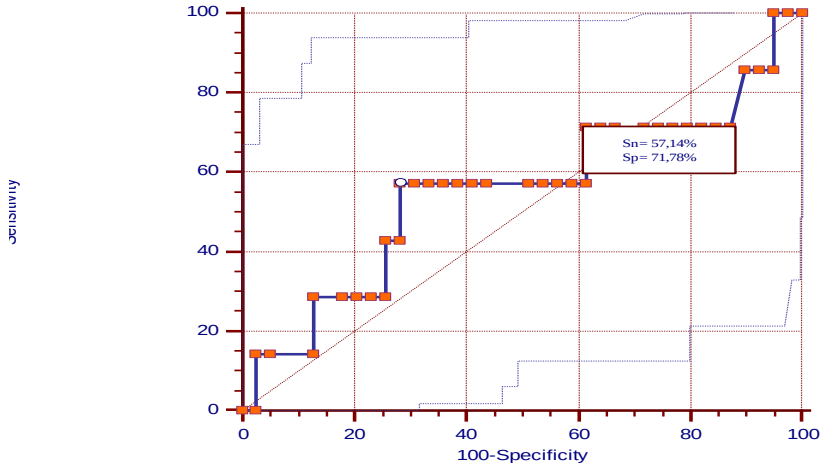


**Figure 2.** ROC curve regarding the evaluation of macrosomia risk using BG from the first trimester of pregnancy (AUC= 0.551).

Specificity, sensitivity and cut-off values of glycemia determined in the first trimester of pregnancy in detecting macrosomia risk, along with the positive and negative predictive values are given in Table 4.

The best relation between specificity and sensitivity was observed at the cut-off value of 83.6 mg/dl. For the cut-off value of de 92 mg/dl sensitivity rises with the decrease of specificity. The test for both cut-off values has a low PPV and a higher NPV. For the superior limit of the tested glycemic values (120 mg/dl), the sensitivity of detecting macrosomia is of 100%, and for the inferior limit, of 80 mg/dl, sensivity and specificity are resembling to those belonging to the cut-off value of 83.6 mg/dl.

**Table 4.** Specificity, sensitivity and cut-off values for the ROC curves.

| CUT- OFF VALUE | PPV (CI 95%) | NPV (CI 95%) | Sensitivity (CI 95%) | Specificity (CI 95%) |
|---|---|---|---|---|
| ≤65 mg/dl | 0.0 (0.0- 97.5) | 84.4 (70.5- 93.8) | 0.0% (0.0- 41.0) | 97.44% (86.5- 99.9) |
| 83.6 mg/dl | 20 (5.7- 43.7) | 88.5 (69.8- 97.6) | 57.14% (18.4- 90.1) | 58.97% (42.1- 74.4) |
| 92 mg/dl | 14.3 (4.8- 30.3) | 81.8 (48.2- 97.7) | 71.43% (29.0- 96.3) | 23.08% (11.1- 39.3) |
| 100 mg/dl | 14.3 (5.4- 28.5) | 75.0 (19.4- 99.4) | 85.71% (42.1- 99.6) | 7.69% (1.6- 20.9) |

## Discussions

The American Diabetes Association (2010) appreciates that gestational diabetes complicates up to 7% of the pregnancies (1 – 14%, depending on the studied population and diagnostic method) [9]. The impact and incidence of gestational diabetes are difficult to evaluate worldwide because there are no unanimous accepted criteria for screening, diagnosis and treatment. Therefore globally gestational diabetes' prevalence is estimated at an approximate 4% of the pregnant women. In Europe gestational diabetes affects around 2 – 6% of the pregnancies [10].

According to Carpenter and Coustan's criteria, gestational diabetes diagnosis is made if 2 or more values of OGTT are not normal. However, studies have shown that pregnant women with only one abnormal value present an increased risk for macrosomia and other co-morbidities [11].

Fetal macrosomia is associated with important maternal and neonatal morbidity. On the long term, newborns that are bigger for the gestational age have higher risk for developing obesity during childhood, adolescence and adulthood, and thus present a higher risk of developing cardiovascular and metabolic complications. Currently, over a billion adults are overweight and more than 600 million are obese. This is why the prevention of fetal macrosomia and childhood obesity are important problems for the medical system. Fetal growth is determined by a complex interaction of different genetic and environmental factors, therefore the evaluation of a pregnancy predisposed to fetal macrosomia is difficult. Prevention of fetal macrosomia is totally dependent on the correct identification of risk factors. Mother's weight, weight gain during pregnancy and glycemic control are risk factors for fetal macrosomia whose control can bring benefits not only to mother's health but also to the baby's health. The ideal method for optimizing mother's weight and glucose homeostasis isn't yet settled, though a series of promising progresses have been reported recently.

Studies have shown that the increase of glucose values over 80mg/dl increases the risk of macrosomia, the risk increasing significantly if fasting blood glucose is over 90mg/dl [7]. Lapolla and its collaborators have proved that the risk of giving birth to a macrosomic fetus doubles if glycemia exceeds the value of 85mg/dl [12]. Some authors consider pathologic a BG value over 90 mg/dl in the case of pregnant women [13]. First trimester BG value in the range of 92-125 mg/dl may be associated with adverse pregnancy outcomes [14]. In this study,

pregnant women with fasting glucose value in the first trimester over 126 mg/dl received initially lifestyle change (diet and exercise) recommendations to control their BG.

In the present study, first trimester BG value showed a low accuracy in evaluating macrosomia's risk. The best balance between sensitivity and specificity was recorded for the cut-off value of 83.6 mg/dl.

Between first trimester glycemia and glycemias' values within OGTT wasn't found any correlation. Instead in the study group, third trimester glycemia was significantly increased than in the control group (p= 0.04).

Because the study included a small number of cases, we are not sure of its relevance and therefore do not have sufficient statistical power and cannot draw a definitive conclusion.

### Conclusions

First trimester glycemia has a low diagnostic accuracy in appreciating fetal macrosomia, having mostly a negative predictive value, and cannot be used as fetal macrosomia track down test for a population with a low risk of developing this illness.

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