

Modern Notions of Health of Newborns from Mothers with Gestational Diabetes Mellitus

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ABSTRACT

The aimed of the study was to research of health of newborns from mothers with gestational diabetes mellitus.

Methods: The study included 210 pregnant women with gestational diabetes mellitus (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 No. 29 named after N.E. Bauman in Moscow. This was a prospective case-control study.

Results: One of the leading problems of the early neonatal period was morpho-functional immaturity: more than half of the children from mothers with GDM were born with signs of immaturity - 115 (54.8%). In the "on insulin therapy" group, children were 5 times more likely to have cardiomyopathy than those from mothers who were on a diet. With the same frequency in the control group, and for newborns from mothers with GDM, heart defects occurred: 20 (9.5%) and 24 (12.1%), respectively ($p > 0.05$). The main part of them were small

(valvular) heart defects: defects of the interventricular and interatrial septums (18 (8,6%) in GDM group). Conclusion: The level of health in the early neonatal period of newborns from mothers with GDM in modern conditions is determined mainly by morpho-functional impairments. The incidence of newborns from mothers who were on insulin therapy was higher than from mothers who only had a diet.

Key words: gestational diabetes mellitus, macrosomia, diabetic fetopathy, morpho-functional immaturity, cardiomyopathy, early neonatal period.

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INTRODUCTION

At this time in the modern literature there is almost no information on the most significant manifestations of diabetic fetopathy (DF) in children who were born to mothers with gestational diabetes mellitus (GDM), the main problems of the early neonatal period. This is due to the fact that the problem of complications in children from mothers with GDM is not limited only to the "traditional" symptom complex of diabetic fetopathy. According to data of J.E. Friedman (2015), Dell'Edera D., Sarlo F., Allegretti A. et al. (2017), existing before pregnancy disorders of carbohydrate and lipid metabolism, GDM, increase the risk of neural tube defects, minimal heart defects, liver steatosis and intestinal dysbiosis in newborns.^{1,2,3}

According to many authors, GDM today in developed countries does not affect the level of stillbirth, the need for resuscitation, the frequency of respiratory distress syndrome (RDS) (Billionnet C., Mitanchez D., Weill A. et al., 2017; Nikitina I.L., Konoplya I.S., Polyanskaya A.A. and others., 2017; Domanski G., Lange A.E., Ittermann T., 2018).^{4,6} What determines the level of neonatal disadvantage of children born by mothers with GDM in modern conditions?

OBJECTIVES

The aimed of the study was to research of health of newborns from mothers with gestational diabetes mellitus.

METHODS

The study included 210 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 No. 29 named after N.E. Bauman in Moscow. This was a prospective case-control study. 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 to competitiveness of the Peoples` Friendship University of Russia (RUDN University) «5-100» 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 (2014).⁷

The newborns study: 1) Assessment in the delivery room (anthropometric characteristics, including measurement of head circumference (HC), chest circumference (ChC), Quetelet index -I; Apgar score measurement; determination of phenotypic signs of diabetic fetopathy (DF) (Evsyukova I.I., Kosheleva N.G., 2012)⁸; 2) glycemia level in capillary blood; 3) clinical assessment of the early neonatal period; 4) echocardiography (Phillips HD11XE machine), neurosonography (Mylab 70 machine) on the third day of

life. The diagnosis “DF” was made in the presence of two or more phenotypic / clinical-morphological or a combination of one of them with one or more clinical and laboratory ones of a newborn.

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-Whitney criterion was used (significance level $p < 0.05$).

RESULTS

The examined mothers with GDM gave birth to 210 live, full-term newborns, 200 of women without carbohydrate metabolism disorder.

Table 1: Anthropometric characteristics of newborns

group \ indicators	GDM (total) n=210	GDM therapy n=102	insulin n=108	GDM diet therapy n=108	Control n=200
Macrosomia	55 (26,2%)	22 (21,6%)	30 (27,3%)	12 (6,0%)*	
Fetal growth retardation, I-III grade	14 (6,7%)	7 (6,9%)	8 (7,3%)	0	
Weight, gr	3670 (3260; 4000)	3585 (3250; 3900)	3690 (3300; 4010)	3300 (3130; 3590)	
Hight, cm	53,0 (51,0; 54,0)	53 (51;54)	53 (51; 54)	52 (51; 53)	
Quetelet-I index	69,4 (64,0; 73,8)	68,8 (62,7; 72,4)	69,6 (64,7; 73,8)	65,4 (61,4; 69,4)	
Chest circumference, cm	35 (34,0; 36,0)	35,0 (34,0; 36,0)	35,0 (34,0; 36,0)	34 (43,0; 35,0)	
Difference between head circumference - chest circumference, cm	1,0 (1,0; 1,0)	1,0 (1,0; 1,0)	1,0 (1,0; 1,0)	1,0 (1,0; 1,0)	

Note: * - the differences are statistically significant between the groups «GDM (total)» and «Control» ($p < 0,05$). As can be seen from table 1, 55 (26,2%) newborns from mothers with GDM had macrosomia.

Table 2: Anthropometric characteristics of newborns with DF, 5%, 95%.

group \ indicators	DF, n=97	Without DF, n=113
Macrosomia	46 (47,4%)	11 (9,0%)*
Fetal growth retardation, I-III grade	2 (4,1%)	11 (9,0%)
Weight, gr	3979 (2610; 5050)	3654 (2590; 4630)*
Hight, cm	53,5 (49,0; 57,0)	52,6 (48,0; 57,0)*
Quetelet-I index	73,2 (54,4; 88,6)	69,2 (54,0; 84,1)*
Chest circumference, cm	35,6 (32,0; 39,0)	34,9 (32,0; 38,0)*
Difference between head circumference - chest circumference, cm	0,6 (-2,0; 2,0)	0,8 (0; 2,0)*

Note: * - the differences are statistically significant between the compared groups ($p < 0.05$). DF- diabetic fetopathy.

For children with DF symptom complex, macrosomia was noted for 46 (47.4%) (Table 2). The Quetelet-1 index was higher in the DF group (73.2 (54.4; 88.6)), the differences were statistically significant ($p < 0.05$) than in the group of

healthy children. DF of newborns from mothers with GDM on diet therapy was diagnosed 1.4 times less than from mothers on insulin therapy: 36 (35.4%) and 51 (50.0%), respectively (the

differences are statistically significant, $p = 0.02$.
 Macrosomia was not a leading symptom (Fig. 1). The most frequently encountered are: soft tissue pasty (for 9/10

children with DF), a cushingoid body type (short neck, moon face and various signs of morpho-functional immaturity (Fig. 1)).

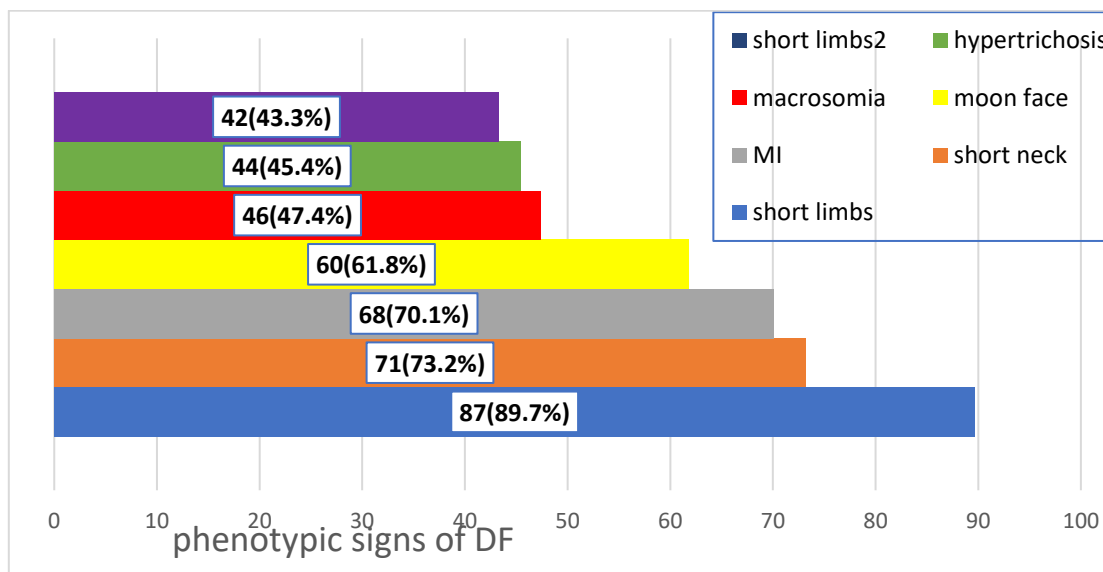


Fig. 1. The main phenotypic signs of DF of the examined newborns.

Note: MI- morpho-functional immaturity.

Assessment of newborns with the Apgar scale from mothers with GDM was not statistically significantly different from the control group; there were no differences among

newborns from mothers who received insulin and were on diet therapy (Table 3).

Table 3: The main complications of the early neonatal period

group \ indicators	GDM (total) n=210	GDM insulin therapy n=102	GDM diet therapy n=108	Control n=200
Assessment with the Apgar scale at the 1-st/5-th min, points, Me, 25%, 75%	8,0 (8,0; 9,0)/ 9,0 (8,0; 9,0)	8,0 (8,0; 9,0)/ 9,0 (8,0; 9,0)	8,0 (8,0; 9,0)/ 9,0 (8,0; 9,0)	8,0 (8,0; 9,0)/ 9,0 (9,0; 10,0)
Morphofunctional immaturity	115 (54,8%)	58 (56,9%)	57 (52,7%)	6 (3,0%)*
CNS depression syndrome	73 (34,7%)	40 (39,2%)	32 (29,6%)	12 (6,1%)*
reduced muscle tone	103 (49,0%)	33 (32,4%)	42 (38,9%)	24 (12,1%)*
Suppression of sucking reflex	59 (28,1%)	59 (57,8%)	24 (21,8%)**	12 (6,1%)*
Hypoglycemia	37 (17,6%)	21 (20,6%)	16 (14,8%)	6 (3,0%)
Hyperbilirubinemia	29 (13,8%)	17 (16,7%)	13 (12,0%)	24 (12,1%)
IRDS	22 (10,5%)	12 (11,8%)	11 (10,2%)	0
Need for artificial ventilation	6 (2,7%)	3 (2,9%)	2 (1,8%)	0
cardiomyopathy	17 (7,8%)	14 (13,7%)	3 (2,7%)**	0

Note:

CNS- central nervous system
 MI- Morphofunctional immaturity
 IRDS – Infant respiratory distress syndrome,

the differences are statistically significant ($p < 0,05$):

*- between the groups « GDM (total)» and « Control»

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

One of the leading problems of the early neonatal period was MI: more than half of the children from mothers with GDM were born with signs of immaturity - 115 (54.8%) (Table 3). This is more often than in the control group. (!). The frequency of occurrence of MI symptoms in a cohort of those who received insulin or only diet therapy did not differ.

According to the Table 3, central nervous system (CNS) depression syndrome complicated the early neonatal period for one-third of newborns from mothers with GDM (Table 3), and for 2/3 with DF (59 (60.2%)). Then, in the control group this complication occurred with 12 children (Table 3). Increased echogenicity of the periventricular zone was found for a half of the newborns with GDM (106 (50.4%)), whereas in the control group 2.4 times less (42 (21.0%)), $p < 0.05$. In case of DF, this symptom was even more common - for 58 (59.8%) of newborns.

A decrease in muscle tone, inhibition of reflexes at the assessment of births in the delivery room was also noted for a half of the newborns from mothers with GDM (Table 3), weak suck for a third, whereas in the control group only for 12. The vast majority of newborns with DF were not able to perform the act of sucking at all when they were attached to the breast early. -74 (76,3%).

Perinatal CNS damage is 1.3 times, and a decrease in the sucking reflex is 2.6 times more often observed for newborns from mothers on insulin therapy compared to those who received a diet (for the last indicator the differences are statistically significant, $p < 0,05$).

Hypoglycemia was also several times more common for children from mothers on insulin therapy, compared with those who received only a diet: every 5th and every 7th, respectively. However, the differences were not statistically significant.

Hypoglycemia in the early neonatal period was observed for 37 (17.6% of newborns from mothers with GDM), in the control group only for 6.

Hyperbilirubinemia was much less common, only for every tenth one, which is comparable with the control group - 24 (12.1%).

Severe "typical" complications of diabetes mellitus were noted only for a small number of newborns, the most frequent was hepatomegaly for 54 (25,7%), with DF-for 45 (46,4%); IRDS – for every tenth one - 22 (10,5%), almost all of them had DF - 20 (20,6%).

Hypertrophic cardiomyopathy was diagnosed for 17 (7.8%, all children with DF). According to the Table 3, in the "on insulin therapy" group, children were 5 times more likely to have cardiomyopathy than those from mothers who were on a diet. With the same frequency in the control group, and for newborns from mothers with GDM, heart defects occurred: 20 (9.5%) and 24 (12.1%), respectively ($p > 0.05$). The main part of them were small (valvular) heart defects: defects of the interventricular and interatrial septums (18 (8,6%) in GDM group).

DISCUSSION

However, according to the Table 1, macrosomia was not a leading phenotypic feature for newborns from mothers with GDM, and occurred only with every 4th one.

Even for children with the symptom complex, DF was observed in less than a half (Table 2). It correlates with current data on the frequency of macrosomia with GDM in developed countries: 14,6-45,0% (Kc K., Shakya S., Zhang H., 2015; Billionnet C., Mitanchez D., Weill A. et al., 2017).^{9,10} In a large population study C. Billionnet, D. Mitanchez, A. Weill et al. (2017) noted that fetal weight of more than 4000 g for patients receiving insulin therapy was more common than with GDM on diet therapy (18.2% and 14.6%, respectively).¹⁰ This was one of the reasons to consider GDM at insulin therapy as a more serious form of carbohydrate metabolism disorder.

According to our data - a diametrically opposite situation (Table 1), which may be due to a delay in the diagnosis of GDM and the late prescription of insulin therapy ($p > 0.05$). The children of mothers who received only diet therapy were larger (body weight, Quetelet index 1) than those who were on insulin therapy (although the differences are not statistically significant, $p > 0.05$). Therefore one cannot but agree with J. Crus, R. Grandia, L. Padilla et al. (2015), who think that fetal macrosomia is a kind of indicator of the quality of obstetric and endocrinological care for GDM.¹¹ According to the authors, one of the leading causes of high frequency of macrosomia is the delay in diagnosis (identification of GDM after 26 weeks of gestation).

In general, anthropometric indicators (weight, height, breast circumference) and their derivatives in the groups on diet and insulin therapy did not differ significantly (Table 1).

For children with DF, given the high level of disproportionate macrosomia (47.4%), the Quetelet index 1 was significantly higher than for newborns without DF (Table 2).

The problem of DF today is not framed with the question of macrosomia. In spite of the fact that pregnant women who were on dietary therapy of GDM more often gave birth to big children than those who received insulin, DF of their newborns was diagnosed 1.4 times less often: 39 (35.4%) and 51 (50.0%), respectively (the differences are statistically significant, $p = 0.02$). Even among the external indicators for newborns with DF, macrosomia was not the leading one (Fig. 1). Among the phenotypic signs of DF, the most frequent were: soft tissue pasty (for 9/10 children with DF), cushingoid body type (short neck, moon-shaped face, and various signs of morpho-functional immaturity (Fig. 1)).

As our study showed, for the diagnosis of DF, clinical and laboratory parameters, disorders of adaptation processes, rather than anthropometric characteristics, were much more important.

At the same time, the assessment of newborns with the Apgar scale from mothers with GDM was not statistically significantly different from the control group; there were no differences among newborns from mothers who received

insulin and those who were on diet therapy (Table 3). The obtained data confirmed the opinion of many authors that in modern conditions the prevalence of non-severe forms of DF in the GDM, the Apgar score may not be a sufficient criterion for the health status of newborns. (Ovesen P.G., Jensen D.M., Damm P. et al., 2015; Kc K., Shakya S., Zhang H., 2015; K.P. Yeagle, J.M. O'Brien, W.M. Curtin, S.H. Ural (2018)).^{9,12,13} According to K.P. Yeagle, J.M. O'Brien, W.M. Curtin, S.H. Ural (2018), the Apgar score for newborns from mothers with GDM allows only to understand whether a child needs resuscitation care.¹³ This situation is due to the fact that functional problems come to the first place: manifestations of morpho-functional immaturity, perinatal damage of the central nervous system.

The high incidence of morpho-functional immaturity of newborns from mothers with GDM (more than a half of those examined) was by not due to the period of gestation. The average gestational term at which delivery occurred to patients with GDM was 39.5 (38.5; 40.0) weeks (Me, 25%, 75%), including those with morpho functional immaturity 39.5 (38, 0; 39.5), and without such - 39.5 (38.5; 40.0) weeks, the differences are not statistically significant, $p > 0.05$.

According to the Table 3, CNS depression syndrome complicated the early neonatal period of one-third of newborns from mothers with GDM (Table 6), and of 2/3 with DF (59 (60.2%)). Then, as in the control group, this complication occurred with 12 children (Table 3). This is completely correlated with the literature data on the high frequency of neurological disorders of newborns with mother's GDM (Litvinenko, I.A., 2012; Nikitina, I.L., Konoplya, I.S, Polyanskaya, A.A, and others., 2017).^{5,14} Moreover, one of the main characteristics is the syndrome of CNS depression. The reasons for this are very diverse: starting from the morphological changes of placental hyperglycemia (edema, stromal fibrosis, etc.), cross-reaction of proteins of the nervous tissue with antibodies to insulin and its receptors, finally, difficult labor because of macrosomia (Litvinenko I.A., 2012; Mikhalev E.V., Shanina O.M., Saprina T.V., 2015).^{14,15}

The urgency of perinatal CNS lesions of children from mothers with GDM problem is confirmed by postnatal sonography (the third day of life). Increased echogenicity of the periventricular zone was detected for a half of the newborns with GDM (106 (50.4%)), whereas in the control group 2.4 times less (42 (21.0%)), $p < 0.05$. In case of DF, this symptom was even more common - for 58 (59.8%) of newborns.

A decrease in muscle tone, inhibition of reflexes in the assessment of births in the delivery room was also noted for a half of the newborns from mothers with GDM (Table 3), sluggish suction for a third, whereas in the control group only for two children. The overwhelming majority of newborns with DF were not able to perform the act of sucking at all, with an early attachment to the breast — 74 (76.3%).

As we can see from the Table 3, the state of newborns from mothers who received insulin therapy was more severe than in the group with diet therapy, although the Apgar score was practically no different, and the frequency of fetal macrosomia was higher. Thus, perinatal CNS damage is 1.3

times, and the decrease in the sucking reflex is 2.6 times more often observed for newborns from mothers on insulin therapy compared to those who had a diet (for the last indicator the differences are statistically significant, $p < 0.05$).

Hypoglycemia was a bit more common for children from mothers on insulin therapy, compared with those who only had a diet: for every 5th and for every 7th, respectively. However, the differences were not statistically significant. As for the effect of therapy on the frequency of hypoglycemia in newborns, there is no definite data. While some researchers have noted a higher incidence of hypoglycemia when using insulin therapy during pregnancy (compared with diet or oral antidiabetic drugs) (Rowan J.A., Hague W.M., Gao W. et al., 2008; Begum S., Dey S.K., Fatema K., 2018), others did not find such dependencies. (Bogdanet D., Egan A., Reddin C. et al., 2018).^{16,17,18} Perhaps the risk of neonatal complications is not due to the nature of the therapy, but to the fact that patients who need insulin had a higher "baseline" risk, pregestational obesity, excessive excessive gestational weight gain, and other aggravating moments.

In general, hypoglycemia in the early neonatal period was observed for 37 (17.6% of newborns from mothers with GDM), in the control group only for 62.

Hyperbilirubinemia was much less common, only for every tenth one, which is comparable with the control group - 24 (12.1%).

Severe "typical" complications of diabetes were noted only in a small number of newborns, of which the most frequent was hepatomegaly for 54 (25.7%), with DF for 45(46,4%); IRDS for every tenth one - 22 (10,5%), while almost all the children had a diagnosis of "DF" - 20 (20,6%).

Hypertrophic cardiomyopathy was diagnosed for 17 (7.8%, all children with DF). As follows from table 3, in the "on insulin therapy" group, children were 5 times more likely to have cardiomyopathy than those born from mothers on diet therapy. With the same frequency in the control group, and for newborns from mothers with GDM, there were heart defects: 20 (9.6%) and 24 (12.1%), respectively ($p > 0.05$). Most of them were small (valvular) heart defects: interventricular and interatrial septal defects (18 (8.7%) in the group with GDM).

Thus, the modern features of the course and the current level of diagnosis of GDM cause changes in the health status of newborns. "Severe", "typical" forms of DF are not leading in the structure of neonatal morbidity. The main manifestations of trouble in the early neonatal period are associated with morphofunctional immaturity, perinatal damage of the central nervous system, misadaptation in the early neonatal period. However, these morpho-functional disorders, as a rule, are associated with epigenetic changes, which, under the conditions of a pandemic of the metabolic syndrome, sharply actualizes the problem of GDM.

CONCLUSION

1. The level of health in the early neonatal period of newborns from mothers with GDM in modern conditions is determined mainly by morpho-functional impairments: morpho-functional immaturity, perinatal

- CNS damage, maladjustment in the early neonatal period.
2. CNS depression syndrome was observed for a third of newborns; decrease in muscle tone, depression of reflexes, signs of morphofunctional immaturity - for a half of newborns.
 3. The incidence of newborns from mothers who were on insulin therapy was higher than from mothers who only had a diet: hypertrophic cardiomyopathy occurred 5 times more often, depression of reflex activity (sucking reflex) - 2.6 times more often, there was a tendency to more frequent perinatal CNS and hypoglycemia.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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