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Predictors of Diabetic Fetopathy in Pregnant Women with Gestational Diabetes

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ABSTRACT

Objective: Gestational diabetes mellitus (GDM) is an important cause of maternal and perinatal complications. GDM forms a symptom complex of diabetic fetopathy (DF) on the fetus, which leads to adverse perinatal outcomes and to long-term metabolic disorders in posterity offspring, affecting the quality of their subsequent life.

Materials and methods: The study was conducted at the base clinic of the Department of Obstetrics and Gynecology with a Perinatology Course of the RUDN University - City Clinical Hospital No. 29 named after N.E. Bauman. It included a retrospective and prospective analysis of childbirth histories of 255 pregnant women with GDM and development records of their newborns, delivered in 2017-2019 at the full-term gestation. High-performance liquid chromatography combined with tandem mass spectrometry (HPLC-MS/MS) was used to determine metabolites and amino acids in the newborns blood to reveal the symptom complex of DF and its separate components.

Results: The findings confirmed the influence of age, late detection of GDM, excessive gestational weight gain (GWG), pregestational obesity and familial obesity on the development of GDM, including the epigenetic nature of obesity.

Conclusion: The obtained indicators of metabolomicand amino acids, indicating pronounced metabolic disorders in patients, can contribute to the prognosis and timely diagnosis of DF.

KEYWORDS

Gestational Diabetes Mellitus, Diabetic Fetopathy, Metabolic Syndrome, Metabolic Homeostasis.

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Introduction

Gestational diabetes mellitus (GDM) is a disease characterized by hyperglycemia, first detected during pregnancy but not meeting the criteria of overt diabetes.The introduction of new diagnostic criteria adopted by major international medical associations contributes to objective accounting for the prevalence of diabetes [1-3]. In the Russian Federation, according to the clinical protocol, a two-phase screening is mandatory in pregnant women to detect GDM [1, 4].

GDM is an important cause of maternal and perinatal complications [5-9]. In addition to high occurrence of premature delivery, pre-eclampsia, cesarean section (24,1% - 57,4%) [6-8, 10], GDM has a negative impact on the fetus, forming placental insufficiency (PN) and symptom complex (DF) that lead to adverse perinatal outcomes and remote effects that determine the health of children [8, 11, 12]. According to national and international authors, GDM is important in the epigenetic programming of obesity[11, 13-15].

Diabetic fetopathy (DF) is defined as a neonatal period disease that develops in newborns whose mothers suffer from diabetes mellitus or GDM and is characterized by polysystemic lesions, metabolic and endocrine dysfunction [6, 8, 16, 17].

Systematic hyperglycemia leads to the formation of DF, so DF is a consequence of decompensation of GDM and metabolic changes inherent in GDM. Children born with DF are in high risk group for insulin resistance, obesity, type 2 diabetes mellitus both in childhood and adult age.

Thus, GDM can be considered as a disease that contributes to the development of metabolic disorders in offspring that affect the quality of subsequent life [11, 12, 13, 14].

The studies of recent years link the growth of GDM (up to 17-19%) to the obesity pandemic, including obesity in women of reproductive age(40%) [18-22].

According to a number of authors, the high-risk group for GDM development includes patients who have a familial history of obesity, which confirms the genetic and epigenetic nature of obesity [13, 14, 20, 23, 24].

In a large scale study by Torloni et al. [21], it is shown that an increase of BMI by 1 kg/m2 can lead to a 0.92%-increase in GDM development, and a 1 kg/m2 decrease in BMI is associated with a decrease in the prevalence of GDM by almost 1%.[14.]

Some authors point out the importance of such a predictor of GDM development as excessive weight gain during pregnancy (GWG), which, according to international statistics, is 2-3 times more frequent than insufficient weight, and is recorded in 40-59% of women [15, 24-26].

At present, researchers are interested in special phenotypes of diseases called “metabolically healthy” (MHO) and “metabolically unhealthy” obesity (MUO). Healthy metabolic obesity is primarily associated with young age, higher physical activity and shorter duration of obesity [19, 27].

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The data of different authors showed that the prevalence of this phenomenon in the obese population varies widely from 6.0% to 38.4% [24, 27, 28].

MUO, as opposed to healthy obesity, is accompanied by metabolic changes and insulin resistance (IR) [18-20, 28]. Preconception IR leads to early manifestation of GDM, deeper metabolic disorders and affects intrauterine programming.

Patients with MUO are in the high risk group for GDM and should be considered for early detection and compensation of GDM.

Metabolomics is in the farthest position to reflect phenotypic and pathophysiological conditions in the body; it examines a set of initial, intermediate and terminal metabolic indicators [17, 21,22, 29].

In this regard, omix technologies open up new perspectives in the study of GDM and its consequences for offspring, because they make it possible to determine the scale of metabolic changes affecting the intrauterine state of the fetus.

Materials and Methods

The study was conducted at the base clinic of the Department of Obstetrics and Gynecology with a Perinatology Course of the RUDN University - City Clinical Hospital No. 29 named after N.E. Bauman. The study has been approved by the Ethics Committee of RUDN University - City Clinical Hospital No. 29 named after N.E. Bauman, Moscow in accordance with the Helsinki Declaration "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, Protocol number ZL225FM from "06"June 2020. It contained a retrospective and prospective analysis of childbirth histories of 255 pregnant women with GDM and development records of their newborns, delivered in 2017-2019 at the full-term gestation in the maternity ward of the Hospital. The study included 255 patients aged 23 to 43 years and their newborns with diabetic fetopathy (DF) or its individual signs. The patients were divided into three groups: the first one was a group of women with GDM on diet therapy (97), the second - with GDM on insulin therapy (87), and the third - without GDM (71). All of them had a spontaneous singleton pregnancy, were comparable in socioeconomic status, obstetric and gynecological history, and delivered newborns between 37 and 40 weeks of gestation.

The methods of the study included:

- Clinical anamnesis research (survey).
- Clinical laboratory research.
- Instrumental examination: ultrasound with fetal fetometry, dopplerometric study of the utero-placental blood flow, cardiotocography (CTG) to assess fetal condition.
- Statistical data processing.
- High-performance liquid chromatography combined with tandem mass spectrometry (HPLC-MS/MS) to determine metabolites and amino acids in the blood

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(tetradecanoylcarnitine (C14), acetylcarnitine (C2), alanine, methionine, phenylalanine, tyrosine, valine, leucine+isoleucine complex) in 70 pregnant women with gestational diabetes mellitus at full-term pregnancy and 50 pregnant women of the control group.

The examination of the patients was carried out in accordance with the regulations adopted in Russia [1, 4].The GDM diagnosis was made on the basis of diagnostic criteria approved by the Ministry of Health of the Russian Federation in the form of clinical guidelines [1]. DF was assessed in the newborns, also by neonatologists, in the antenatal and early postnatal period.

The clinical diagnosis of DF was made in the presence of two or more morphological signs of the symptom complex.
Statistical data processing was performed using the program Statistica v. 10.0. (StatSoft ©Inc., USA). Absolute and relative frequencies were specified for all qualitative signs; the median (Me), 25% and 75% rates - for quantitative signs. When comparing binary features to determine the statistical significance of differences, we used the exact Fisher criterion, for quantitative features - the Mann-Whitney criterion (significance level $p < 0.05$).

Results and Discussion

The obtained data confirmed the influence of age on the development of GDM. The patients receiving insulin therapy were older than others - 34.0 years in average (25.0; 43.0). At the same time, the average age of patients on diet was 32.0 years (24,0; 38,0).

DF development was influenced by GDM late detection at 30 weeks (27.5; 35;0). Among women who gave birth to children with signs of DF, the average gestational age for detecting GDM was 29 weeks (21.0; 33.0). The average age of the first visit to an endocrinologist was 30 weeks (27.5; 35.0). Late visits to the doctor, the absence of pregravid preparation (only in 1.1% of patients) indicated low patients' compliance. The consequence of the above was profound metabolic changes, which resulted in the lack of proper effect from insulin therapy. Among all newborns, the number of children with DF (presence of two or more signs) was 91 (49.5%). However, some phenotypic signs of DF were present in the vast majority of newborns from mothers with GDM.

DF incidence in newborns from mothers receiving insulin therapy was higher than from mothers on a diet (51.7% of mothers with GDM on insulin therapy, 37.1% of mothers on diet therapy, $p < 0.05$). Such a risk factor as obesity (body mass index BMI - more than 30 kg /m2) was observed in 43% of patients with GDM on insulin therapy, and in 40% on diet therapy. Overweight (25.0-29.9 kg/m2) had 38% of patients with GDM on insulin therapy and 37% without insulin therapy (Table 1).

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Table 1. Main clinical and anamnesis risk factors of diabetic fetopathy

Group Indicator	Total patients with GDM n=184	Patients with GDM on insulin therapy n=97	Patients with GDM on diet therapy n=87	Control group n=71
Age, years (Me,25%,75%)	33.0 (26.0; 36.0)	34.0 (25.0; 43.0)	32.0 (24.0; 38.0)	29.3 (27.0; 33.0) *
Gestational age of diagnostics, weeks	30 (27.5; 35.0)	31 (27.5; 35.0)	29 (26; 32.0)	0
Pregestational BNI, (Me,25%,75%)	29.1 (23.7; 34.7)	30.1 (24.5; 36.3)	28.2 (22.8; 33.9) **	20.8 (19.7; 22.8) *
Obesity, Class I-III	77 (42.0%)	46 (47.4%)	31 (35.6%)	4(5.6%) *
Familial obesity	77 (41.8%)	41 (42.3%)	36 (29.0%)	5 (7.0%) *
Mother's macrosomia	38 (20.6%)	22 (22.7%)	16 (18.4%)	6*
Pregravid preparation	2 (1.1%)	1 (1%)	1 (1.1%)	1 (1.4%)
GWG, kg	11.5 (3;20)	12 (3;20)	11 (7;16)	10 (4;22)
DF	91 (49.5%)	57 51.7%	44 37.1%	0

Note:
($p<0.05$):
*- among the groups "Total patients with GDM" and "Control group"
**- among the groups "Patients with GDM on insulin therapy" and "Patients with GDM on dient therapy"

The incidence of familial obesity (parents and/or grandparents) in mothers who gave birth to infants with DF is 10% higher than in the group without DF (39.1% and 29.3% respectively). It is noteworthy that the occurrence of mothers' excessive weight at their own birth was noted six times higher than in the control group (38;6). The obtained data agree with other authors' opinion about epigenetic programming of obesity[13, 20, 23, 24].
The results showed that the DF formation was significantly influenced by gestational weight gain (GWG) - more than 11 kg in women with GDM. At that, pregestational obesity was observed in 42% of patients.The study of metabolomic homeostasis showed a direct correlation between the severity of GDM with DF development and the level of metabolites. (Table 2)

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Table 2. Indicators of metabolomic homeostasis in pregnant women with gestational diabetes mellitus

Group Metabolites	**Diet therapy 40**	**Insulin therapy 30**	**Control group 50**	**P**
Alanine, μmol\l	238±4.9	623±3.7	204±2.4*	0.025
Methionine, μmol\l	26.3±3.6	46.7±4.9	24.3±7.1*	0.032
Tyrosine, μmol\l	69.4±3.1	89±4.2**	72±4.2*	0.037
Phenylalanine, μmol\l	66.3±5.4	123.12±3.4	61.3±3.2*	0.04
Leucine+Isoleucine, μmol\l	284±32.4	410±23.4	232±22.4*	0.04

Note:
($p<0.05$):
*- among the groups "Insulin therapy" and "Control group"
**- among the groups "Patients with GDM on insulin therapy" and "Patients with GDM on dient therapy"

Relatively favorable metabolomic equilibrium parameters were found in patients undergoing diet therapy: alanine 238±4.9 μmol\l, methionine 26.3±3.6 μmol\l; phenylalanine 66.3±5.4 μmol\l; tyrosine 78.4±6.1 μmol\l, leucine+lsoleucine 284±32.4 μmol\l. The above-described metabolites are comparable with the control group.

The highest indicators of the amino acid composition were recorded in the blood of patients with GDM on insulin therapy. There was an increase in alanine, methionine, phenylalanine, tyrosine, valine, leucine + isoleucine. The presented data were observed in patients with difficulties in achieving target glycemic levels. It is in this group that the birth of children with DF was noted in more than half of the cases.

The patients who gave birth to children with DF had the lowest levels of the following metabolomes: C2 and C14 (Table 3).Given that C2 (acetylcarnitine) is a biologically active form of L-carnitine, its decrease slows down the transport of fatty acids to mitochondria and the regeneration of nerve cells, which, in combination with an increased content of C14 (tetradecanoylcarnitine), has a polysystemic effect on the fetus, including lipid metabolism [12, 17, 29].

Table 3. Indicators of metabolomic homeostasis in pregnant women with diabetic fetopathy

	DF Presence	**DF absence**	**P**
C2,μmol\l	4.09±0.02	6.56±0.41	0.027
C14,μmol\l	0.3250±0.09	0.2863±0.03	0.036

From the standpoint of bioenergy, a high content of alanine is a response to hypoxia, a decrease in energy supply to cells, a lack of neurotransmitters; it indicates possible formation of placental insufficiency. An increase in the level of valine can be described as ATP deficiency, which causes tissue hypoxia, activation of gluconeogenesis and, finally, impaired fetoplacental blood flow [17].

The toxic effect of increased phenylalanine on the fetal brain has been described; it also limits the

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supply of tyrosine and tryptophan through the blood-brain barrier and inhibits the synthesis of essential neurotransmitters [17, 29].

It becomes obvious that the abnormally high content of the listed metabolites, revealed in this study, lead to marked changes in metabolomic homeostasis in the body of a pregnant woman, to placental insufficiency formation, DF and programming of the newborn metabolism towards the development of obesity and metabolic syndrome in children in their later life.

Conclusion

Significant predictors for possible DF in patients with GDM are:

1. Familial nature of obesity.
2. The mother's weight at her birth (over 4000 g).
3. Pregestational obesity.
4. Excessive weight gain during pregnancy;
5. Low patient compliance: lack of pregravid preparation, late detection of GDM, which leads to a decompensated course of GDM and development of DF.

The obtained indicators of metabolomic homeostasis (acetylcarnitine, tetradecanoylcarnitine) and amino acids (alanine, phenylalanine, tyrosine, valine, leucine, isoleucine), indicating pronounced metabolic disorders in patients, can contribute to the prognosis and timely diagnosis of DF.

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