Peculiar Properties of Metabolism Women with Gestational Diabetes Mellitus

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ABSTRACT

The aimed of the study was to evaluate the peculiar properties of metabolism and the value of markers of insulin resistance women with gestational diabetes mellitus.

Methods: This was a prospective case-control study. The study included 219 pregnant women with GDM and 200 without disorders of carbohydrate metabolism, who gave birth during the period: II quarter of 2017– III quarter of 2018 in the maternity ward of the city clinical hospital №29 named after N.E Bauman in Moscow.

Results: The combination of GDM and obesity was observed for 94 (42.9%) patients. For 123 (56.2%) women obesity was family-like, occurring with relatives of the 1st and 2nd lines. In the group on dietary therapy, the proportion of pregnant women with obesity of grade 1-3 was 50%, which is 1.3 times less than among those who received insulin. Indicators of the level of insulin resistance (IR), the lipid spectrum of blood plasma was significantly worse in the group which received diet therapy: cholesterol 6,3 (5,7; 6,9) mmol / L, high density lipoproteins (LHL) 3,2 (2,8; 3,9) mmol / L, C-peptide 2,9 (1,9; 5,2 mmol / L) comparing to the group on insulin therapy: cholesterol 5,9 (5,4; 7,2) mmol / L, LHL 3,2 (2,6; 4,1) mmol / L, C-peptide 22,2

INTRODUCTION

The frequency of gestational diabetes mellitus (GDM) is increasing now with a lightning rate. The explosive growth of this disease associate with obesity because the combination of pre-gestational obesity and GDM is a common situation in present.¹ According to the facts by A.J. Reichelt at al. over the past 20 years, among patients with GDM, the proportion of having pregestational obesity has increased at least twice.² Obesity and diabetes was named by the world community at the I International Congress on obstetrics, fetal and neonatal medicine in London in 2017 "tsunami of the 21st century». ³ The combination of pregestational obesity and gestational diabetes mellitus GDM is currently the most common situation. In addition, there is an epidemiologically significant increase in the influence of other diabetogenic factors (age, assisted reproductive technologies, etc.), which cannot but affect not only the frequency, but also the nature of GDM. 4-6 Patients who had diabetes during pregnancy and their offspring has a 4-7-fold increased risk of obesity, cardiovascular diseases, type 2 diabetes.^{7,8} Due to the common etiological factors (genetic and epigenetic), pathogenetic mechanisms and clinical manifestations, a number of authors consider GDM not as an independent disease, but only as one of the manifestations of the metabolic syndrome.9,10

(1,6; 2,8) mmol / L (Me 25%,75%). The most frequent complication of pregnancy for patients with GDM was moderate pre-eclampsia, occurred with 126 (57.5%) women comparing to the control group - 6 (18.2%). For 77 (35.5%) patients with GDM pregnancy was complicated by the threat of interruption in the 1st trimester and for 53 (24.2%) in the 2nd trimester.

Conclusion: In the conditions of late diagnosis of GDM, late initiation of insulin therapy, indicators of IR level were worse for patients on diet therapy comparing to those who received insulin (C-peptide level, LDL). Information obtained allow us to consider GDM as a special form of metabolic syndrome.

Keywords: diabetes mellitus, insulin Resistance, GDM Pregnancy Correspondence:

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OBJECTIVES

The aimed of the study was to evaluate the peculiar properties of metabolism and the value of markers of insulin resistance women with gestational diabetes mellitus.

METHODS

This was a prospective case-control study. The study included 219 pregnant women with GDM and 200 without disorders of carbohydrate metabolism, who gave birth during the period: II quarter of 2017– III quarter of 2018 in the maternity ward of the city clinical hospital №29 named after N.E Bauman in Moscow. Only single-fetus full-term pregnancies were included in the study. (37,0-41,0 weeks of gestation). Exclusion criteria: multiple pregnancy, premature labor, post-term pregnancy. Informed written consent was obtained from all patients in this study.

This study was funded by the Ministry of Education and Science of the Russian Federation on the programme to improve the competitiveness of the Peoples' Friendship University of Russia (RUDN University) among the world's leading research and education centres in 2016–20. The diagnosis of GDM was made on the basis of diagnostic criteria approved by the Ministry of Health of the Russian Federation in the form of clinical guidelines (2016)¹¹. Among those examined with GDM 102 (46.5%) received insulin therapy, 110 had only a diet, 7 (3.2%) had diagnosed GDM only ex post (the birth of a child with phenotypic signs of diabetic fetopathy (DF)). The survey of the examined patients was conducted, studying: 1) family history of disorders of carbohydrate metabolism and obesity, 2) chronic somatic and gynecological diseases, 3) reproductive history, 4) complications of this pregnancy, the terms of GDM detection.

For the surveyed women in their plasma after fasting (with the onset of labor) were determined: C-peptide chemiluminescent method (analyzer Immulyte 2000 Xpi), fructosamines with alkaline reduction method, cholesterol, high- and low-density lipoproteins (HDL, LDL), triglycerides spectrophotometrically (analyzer ADVIA 1800). Glycosylated hemoglobin (HbA1C) was studied in venous blood by immune-inhibition method.

Statistical data processing was performed using the program Statistica v. 10.0. (StatSoft ©Inc., USA). For all

qualitative signs, absolute and relative frequencies are indicated, for quantitative - median (Me), 25%, 75%. When comparing binary features to determine the statistical significance of differences the exact Fisher criterion was used, and for quantitative traits the Mann-Whithey criterion was used (significance level p<0.05).

RESULTS

For the purpose of a general description of the level of maternal health, the study groups compared the frequency of typical clinical and anamnestic risk factors for GDM described in the literature (Domanski G., Lange A.E., Ittermann T., 2018; F.F. Burumkulova, V.A. Petrukhin , 2014).^{5,12} Table 1.

GDM(total)	GDM insulin therapy	GDM diet therapy	Control
n=219	n=102	n=110	n=200
32,2	32,0	32,0	29,3
(29,0; 36,0)	(29,0; 37,0)	(28,0; 36,0)	(27,0; 33,0)*
79,0	81,0	76,0	56,0
(63,0;96,0)	(67,0; 97,0)	(62,0; 90,0)**	(54,0; 65,0)*
28,3	29,0	27,5	20,0
(23,7; 34,7)	(24,5; 36,3)	(22,8; 33,9)**	(19,8; 22,5)*
94	51	42	0
(42,9%)	(50,0%)	(38,2%)	
113	54	53	8
(51,6%)	(5,8%)	(48,2%)	(24,2%)*
70	36	34	2
(32,0%)	(35,4%)	(30,9%)	(6,1%) *
123	57	61	11
(56,2%)	(55,9%)	(55,4%)	(33,3%)*
20	8	12	2
(9,1%)	(7,8%)	(10,9%)	(6,1%)
10	7	3	2
(4,5%)	(6,9%)	(2,7%)	(6,1%)
n=110	n=54	n=51	n=8
24	15	9	1
(21,8%)	(27,8%)	(17,6%)	(12,5%)*
31	18	13	0
(28,2%)	(33,3%)	(25,5%)	
	GDM(total) n=219 32,2 (29,0; 36,0) 79,0 (63,0; 96,0) 28,3 (23,7; 34,7) 94 (42,9%) 113 (51,6%) 70 (32,0%) 123 (56,2%) 20 (9,1%) 10 (4,5%) n=110 24 (21,8%) 31 (28,2%)	GDM(total) n=219GDM insulin therapy n=102 $32,2$ $32,0$ (29,0; 36,0) $(29,0; 37,0)$ $79,0$ $81,0$ (63,0; 96,0) $(67,0; 97,0)$ $28,3$ $29,0$ (23,7; 34,7) $(24,5; 36,3)$ 94 51 (42,9%) $(50,0\%)$ 113 54 (51,6%) $(5,8\%)$ 70 36 (32,0%) $(35,4\%)$ 123 57 (56,2%) $(55,9\%)$ 20 8 (9,1%) $(7,8\%)$ 10 7 (4,5%) $(6,9\%)$ $n=110$ $n=54$ 24 15 (21,8%) 31 18 (28,2%) $(33,3\%)$	GDM(total) n=219GDM insulin therapy n=102GDM diet therapy n=110 32.2 32.0 32.0 $(29,0; 36,0)$ $(29,0; 37,0)$ $(28,0; 36,0)$ $79,0$ $81,0$ $76,0$ $(63,0; 96,0)$ $(67,0; 97,0)$ $(62,0; 90,0)^{**}$ $28,3$ $29,0$ $27,5$ $(23,7; 34,7)$ $(24,5; 36,3)$ $(22,8; 33,9)^{**}$ 94 51 42 $(42,9\%)$ $(50,0\%)$ $(38,2\%)$ 113 54 53 $(51,6\%)$ $(5,8\%)$ $(48,2\%)$ 70 36 34 $(32,0\%)$ $(35,4\%)$ $(30,9\%)$ 123 57 61 $(56,2\%)$ $(55,9\%)$ $(55,4\%)$ 20 8 12 $(9,1\%)$ $(7,8\%)$ $(10,9\%)$ 10 7 3 $(4,5\%)$ $(6,9\%)$ $(2,7\%)$ $n=110$ $n=54$ $n=51$ 24 15 9 $(21,8\%)$ $(27,8\%)$ $(17,6\%)$ 31 18 13 $(28,2\%)$ $(33,3\%)$ $(25,5\%)$

Fable 1: The main clinical and anamnestic risk factors of GDM for the examined wom	nen
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Note:

BMI - body mass index, D-Diabetes mellitus, PCOS - Polycystic Ovary Syndrome, the differences are statistically significant (p< 0.05):

*- between groups «GDM total» and «Control»,

**- between groups «GDM insulin therapy» and « GDM diet therapy»

According to the Table 1, the pre-gestational body mass index (BMI) of pregnant women with GDM and the control group was 28,3 (23,7; 34,7) and 20,0 (19,8; 22,5) respectively (Me, 25%, 75%). The combination of GDM and obesity was observed for 94 (42.9%) patients. For 123

(56.2%) women obesity was family-like, occurring with relatives of the 1st and 2nd lines. In the group on dietary therapy, the proportion of pregnant women with obesity of grade 1–3 was 50%, which is 1.3 times less than among those who received insulin (Table 1).

Table 2: Insulin resistance biochemical markers of examined women, Me	25%, 75%
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group	GDM insulin therapy	GDM diet therapy
indicators		
HbAlc, %	5,34 (5,1; 5,8)	5,34 (5,1; 5,8)
Cholesterol, mmol / L	5,9 (5,4; 7,2)	6,3 (5,7; 6,9)
Triglycerides, mmol / L	3,1 (2,3; 3,5)	2,9 (2,1; 3,3)

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HDL, mmol / L	1,6 (1,3; 1,8)	1,6 (1,4; 2,0)
LHL, mmol / L	3,2 (2,6; 4,1)	3,2 (2,8; 3,9)
Atherogenic coefficient	2,9 (2,6; 3,4)	2,8 (2,3; 3,5)
Fructosamines, mmol / L	2,9 (2,4; 3,2)*	2,3 (2,1; 2,9)
C-peptide, mmol / L	2,2 (1,6; 2,8)*	2,9 (1,9; 5,2)

Note:

HDL- high density lipoproteins, LHL- low density lipoproteins

*- the differences are statistically significant (p< 0.05) between the compared groups.

According to the Table 2, indicators of the level of insulin resistance (IR), the lipid spectrum of blood plasma was significantly worse in the group which received diet therapy: cholesterol 6,3 (5,7; 6,9) mmol / L, high density lipoproteins (LHL) 3,2 (2,8; 3,9) mmol / L, C-peptide 2,9

(1,9; 5,2 mmol / L) comparing to the group on insulin therapy: cholesterol 5,9 (5,4; 7,2) mmol / L, LHL 3,2 (2,6; 4,1) mmol / L, C-peptide 22,2 (1,6; 2,8) mmol / L (Me 25%,75%). It should be noted that the levels of glycated hemoglobin in both groups did not differ statistically.

Group	GDM (total)	GDM insulin	GDM diet therapy	Control
	n=219	therapy	n=110	n=200
Indicators		n=102		
Early toxicosis	55	32	23	10 (30,3%)
	(25,1%)	(31,4%)	(20,1%)	
Pre-eclampsia	126	63	59	6 (18,2%)*
	(57,5%)	(61,8%)	(53,6%)	
Threat of interruption - I trimester	77	36	39 (35,5%)	4 (12,1%)*
	(35,5%)	(35,3%)		
Threat of interruption - II trimester	53	29	24	1 (3,0%)*
	(24,2%)	(28,4%)	(21,8%)	
Threat of interruption - III trimester	23	7	15	-
	(10,5%)	(6,9%)	(13,6%)	
The use of progesterone drugs	86	44	40	8 (24,2%)*
	(39,3%)	(43,1%)	(36,4%)	
Duration of progesterone drugs use,	11,0	11,0	13,0	8,0
weeks (Me, 25%,75%)	(5,8; 19,0)	(5,0; 18,0)	(5,0;20,5)	(4,0; 16,0)

Table 3: Pregnancy complications of examined women

Note:

*- the differences are statistically significant between the groups « GDM (total) » и « Control» (p< 0,05).

According to the Table 3, the most frequent complication of pregnancy for patients with GDM was moderate preeclampsia, occurred with 126 (57.5%) women comparing to the control group - 6 (18.2%). For 77 (35.5%) patients with GDM pregnancy was complicated by the threat of interruption in the 1st trimester and for 53 (24.2%) in the 2nd trimester. 86 (39.3%) of them received progesterone drugs as a treatment, which is 1.6 times more often than pregnant women without carbohydrate metabolism disorders.

DISCUSSION

According to the Table 1, pregnant women with GDM were older and had a greater body weight than patients in the control group. This is another confirmation of the significance of age and overweight as the main diabetogenic factors. ^{5,13,14}

The data of obesity frequency of pregnant women with GDM is really impressive: this is almost a half of those who were examined (Table 1). Indeed, we can talk about a kind of "pathological duet" - obesity and GDM. Moreover, for 2/3 of the patients with GDM obesity was family-like, occurring among relatives of the 1st and 2nd lines. Genetic and /or epigenetic nature of obesity, metabolic syndrome today can be considered a proven fact (Friedman J.E., 2015; Moen G.H. at al., 2017; Bogdanet D. at al., 2018).¹⁵⁻¹⁷ In this

regard, GDM undoubtedly, should be considered as one of the manifestations of the metabolic syndrome.

As can notice in the Table 1, patients with overweight and obesity were more likely to have need for insulin therapy than those of normal weight. Indeed, in the group on diet therapy, the proportion of pregnant women with obesity of grade 1–3 was 1.3 times less than among those who received insulin (Table 1). This would allow GDM, which requires insulin therapy, to be considered as a more severe form of gestational diabetes mellitus with bigger IR than dietary GDM.

However, indicators of the level of IR, plasma lipid spectrum were significantly worse in the group receiving diet therapy: higher cholesterol, LDL, atherogenic coefficient (p>0,05), C-peptide level (the differences are statistically significant, p <0.05) (Table 2).

Probably, the explanation of this fact may be associated with the later periods of diagnosis of GDM in the group who received only diet therapy as comparing to insulin therapy.: 26,0 (21,0; 30,0) and 24,0 (14,0;28,0) weeks, respectively (Me, 25%,75%, the differences are statistically significant (p < 0.05)). Likewise, different terms of regular visits to an endocrinologist: 29,0 (23,0;32,0) weeks for patients on insulin therapy and 30,0 (26,5;35,0) weeks on diet therapy (p < 0.05). Moreover, this difference was not due to the early manifestation of GDM (in the 1st

trimester), but a statement of fasting hyperglycemia at the end of the second and third trimesters for a half of the patients on diet therapy (57 (51.8%)). Regarding to the complications of pregnancy for patients with GDM, then, as follows from table 3, the most frequent was preeclampsia of moderate grade.

According to the Table 3, the most frequent complication of pregnancy for patients with GDM was moderate preeclampsia.

This disease occurred with almost every 3rd pregnant woman, which is 3 times more often than in the control group (Table 3, the differences are statistically significant (p <0.01)). It correlates with the literature data, a high incidence of pre-eclampsia for pregnant women with various types of diabetes.¹⁸⁻²⁰

Also we should note the fact that for patients with GDM significantly more often than for those in the control group, the threat of termination was diagnosed in the first half of pregnancy (Table 3), the differences are statistically significant (p < 0.01). This ended up with more frequent prescription of progesterone analogues: more than 35% of those examined with GDM received progesterone preparations starting from the 1st trimester, which is 1.6 times more often than pregnant women without carbohydrate metabolism disorders. The average duration of the treatment course was 11 weeks, the maximum was 36 weeks.

The question of prescribing progesterone, especially for patients with pre-gestational IR, is extremely relevant today due to the widespread use of assisted reproductive technologies and the was introduction of these drugs into the arsenal of therapeutic tools. What comes first: a low level of endogenous progesterone in the first half of pregnancy for patients with GDM (Ngala R.A. et al., 2017) or the action of exogenous progesterone drugs that provoke hyperglycemia?²⁰⁻²³

Literature data on this subject is completely polar: from the statement of high rates of IR in progesterone analogues treatment to the absence of any significant effect²⁴⁻²⁷ So modern features of GDM flow, characterized by a high frequency of IR, dyslipidemia, hypertensive disorders, epigenetic unfavorable background (family nature of obesity), allow us to consider GSD in the framework of the concept of metabolic syndrome.^{2,28-31}

CONCLUSION

- In the conditions of late diagnosis of GDM, late initiation of insulin therapy, indicators of IR level were worse for patients on diet therapy comparing to those who received insulin (C-peptide level, LDL).
- 2. Unreasonable prescription of progesterone analogs to pregnant women with pregestational IR should be avoided. Examined with GDM received progesterone analogues 1.6 times more often than pregnant without carbohydrate metabolism disorders.
- 3. Information obtained allow us to consider GDM as a special form of metabolic syndrome.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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