ВЕСО-РОСТОВЫЕ ПОКАЗАТЕЛИ ДЕТЕЙ, РОЖДЕННЫХ ОТ МАТЕРЕЙ С ГЕСТАЦИОННЫМ САХАРНЫМ ДИАБЕТОМ, ОБУСЛОВЛЕННЫМ МУТАЦИЯМИ В ГЕНЕ ГЛЮКОКИНАЗЫ

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ОБОСНОВАНИЕ. Гестационный сахарный диабет (ГСД), обусловленный мутациями в гене глюкокиназы (*GCK*), является наиболее частой моногенной формой диабета, дебютирующей во время беременности. В отличие от остальных моногенных форм, назначение инсулинотерапии беременным с мутациями в гене *GCK* должно базироваться на генотипе плода, который до рождения, как правило, неизвестен. В настоящем исследовании мы оценили влияние инсулинотерапии на показатели веса и роста детей при рождении в зависимости от наличия или отсутствия у них аналогичной мутации.

ЦЕЛЬ. Изучить особенности весо-ростовых показателей детей, рожденных от матерей с ГСД, обусловленным мутациями в гене глюкокиназы, в зависимости от терапии.

МЕТОДЫ. В исследование было включено 38 пациенток с ГСД, обусловленным мутациями в гене *GCK*, и 45 их детей. Молекулярно-генетическое исследование беременных проведено с помощью метода высокоэффективного параллельного секвенирования (панель «Сахарный диабет»). Поиск аналогичных мутаций у детей проводился методом прямого секвенирования Сэнгера. Пациентки были разделены на 3 группы в зависимости от генотипа детей и получаемой во время беременности терапии. Проводилось сравнение весо-ростовых показателей детей при рождении с последующей оценкой влияния на них инсулинотерапии.

РЕЗУЛЬТАТЫ. Мы выявили статистически значимые отличия показателей роста (p=0,04) и веса (p=0,031) новорожденных детей в зависимости от генотипа ребенка и терапии матери. Показано, что риску развития макросомии подвержены младенцы, не унаследовавшие материнскую мутацию. Получено достоверное снижение показателей веса у детей с мутациями в гене *GCK*, чьи матери получали инсулинотерапию во время беременности. Однако оно укладывается в диапазон допустимых значений и не опосредует риски, связанные с гипотрофией новорожденного.

ЗАКЛЮЧЕНИЕ. При отсутствии возможности проведения пренатального молекулярно-генетического исследования назначение инсулинотерапии пациенткам с ГСД, обусловленным мутациями в гене *GCK*, способно предотвратить развитие макросомии у ребенка без аналогичной мутации и не приводит к патологическому снижению массы тела новорожденного, унаследовавшего материнскую мутацию. Важно придерживаться более мягкой тактики в достижении целевых показателей гликемии в отличие от пациенток с ГСД, обусловленным иными причинами.

КЛЮЧЕВЫЕ СЛОВА: гестационный сахарный диабет; глюкокиназа; макросомия; инсулинотерапия

BIRTH WEIGHT AND LENGTH IN OFFSPRINGS OF MOTHERS WITH GESTATIONAL DIABETES MELLITUS DUE TO MUTATIONS IN *GCK* GENE

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BACKGROUND. Gestational diabetes (GDM) due to *GCK* gene mutations is the most frequent form of monogenic diabetes mellitus (DM) presenting during pregnancy. It has been suggested that the use of insulin in pregnancies with fetuses carrying *GCK* mutations may lead to intrauterine growth retardation. In the present study we evaluated the effect of insulin therapy during pregnancy on birth weight and length in the offsprings of mothers with GDM due to *GCK* mutations.

AIMS. The aim was to study birth weight and length in offsprings of mothers with gestational diabetes mellitus due to mutations in *GCK*, depending on the therapy during pregnancy.

MATERIALS AND METHODS. The study included 38 patients with GDM caused by *GCK* gene mutations (18.7%) and the 45 offsprings. To define molecular basis of GDM in pregnant women we used a targeted NGS. 'Diabetes panel' genes were

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sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). To found the same mutations in their offsprings was used Sanger sequencing. All children were divided into 3 groups depending of their genotype and therapy received by the mothers during pregnancy.

RESULTS. We found statistically significant differences in birth length (p=0.04) and weight (p=0,031) depending on the genotype of the child and therapy in the mother. The risk of macrosomia was shown in non-mutation-carrying offsprings only. The birth weight in children with *GCK* gene mutations whose mothers received insulin during pregnancy was significantly lower. However, the birth weight remained in the normal range.

CONCLUSIONS. Since prenatal diagnostics in the mothers with *GCK* gene mutations is not always justified, we recommend insulin therapy in order to prevent fetal macrosomia, which, however, should be less aggressive than in GDM due to other causes.

KEYWORDS: gestational diabetes mellitus; glucokinase; macrosomia; insulin therapy

The spectrum of diabetes mellitus in pregnant women is represented by diabetes mellitus types 1 (DM1) and 2 (DM2), gestational diabetes mellitus (GDM) and monogenic forms [1, 2]. The latter include dominant inherited variants of the disease caused by defects in one of the genes that regulate the function of beta cells, which include primarily the subtypes of diabetes MODY (Maturity-Onset Diabetes of the Young) [3]. The genetic defect causing hyperglycemia plays a decisive role in the determination of fetal size in patients with MODY diabetes [4].

Inactivating heterozygous mutations in the glucokinase gene (*GCK*) lead to the development of diabetes mellitus type MODY2 which results in a benign hyperglycemia with early onset and high penetrance [5]. MODY2 has been well studied and is recognised as one of the most common subtypes of monogenic diabetes in the world [6]. In addition, MODY 2 is associated with the development of GDM [7]. Approximately 10% of all cases of GDM are caused by a glucokinase deficiency [8]. Mutations in the *GCK* gene are found in 18.7% (38/203) of patients with GDM [9]. It is extremely important to detect this glucokinase deficiency in patients with GDM, because only these cases carry a risk of macrosomia and fetopathy mediated by the foetus genotype, regardless of the hyperglycemia in the mother.

The progeny of *GCK*/GDM mothers provide a unique view for understanding the effects of moderate hyperglycemia in utero, which differs from those in DM1 or DM2 due to its significantly less variability and its small response to insulin therapy. In this case, the development of macrosomia is characteristic only of infants without a mutation in the *GCK* gene because they are susceptible to the maternal hyperglycemia, and their weight on average exceeds the average birth weight by 700 g [10]. Children who inherit the mutation have the same homeostatic glucose level as their mothers, and maintain a higher glucose level as normal. Therefore, minor hyperglycemia in these cases does not adversely affect the weight of the child, and the use of insulin for the treatment of *GCK*/GDM is an independent risk factor for the birth of a low birth-weight baby [11].

Despite the large number of studies on GDM caused by mutations in the *GCK* gene, the features of fetal weight and height based on the genotype have been analysed in retrospective studies conducted on small samples and often represent a description of individual clinical cases [12, 13]. In addition, the effect of the antihyperglycemic therapy received by the mother with *GCK*/GDM on the fetal weight and height, depending on the fetal genotype has not been studied.

AIM

We designed this study to assess the effect of insulin therapy for pregnant mothers with GDM caused by mutations in the *GCK* gene on the birth weight and height rates of their infants (with or without a similar mutation).

MEDIANTHODS

Study design

We identified pregnant women with GDM caused by *GCK* mutations based on the results of molecular genetic studies. All newborns and children from previous GDM pregnancies were tested for the presence of similar mutations. We compared weight and height indices of infants according to their genotypes and based on the therapy received by their mothers.

Acceptance criteria

We enrolled 203 patients with GDM and negative autoantibodies titers (ICA, IA2, IA, GAD) in the study. GDM was diagnosed according to the recommendations of the Russian National Consensus 'Gestational Diabetes Mellitus: Diagnosis, Treatment and Postnatal Observation' [14].

Conditions of the study

This research was initiated within the framework of the grant of the Russian Science Foundation No. 16-15-10408. We examined the patients according to the standards of the Moscow Regional Research Institute of Obstetrics and Gynecology (MRRIOG, director is Prof. V.A. Petrukhin). Molecular genetic analyses were conducted in the laboratory of the department of hereditary endocrinopathies of the National Medical Research Center of Endocrinology of the Ministry of Health of the Russian Federation (head of the department, MD A.N. Tyulpakov).

Duration of the study

2016-2017

Description of medical participation

Pregnant women monitored their glycemia daily using personal glucometers and recording each obtained level in the self-control diary. Insulin therapy (basic-bolus regimen) was prescribed only in cases of dietotherapy ineffectiveness. According to the recommendations of the national guideline 'Neonatology', the pregnancy was considered full-term at anytime during the 37th–42nd week [15]. Newborns' weight and height were assessed immediately after birth, calculating standard deviation (SD) values according to the gestational age, using the 'Auxology' programme (Pfizer). We defined intrauterine growth retardation (or 'small for gestational age') as a decrease in body weight and height at birth below the 10th percentile for the gestational age. We considered any birth weights <2500 g at any gestational age as low (hypotrophy). And, we diagnosed diabetic fetopathy (DFP) in newborns with an increase in body weight at birth above 2 SD, in combination with signs of disproportionate development (large parenchymal organs, short neck and limbs, small head, broad shoulder girdle, thick nuchal fold), thickening and oedema of the subcutaneous fat layer, and signs of neonatal hypoglycaemia.

Venous blood samples for the molecular genetic study (MGS) were obtained at the time of GDM diagnosis. Genomic DNA was isolated from peripheral blood leukocytes by a standard method (Pure Link Kit, Genomic DNA Mini Kit, Life Technologies, USA). We used a high-performance parallel sequencing (NGS) method for the molecular genetic analysis of mothers, with a primer panel for multiplex PCR and sequencing using Ion Ampliseq™ Custom DNA Panel technology (Life Technologies, USA) developed in the department of hereditary endocrinopathies of the National Medical Research Center of Endocrinology. Sequencing was performed on a semiconductor sequencer PGM (Ion Torrent, Life Technologies, USA). We used the Torrent Suite 4.2.1 software module (Ion Torrent, Life Technologies, USA) and the Annovar software package (version 2014Nov12) for bioinformatic processing of the sequencing results. We interpreted the results and assessed the pathogenicity of nucleotide changes according to international recommendations [16]. Subsequently, we tested the newborn children for similar mutations using the sequencer Genetic Analyzer Model 3130 (Life Technologies, USA) [17].

Analysis in groups

Our final analysis group included 38 patients with GDM caused by *GCK* gene mutations, and 45 children (from 36 current deliveries and 9 previous pregnancies). We analysed the outcome of 41 pregnancies taking place with GDM caused by heterozygous mutations in the *GCK* gene. We formed 3 groups of patients depending on the presence or absence of mutations in the *GCK* gene in each child (C+ and C–, respectively) and the therapy received by the mother (M) during pregnancy (M+/Insulinotherapy, M+/Dietotherapy).

Group 1: M+/C+/Insulinotherapy (Mother *GCK*+/ Child *GCK*+/ Insulinotherapy): 22 infants with a *GCK* gene mutation, whose mothers received insulin therapy.

Group 2: M+/C+/Dietotherapy (Mother *GCK*+/ Child *GCK*+/Dietotherapy): 7 children with a *GCK* gene mutation, whose mothers were prescribed a diet.

Group 3: M+/C-/Insulin therapy (Mother *GCK*+/ Healthy child/Insulin therapy): 16 newborns who did not inherit the maternal mutation, whose mothers received insulin therapy during pregnancy.

Methods of recording outcomes: we created databases to record clinical data of the gestation course, glycemic level, insulin doses, MGS results and weight and height indices of newborns. We interviewed the mothers to obtain weight and height rates of children from previous pregnancies with GDM.

Ethical review

The local ethics committee of the MRRIOG approved this study (Protocol No. 88 of 30/06/2016). Al participant patients signed informed consent forms, including for the examination of their children.

Statistical processing

We used Microsoft Office Excel 2010 and Statistica 6.0 for statistical processing of the data. The statistical significance was determined using the Mann–Whitney test. We considered differences significant at $p < 0.05$. We performed Kruskal–Wallis variance and correlation analysis using Spearman (R) and Gamma (G) coefficients calculations. The data are presented as medians (lower quartile, upper quartile).

Table 1. Clinical characteristics of patients by groups

	Group 1 (n = 22)	Group 2 (n = 7)	Group 3 (n = 16)
Gender (boys/girls)	10/12	5/2	10/6
Gestational age, m, weeks	38.7±1.2	39 ±1.2	37.7±2.2
Weight, g, median	3125 [2800;3300]	3540 [3290;3670]	3550 [2930;3890]
Weight SD, median	-0.51 [-1.17;0.17]	0.44 [0.21;0.7]	0.66 [0.48;1.92]
Height, cm, median	50 [48;51]	53 [52;54]	52 [49;53]
Height SD, median	0.4 [0.16;1.01]	1.2 [0.7;2.3]	0.7 [-0.04;2.1]
Average daily glycemia, mmol/l	6.3 [2.1;11.3]	-	6.18 [2.7;12]
Initiation of insulin therapy, weeks	12.5 [1;30]	-	14.5 [5;34]
Dose of insulin, U/kg	1.2 [0.8;1.4]		0.7 [0.5;0.8]

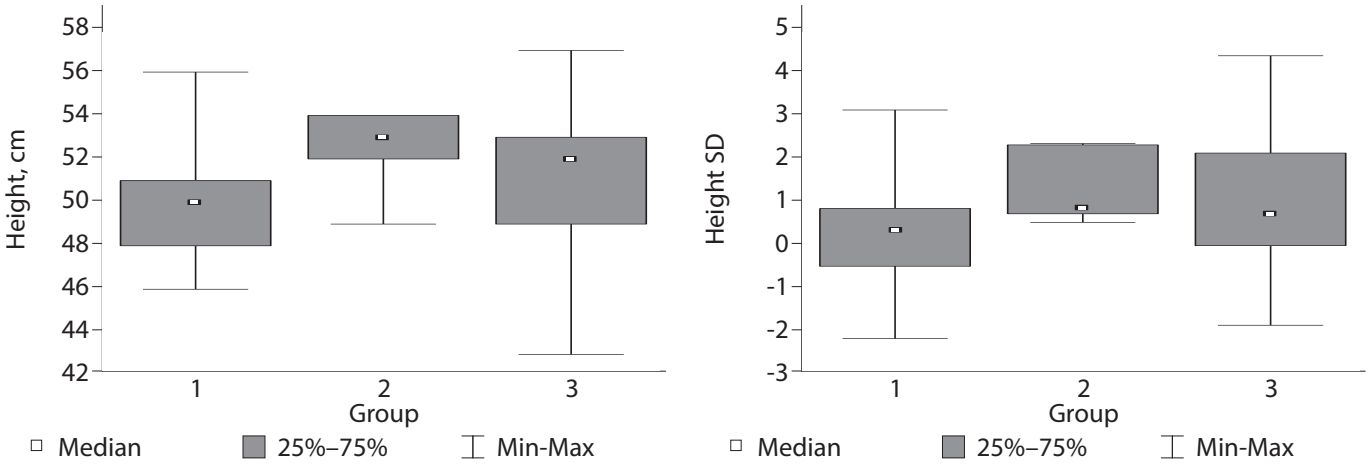

Fig. 1. Indices of height and SD in newborns

RESULTS

Study subjects (participants)

We found *GCK* gene mutations in 18.7% (38/203) patients with GDM. The average age of the patients was 27.0 years [24.0, 30.0]. The median gestational age at the time of GDM diagnosis was 9 weeks [7, 20]. The delivery terms ranged from 31 to 42 weeks and were not statistically different between groups (p = 0.21), being 38.7 ± 1.2 weeks in group 1, 39 ± 1.2 weeks in group 2 and 37.7 ± 2.2 weeks in group 3. In two cases, preterm labours took place at week 36 (group 1) and at week 31 (group 3).

We used the Sanger method to search for similar mutations in 45 children. The results were collected into 3 groups: group 1 included 22 children (10 boys and 12 girls) with mutations in the *GCK* gene, whose mothers received insulin therapy during pregnancy. Group 2 included 7 children (5 boys and 2 girls) with *GCK* gene mutations, whose mothers underwent dietotherapy during pregnancy. Group 3 comprised 16 children (10 boys and 6 girls) without mutations in the *GCK* gene. All mothers of children in Group 3 received insulin therapy during pregnancy. The times to initiation of insulin therapy and the glycemia levels in groups 1 and 3 were not significantly different. Clinical characteristics of the patients are presented in Table 1.

Primary results of the study

The Kruskal–Wallis variance analysis revealed the presence of statistically significant differences in growth (p = 0.04) and weight (p = 0.031) indices of newborns.

In group 1, the heights of newborns ranged from 46 to 56 cm. The median height was 50 cm [48, 51], and the standard deviation coefficient was −2.2 to 2.3 (median 0.44 [0.16, 1.01]). Only 1 child had height SD <−2 SD (with weight SD −1.44), due to fetoplacental insufficiency. In group 2, the heights of children ranged from 49 to 54 cm (median 53 [52, 54]) and were significantly higher (p = 0.013) than those of children in group 1. The standard deviation coefficient varied from 0.5 to 2.3 SD (median 1.2 [0.7, 2.3]). In group 3, the heights of children ranged from 43 to 57 cm (median 52 [49, 53]) and did not differ significantly from the indices in group 1 (p = 0.15) or group 2 (p = 0.32). The standard deviation coefficient ranged from -1.89 to 4.37 SD (median 0.7 [-0.04, 2.1]) (Figure 1).

The weights of newborns in Group 1 ranged from 2,560 to 3,960 g (median 3125 [2800, 3300]). The standard deviation coefficient varied from −1.79 to 0.87 SD (median −0.51 [−1.17, 0.17]). In 1 case of preterm delivery at week 36, the SD weight was −1.9 SD (height SD of −0.5). Insulin therapy in this patient was initiated at the stage of pregnancy planning (the maximum dose in the III trimester was 1.1 U/kg). However, the glycemic

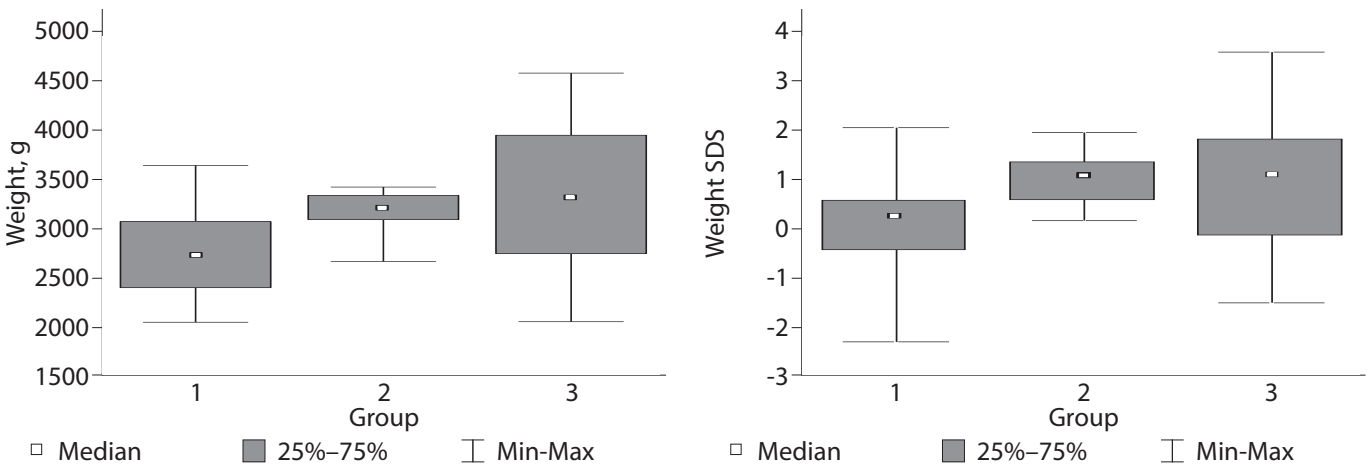

Fig. 2. Показатели веса и SDS веса новорожденных детей.

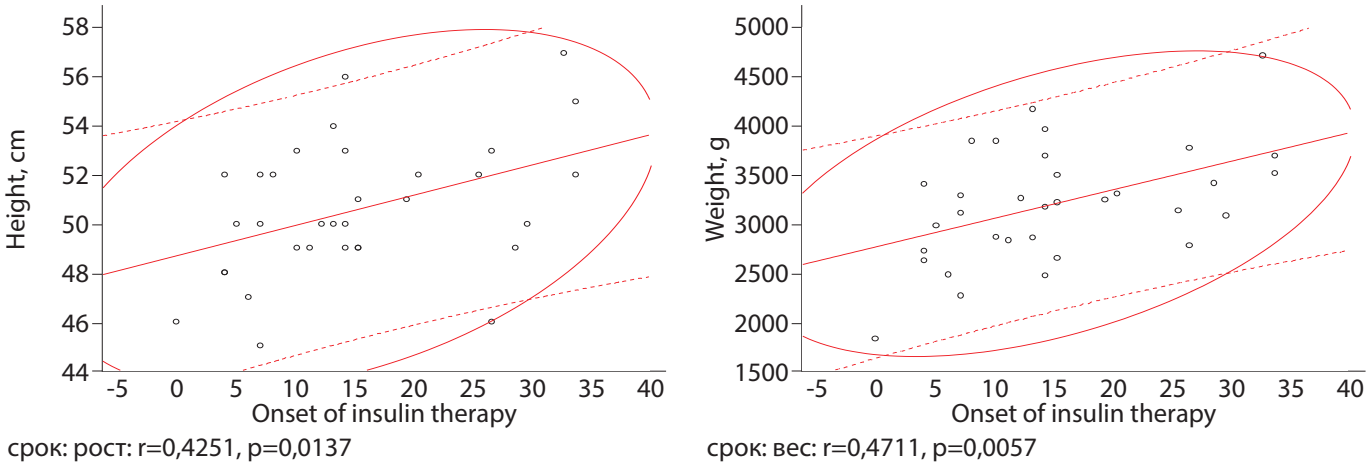

Fig. 3. Взаимосвязь весо-ростовых показателей новорожденных детей и срока начала инсулинотерапии у беременных с *GCK*/ГСД.

indices did not reach the target values (up to 8.3 mmol/L in the fasting state, and 10.0 mmol/L 1 hour after meals) throughout the pregnancy. The weights of newborns in group 2 ranged from 3,100 to 3,950 g (median 3540 [3290, 3670]) and were significantly higher than in group 1 (p = 0.02). The standard deviation coefficient varied from 0.5 to 2.3 (median 0.44 [0.21, 0.7]). The weights of newborns in group 3 were between 2310 and 4730 g (median 3550 [2930, 3890]), and the standard deviation coefficient was −1.9 to 3.2 SD (median 0.66 [0.48, 1.92]) in 3 children (18.8%) exceeding 2 SDs. we found a significant difference between the children's weight indexes in patients of groups 1 and 3 (p = 0.036). Diabetes fetopathy signs were noted in 6 (37.5%) newborns, including 1 child born at the week 31 of gestation (weight SD +2.3) (Figure 2).

Adverse events

In this study, we did not encounter any adverse events.

DISCUSSION

Summary of the primary result of the study

We performed a comparative analysis of the weight and height indices of newborns born from mothers with GDM caused by mutations in the *GCK* gene, depending on the presence or absence of a similar mutation in the child and the treatment of mothers received during pregnancy. We found that the risk of macrosomia development is higher for children who did not inherit a similar maternal mutation. On the other hand, children with mutations in the *GCK* gene had decreased weight and height rates when insulin therapy was administered to the mothers during pregnancy.

Discussion of the primary result of the study

In the course of our study, among the patients in groups 1 and 2, we found a correlation in of weight (G = 0.61, p = 0.0058) and height (G = 0.69, p = 0.0019) indices with the therapy received by their mothers during pregnancy (diet/insulin). The weights of newborns whose mothers received dietotherapy were significantly higher than those of newborns in the other groups.

In newborns from women who received insulin therapy during pregnancy, we found a correlation between the onset of insulin therapy and the height and weight indices of the foetuses. Insulin therapies were initiated on pregnancy weeks 1–34.

This relationship was more pronounced in children with mutations in the *GCK* gene than in children without mutations. In fact, the weights of children who did not inherit the maternal mutation (M+/C–) were higher than those of children with mutations (G = 0.41, p = 0.01). It should be noted that an earlier onset of insulin therapy was associated with weight normalisation in children without mutations and weight reduction in children with mutations (Figure 3).

We found 3 newborns with a tendency toward low birth weight in group 1. In 1 patient with a late onset of insulin therapy (week 22) and low compliance (height −1.3 SD/weight −1.4 SD), this retardation was symmetric and mediated by fetoplacental insufficiency. In the other 2two cases, the weight deficit prevailed over the height deficit (height −1.3 SD/weight −1.8 SD, height −0.5 SD/weight −1.4 SD). The insulin therapy (in the 3rd trimester at 1.1–1.4 U/kg) in these cases was started early (at 5 and 7 weeks), with the achievement of strict glycemic targets (up to 5.1 mmol/l fasting, and 7.0 mmol/l after meals) and episodes of hypoglycaemia. In cases where insulin therapy was not aggressive, and glycemic parameters varied over a wider range (up to 12.4 mmol/l after meals), we did not find any newborns with reduced weight and height indices. It should be noted that high glycemic variability and difficulties in achieving glycemic targets despite the use of large doses of insulin in women with *GCK*/GDM suggest that the foetus carries a similar mutation.

In group 3, we found a high percentage (37.5%) of children born with signs of diabetic fetopathy. In half of them, diabetic fetopathy was mediated by the late onset of insulin therapy (after week 29), in others it was mediated by low patient compliance. At the same time, in order to achieve glycemic target values, the patients required lower doses of insulin than patients whose children had inherited a similar mutation.

Thus, this study showed that only infants who do not inherit the maternal mutation are at risk for developing macrosomia. These results coincide with the data of a number of foreign authors [10, 11, 18]. According to the literature, if the mother and child have mutations in the *GCK* gene, the effects eliminate each other, and the baby is born with a normal weight. Only one case in the

literature reported reduction in the birth weight of an infant from a mother with *GCK*/GDM receiving insulin therapy, and this was most likely due to an aggressive decrease in maternal hyperglycemia [19]. In our study, we found a tendency in children with the *GCK* gene mutation, whose mothers received insulin therapy during pregnancy, to present low weight and height rates. However, the low weight was not critical and was within the range of normal anthropometric indicators for newborns.

Limitations of the study

The main limitation of our study is the small number of patients in group 2 (i.e. those who did not receive insulin therapy during pregnancy). All patients in this group were born from previous pregnancies in which the mothers had also had GDM.

CONCLUSION

The 'gold standard' management for diabetes during pregnancy caused by mutations in the *GCK* gene would in theory include pre-natal determination of the foetus genotype. However, given the risks associated with this, and the fact the absence of a pronounced negative effect of insulin therapy on the weight and height at birth, it is difficult to justify the application of this recommendation. Instead expanding the range of target glycemia in patients with *GCK*/GDM will reduce the weight in children with the same mutation, while allowing others without the inherited mutation to develop without macrosomia.

ADDITIONAL INFORMATION

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Conflict of interest. The authors declare having no obvious or potential conflicts of interest related to the publication of this article.

Participation of authors. N.A. Zubkova - study concept and design, data analysis, manuscript writing; O.N. Makretskaya, A.N. Tulpakov –molecular-genetic experiments, study concept and design, data analysis, manuscript writing; F.F. Burumkulova, M.A. Plekhanova, V.I. Ulyatovskaya, A.E. Panov - material collection, data analysis.

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