# PECULIARITIES OF THE COURSE OF GESTATION AND PREGNANCY OUTCOMES IN WOMEN WITH GESTATIONAL DIABETES MELLITUS

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**Abstract**

**Background.** Gestational diabetes mellitus (GDM) is associated with high frequency of obstetric complications, such as gestosis, polyhydramnios, urogenital infection, premature birth. An increase in the number of cases of detection of GDM in pregnant women living in Kazakhstan is noted recently.

**Objective.** This research was carried out in order to see the influence of GDM on the course of the third trimester of pregnancy, outcomes and fetal status in women of Kazakh ethnic group.

**Research design.** Cohort observational study.

**Subjects and Methods.** The main group of research consisted of 61 pregnant women with GDM ($Mean_{age}$= 32.8±6.314), the control group included 39 pregnant women with normal glucose tolerance ($Mean_{age}$=30±5.432 years). The pregnant women in both groups were examined by calculation of body mass index (BMI), determination of fasting plasma glucose and the system of hemostasis. Also, the fetal ultrasound was implemented and the uterine-placental, fetal-placental blood flow were evaluated using the Doppler mode.

**Results.** In the main group initial BMI was equal to Mean=31.1±7.433 kg/m$^2$; we revealed manifestation of gestational hypertension in 36.1%, 95%CI (2.52, 48.6); preeclampsia was diagnosed in 14.8% (95%CI (8; 25.7); the disorders of uteroplacental and fetoplacental blood flow recorded significantly more frequently in main group RR=6.393, 95%CI (1.581-25.840), like the diabetic fetopathy RR=5.115, 95%CI (1.240-21.033). The premature delivery, the prevalence of induction of delivery and intranatal trauma were significantly more frequent in women with GDM.

**Conclusions.** GDM significantly worsens course of gestation.

**Key words:** Gestational diabetes mellitus, pregnancy outcomes, assessment of pregnancy.

## INTRODUCTION

Gestational diabetes mellitus (GDM) is associated with high frequency of obstetric complications, such as gestosis, polyhydramnios, urogenital infection, premature birth (1, 2). Fetal hyperinsulinism that is developing due to the increased glucose income from the mother and its main manifestation - macrosomia- are the main causes of increased injury in delivery and result in a high percentage of cesarean section (3, 4).

The prevalence of GDM in the world has been increased by approximately ~ 16-127% over the last 20 years, depending on ethnicity (5). In the USA this disease is found with high frequency among indigenous American, Asians, Hispanic and African American women in comparison with non-Hispanic white women (6-9). Dornhorst et al. indicated that in Europe GDM is more often diagnosed in Asian women than in European women (10). However, according to the data of the proportion of pregnancies complicated by GDM in Asian countries is lower than the proportion of Asian women living in other countries (11). There are no statistically reliable data on the prevalence of GDM in women living in Kazakhstan. Despite this, an increase in the number of cases of detection of GDM in pregnant women living in the country is noted recently. Therefore, the study of the course of pregnancy complicated by GDM in women living in Kazakhstan is of interest.

### Aim of research

This research was carried out in order to see the influence of GDM on the course of the third trimester of pregnancy, outcomes and fetal status in women of Kazakh ethnic group.

### Research materials and methods

The research was conducted on the basis of Prenatal center No.1 and JSC "National research center for maternal and child health" at Astana city. We have examined pregnant women at the age of 18-42.

In Kazakhstan Kazakhs population is 66.48%,

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*Acta Endocrinologica (Buc), vol. XIV, no. 2, p. 213-218, 2018*

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Slavs population is 20.61%, in the Astana capital - 75.5% and 15.3%, respectively (12). Considering the impossibility of recruiting a comparison group of pregnant of Slavs nationalities in view of the physical absence of a corresponding number of pregnant women of this ethnicity, we have studied the course and the outcomes of pregnancy only for women of Kazakh nationality.

All of them were examined twice during the study period: at the time of enrollment in research at the gestational age of 30-32 weeks as well as on the first day of delivery.

The main group included 61 pregnant women with gestational diabetes mellitus at the Mean age =32.8±6.314 years. The control group included 39 pregnant women with normal glucose tolerance and comparable in age, the mean age was 30±5.432 years.

The criteria for inclusion in the main study group was the presence of gestational diabetes mellitus (the criteria for making a diagnosis of gestational diabetes mellitus was blood glucose level equal to or more than 5.1 mmol/L on fasting state).

The exclusion criteria in the groups were: age of the understudied women less than 18 years old, multiple pregnancy and pregnancy after in vitro fertilization, pre-pregnancy disorders of carbohydrate metabolism, as well as pre-existing hypertension.

Pregnant women in both group were physically examined with calculation of body mass index (BMI). Besides the physical examination, laboratory studies have been performed with the determination of fasting plasma glucose after an overnight fasting for 8-14 h. on the biochemical analyzer. The system of hemostasis was analyzed through hemostasis analyzer: the concentration of fibrinogen, activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), prothrombin index (PI), soluble fibrin monomer complex (SFMC) were determined.

There were 24 pregnant women with mild GDM that was 39.3% at CI (28.1; 51.9) who were prescribed nutritional therapy (diet №9). 37 pregnant women had GDM of moderate severity and that was 60.7% at CI (48.1; 71.9). The correction of carbohydrate metabolism disorders for these women was conducted with short-acting genetically engineered human insulin, intermediate-acting genetically engineered human insulin, short-acting insulin analogues and long-acting insulin analogues.

Fetal ultrasound was implemented for all of these pregnant women. Diabetic fetopathy was diagnosed in the case of detection of one or more features: fetal overgrowth, hepatosplenomegaly, cardiomegaly, two-contour fetal head, thickening of a hypodermic fatty layer and in cervical fold. At the Doppler mode there was evaluation of uteroplacental, fetoplacental blood flow, fetal hemodynamics according to the resistance index, pulse index and systolic-diastolic ratio in the uterine arteries, umbilical artery and middle cerebral artery of the fetus.

Gestational hypertension was diagnosed at systolic blood pressure (SBP) of 140 mmHg or more or at diastolic blood pressure (DBP) of 90 mm Hg or more when it was measured twice at an interval of 4h for women with normal blood pressure before 20 weeks of pregnancy. Correction of blood pressure for all pregnant women was carried out with Methyldopa. Preeclampsia was diagnosed according to clinical diagnosis and treatment protocol "Arterial hypertension in pregnant women" (13).

Stimulation of deliverywas performed in cases of weakness of delivery in the first period, premature rupture of membranes, as well as other conditions, according to the clinical diagnosis and treatment protocol "Introduction to delivery", "Induction of delivery" by the Ministry of Health of the Republic of Kazakhstan.

Intranatal trauma included maternal trauma of the perineum as damage of the upper part of vagina, as well as bleeding.

Statistical measurement processing was carried out in accordance with generally accepted standards in the IBM SPSS Statistics 21 software (IBM, USA; l) program.

Normal distribution of quantitative traits was determined using descriptive statistics by comparing the values of arithmetic meaning with the median level of asymmetry and excess; as well as by the graphical method, using histograms and quantile charts (Q-Qplots) and calculation of Shapiro-Wilk criteria.

Confidence Intervals Analysis program was used in the description of qualitative data for calculation of the confidence interval for the frequencies.

Comparison of quantitative data was carried out using the U-criteria of Mann-Whitney, since distribution was non-Gaussian. Pearson's chi-squared test, the uncertainty factor were used to compare the nominal data.

The correlations between blood pressure levels and the results of Doppler ultrasound study were investigated using nonparametric correlation analysis (Spearman rank coefficient).

The calculation of relative risk was made by analyzing contingency tables with calculation of 95% of the confidence interval.

For all types of analysis values of p<0.05 were considered as statistically significant.

The research was conducted in accordance with the GSP standards and has been approved by the ethical committee of JSC "Astana Medical University".

## RESULTS AND DISCUSSION

Examination of pregnant women of both clinical groups showed statistically significant differences in their pre-gravid BMI. Thus, in the group of pregnant women with carbohydrate disorders initial BMI (before pregnancy) was equal to Mean=31.1±7.433 kg/m$^2$, while in the group of pregnant women with normal glucose tolerance it was equal to Mean=24.9±5.434 kg/m$^2$, U = 526.5 Z = -4.68 p = 0,000. It should be noted that in the main group there was a prevalence of pregnant women with obesity or overweight of varying degrees, and their share was 77% at 95% CI (65.1, 85.8), while in the control group, the proportion of pregnant women with overweight was equal to 20.5% at 95% CI (10.8, 35.5). These differences are statistically significant-χ2 = 30.72 df = 1, p = 0.0001, strength of relationship of pre-gravid BMI with gestational diabetes according to recommendations of Rea and Parker corresponds to a relatively strong φ = 0.554 p = 0.0001; RR = 3.756, 95% CI (1.995-7.072).

Studying the pregnancy we revealed manifestation of gestational hypertension only in women with gestational diabetes mellitus and its rate was 36.1%, at 95% CI (2.52, 48.6). Considering that cases of gestational hypertension in the control group were not detected, these differences were statistically significant, χ2 = 18.03 df = 1, p =0.0001. At the same time there was revealed relatively strong correlation of gestational diabetes with gestational hypertension, φ= 0.425 p= 0.0001. According to the calculation of the uncertainty coefficient it has been found that the prediction error of gestational hypertension in the presence of gestational diabetes can be reduced to 24.3% (Uncertainty Coefficient, U = 0.243 p = 0.0001).

Along with this the attention was drawn to the existence of significant differences in the levels of systolic and diastolic blood pressure in the study groups, despite taking antihypertensive drugs by pregnant women with gestational hypertension. Thus, in the group of pregnant women with gestational diabetes SBP and DBP were equal to Mean=124.59±15.311 and Mean=82.64±11.428, while in the control group SBP and DBP were equal to MeanSDP=111±7.5 and MeanDBP=72.05±7.3 (USBP=531,5 Z=-4.95 p=0.1 and UDBP= 603.0 Z=-4.36 p=0.000 respectively).

In both study groups we have found the disorder of uteroplacental and fetoplacental blood flow, which have been recorded significantly more frequently in pregnant women with GDM. The prevalence of these disorders was 32.8% at 95% CI (22.3, 45.3) in the main group and 5.1% at 95% CI (1.4, 16.9) in the control group. χ2=10.6 df=1 p=0.0014;Uncertainty Coefficient, U=0,118 p=0,001; φ=0.326p=0.001; RR=6.393 95% CI (1.581-25.840 )).

Taking into consideration the presence of vascular disorders in the system of uteroplacental and fetoplacental blood flow, we investigated the state of homeostasis in both groups of pregnant women.

Analysis of the hemostasiological data of pregnant women of both clinical groups showed statistically significant differences in levels of fibrinogen U= 393.5 Z=-3.01 p=0.003 (median fibrinogen level in the main group was equal to the Mean=4.39±0.7 and in the control group Mean=3.8±0.7). Pregnant women with GDM had significantly higher levels of SFMC (in the main group it was Mean=17.07±5.4 while in the control group it was Mean=13.06±6.28; U= 85,5 Z=-2,12 p=0.033). Also we found that there was a significant shortening of the APTT in pregnant women with gestational diabetes mellitus (in the main group Mean=26.06±5.65, compared to Mean=37.23, SD=5.23 in the control group; U= 186 Z=-5.129 p=0.0001). There were no statistically significant differences in levels of PT, PI, INR in both clinical groups.

At the same time, it should be noted that disorders in the uteroplacental blood flow were detected significantly more frequently among pregnant women of the main group, in which on the background of GDM they had gestational hypertension. Thus, the frequency of disorders in the uteroplacental blood flow in pregnant women with gestational diabetes and gestational hypertension was equal to 40.9%; at 95% CI (23.3, 61.3), while in pregnant women with GDM without arterial hypertension the frequency coefficient of disturbances in blood flow was only 17.9%; at 95% CI (9; 32.7); χ2=3.83 df=1 p=0.05. Uncertainty Coefficient, U=0,053 p=0,053, φ=0,251p=0,05.

Considering high prevalence of disorders of utero-feto-placental blood flow in pregnant women with gestational diabetes and gestational hypertension, we examined the correlation relationship at the level

**Table 1.** Correlation relationship blood pressure levels and the results of Doppler ultrasound study in both study groups

| The variables | Main group | | Control group | |
|---|---|---|---|---|
| | Results | Significance level (p) | Results | Significance level (p) |
| SBP and SDR of the first umbilical artery | $r_s$ =-0.385 | p=0.021* | $r_s$ =0.081 | p=0.609 |
| DBP and SDR of the first umbilical artery | $r_s$ =-0.416 | p=0.012* | $r_s$ =0.050 | p=0.589 |
| DBP and SDR of the second umbilical artery | $r_s$ =-0.393 | p=0.018* | $r_s$ =0.197 | p=0.584 |
| DBP and PI of the second umbilical artery | $r_s$ =-0.333 | p=0.047* | $r_s$ =0.270 | p=0.821 |
| Glycemia and SBP of left uterine artery | $r_s$ =0.337 | p=0.045* | $r_s$ =0.073 | p=0.778 |

*statistically significant results

**Table 2.** The frequency of diabetic fetopathy and congenital malformations of the fetus in both study groups

| The variables | Study groups | Results | Significance level (p) |
|---|---|---|---|
| Macrosomia | Main group | 18%, at 95% CI(10.4; 29.5) | p=0.062 |
| | Control group | 5,1%, at 95% CI(1.4; 16.9) | |
| Swelling of the subcutaneous fat layer | Main group | 4.6%, at 95% CI(1.7; 13.5) | p=0.160 |
| | Control group | - | |
| Hepatosplenomegaly | Main group | 1.6%, at 95% CI(0.3; 8.7) | p=0.422 |
| | Control group | - | |
| Cardiomegaly | Main group | 1.6%, at 95% CI(0.3; 8.7) | p=0.422 |
| | Control group | - | |
| Congenital malformations | Main group | 11.5%,at 95% CI(5.7; 21.8) | p=0.029* |
| | Control group | - | |

*statistically significant results

of blood pressure and blood glucose with the results of Doppler studies in the uteroplacental and fetoplacental blood flow, which is presented in the Table 1.

Along with the disorders in the uteroplacental and fetoplacental blood flow in pregnant women with GDM, we identified signs of diabetic fetopathy in 16 pregnant women from the main group, which accounted for 26.2%; 95% CI (16.8; 38.4), while in pregnant women in the control group big fetus was recorded only in 2 cases (5.1% at 95% CI (1.4: 16.9)); $\chi2$=7.17 df=1 p=0,007.Uncertainty Coefficient, U=0.008 p=0.004,$\varphi$=0.268 p=0.007, RR=5.115, 95% CI (1.24-21.033). Fetopathy in pregnant women with GDM was in the form of macrosomia, hepatosplenomegaly, cardiomegaly and swelling of the subcutaneous fat layer in the fetus. Along with this, congenital malformations of the fetus were revealed in these women (Table 2).

Analysis of pregnancy course revealed that the group of pregnant women with GDM were diagnosed with preeclampsia (14.8% at 95% CI (8; 25.7)), while the incidence of preeclampsia in the control group was not detected ((χ2=26.3 df=1 p=0.012. UncertaintyCoefficient, U=0.156 p=0.002, $\varphi$=0.251 p=0.002).

We investigated pregnancy outcomes, such as the moment of delivery, the frequency of induction of delivery, the frequency of intranatal trauma, and the state of the newborn according to Apgar score in both study groups.

Analyzing the timing of delivery it was found out that in women with gestational diabetes mellitus this time happened significantly earlier than in women of control group. U= 856.5 Z=-2.39 p=0.017. Stimulation of delivery was performed significantly more frequently in women with GDM χ2=10.2 df=1 p=0.001, medium strength relationship was identified φ=0.320 p=0.000, Uncertainty Coefficient, U=0.103 p=0.001. The frequency of cesarean section was also significantly higher in the group of pregnant women with GDM χ2=8.74 df=1 p=0.003, φ=0.296 p=0.003, Uncertainty Coefficient, U=0.066 p=0.003. Intranatal trauma was often registered in pregnant women with GDM χ2=10.7 df=1 p=0.001, a medium strength correlation between GDM and intranatal trauma was revealed, φ=0.327 p=0.000, identified uncertainty factor showed that the error in prediction of intranatal trauma when there is data of GDM may be reduced by 13.2%, Uncertainty Coefficient, U = 0.132 p = 0.001 (Table 3).

Weight of newborns in both groups of the study had no statistically significant difference and was equal in the main and control group to Mean=3710 gr, SD=874.6 and Mean=3676 gr, SD=540 respectively. Assessing the fetal condition by Apgar scale, indicators of women in control group at 5 min were significantly higher U= 853.5 Z=-2,82 p=0.005.

According to the results of our research pre-gravid BMI in pregnant women with GDM had been significantly higher, where the proportion of pregnant women who are overweight was higher by 4 times in

**Table 3.** The outcomes of pregnancy in both study groups

| The variables | Study groups | Results | Significance level (p) |
|---|---|---|---|
| Term of delivery | main group | Mean= 37.16±3.348 weeks | p=0.017* |
| | control group | Mean= 38.85±1.247 weeks | |
| Stimulation of delivery | main group | 36.1%, at 95% CI(25.2; 48.6) | p=0.001* |
| | control group | 7.7%, at 95% CI(2.7; 20.3) | |
| Cesarean section | main group | 55.7%, at 95% CI(43.3; 67.5) | p=0.003* |
| | control group | 25.6%, at 95% CI(14.6; 41.1) | |
| Intranatal trauma | control group | 18%, at 95% CI(10.4; 29.5) | p=0.001* |
| | main group | 7.7%, at 95% CI(2.7; 20.3) | |

*statistically significant results

comparison with the control group. At the same time gestational hypertension was found only in pregnant women of the main group and was caused probably by the presence of GDM.The obtained results correspond to those, who found a strong association between insulin resistance and the development of hypertension (14).

The development of gestational diabetes and gestational hypertension, probably are the most significant causes of vascular disorders in pregnant women with GDM. These vascular disorders probably lie on the basis of development of infringements of uteroplacental and fetoplacental blood flow and the development of diabetic fetopathy identified in the studied group of pregnant women with gestational diabetes. Available vascular disorders reflect the identification of vascular endothelial dysfunction in the group of pregnant women, manifested in the form of coagulation hemostasis disorders. The results of the research of some authors have shown that the risk of hypercoagulation in pregnant women is directly proportional to carbohydrate metabolism disorders (NbA1s above 7.0%), lipid metabolism (cholesterol more than 6.5 mmol/L), and albuminuria (30-300 mg/day) (15). However, according to Dodd *et al.*, even a slight hyperglycemia contributes to the development of diabetic fetopathy (16).

We have found that in pregnant women the presence of GDMincreases the risk of the uteroplacental blood flow by 6.3 times. It is confirmed by a significant excess of disorders of uteroplacental blood flow in pregnant women with GDM. The obtained results correspond to conclusions of Nylund *et al.*, who assessing the uteroplacental blood flow in pregnant women with diabetes has identified its disturbance among women with higher levels of blood glucose (17).

Existing disorders of uteroplacental blood flow in pregnant women against the background of gestational diabetes mellitus and gestational hypertension probably contributed to the deterioration of the pregnancy course, which could be the cause

of diabetic fetopathy and decrease of fetus's life assessment according to Apgar 5I scale.

Excessed body weight in pregnant women of the main group along with fetal macrosomia could contribute to a higher frequency of use of surgical delivery and induction of delivery, which could be a risk factor for exceeding of intranatal trauma frequency in pregnant women in this group.

We have identified that a high incidence of preeclampsia in the main group suggests that existing vascular disorders caused by GDM and gestational hypertension does not only affect the development of the fetus, but also are a risk factor for severe obstetric complications.

**CONCLUSIONS**

1. Pre-gravid BMI in pregnant women with gestational diabetes mellitus was significantly higher and more frequently manifests gestational hypertension.

2. The presence of gestational diabetes increases the risk of disorders of uteroplacental the blood flow by 6.3 times, it is confirmed by a significant excess of disorders of uteroplacental blood flow in pregnant women with GDM.

3. Time of delivery in pregnant women with gestational diabetes mellitus happened significantly earlier. Significantly more frequently were applied surgical delivery; induction of delivery as well as frequency of intranatal trauma was significantly higher.

4. Newborns of mothers with gestational diabetes had diabetic fetopathy more frequently and the level of life of the newborn at 5 minute according to Apgar scale was significantly lower.

**Conflict of interest**
The authors declare that they have no conflict of interest.

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