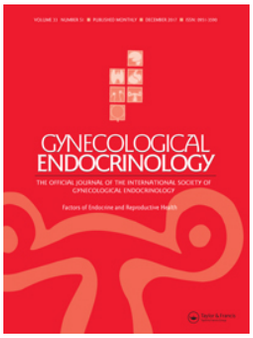

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Risk factors of cerebral ischemia in infants born to mothers with gestational diabetes

J. S. Shupletsova[a], N. V. Bashmakova[a], N. V. Putilova[a], E. G. Deryabina[a], T. B. Tretyakova[a], L. A. Pestryaeva[a] and P. B. Tsyvian[a,b]

[a]Ural Scientific Research Institute of Maternity and Child Care, Yekaterinburg, Russia; [b]Department of Physiology, Ural State Medical University, Yekaterinburg, Russia

ABSTRACT

Objectives: Gestational diabetes mellitus (GDM) is carbohydrate intolerance that occurs during pregnancy. The present study was arranged to determine the risk of cerebral ischemia (CI) in infants born to mothers with gestational diabetes mellitus and *MTHFR* gene polymorphism.

Material and methods: The study includes 70 pregnant women with GDM, divided into two groups depending on existence of cerebral ischemia (CI) in newborn infants. All patients were tested for coagulation cascade components, polymorphisms of the methylenetetrahydrofolate reductase (MTHFR) gene and assessed by thromboelastography (TEG).

Results: We observed that there was an increased frequency (74.2%) of 1298C *MTHFR* genotype carriers among women with CI newborns. The state of hypercoagulation according to both coagulation cascade tests and TEG data was diagnosed in women of this group.

Conclusions: The results of this study suggest that hyperglycemia may program the development of cerebral ischemia in infants born to women with 1298C *MTHFR* gene polymorphism.

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KEYWORDS
Gene polymorphism; gestational diabetes; neonatal cerebral ischemia programing

Introduction

Gestational diabetes mellitus (GDM) is a frequently encountered condition during pregnancy which is related to insulin resistance and inadequate insulin secretion at hyperglycemia. According to the International Diabetic Federation, 20.9 millions (16.2%) infants were born in the world in 2015 to the mothers with GDM or mothers affected by other forms of hyperglycemia [1]. There is a significant concordance in observed incidence of GDM, metabolic syndrome and obesity in the modern population of pregnant women [2,3].

Impact of diabetes on the coagulation system and endothelial functions is known for many years. Hemostatic factors and activities are influenced by the hyperglycemic state. Moreover, pregnancy induces a hypercoagulable state as a physiological mechanism to ensure the hemostatic balance by preventing massive maternal blood loss at delivery [4].

It is important to recognize and monitor GDM tightly due to the risk of adverse effects on the mother and the fetus such as development of preeclampsia, placental insufficiency, prematurity and necessity for cesarean section and its association to birth injuries [5].

High risk of metabolic disturbances, respiratory distress syndrome and neurological injuries was demonstrated in infants born to mothers with GDM. These adverse effects could persist in these infants during a later life [6].

Most of the perinatal neurological injuries (intraventricular hemorrhage, cerebral ischemia) could be considered as a complex developmental disorders, with contributions from both the environment and the gene. It was demonstrated that polymorphisms in methylenetetra-hydrofolate reductase (*MTHFR*) gene are associated with neonatal cerebral injuries in the presence of perinatal hypoxia [7].

Considering the impact of GDM on the coagulation system and placental oxygen transport the influence of gene polymorphisms on the fetus and newborn infant remain still unclear. The objective of the study was to determine the risk of cerebral ischemia in infants born to mothers with gestational diabetes mellitus and *MTHFR* gene polymorphism.

Methods

Recruitment of subjects

A total of 70 subjects were recruited (2011–2016) and gave their informed consent at admission to labor and delivery at Maternity and Child Care Research Institute (Yekaterinburg, Russia) as a part of ongoing investigation of gestational diabetes approved by the institutional ethics committee.

According to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria [8], irrespective of gestational age, the diagnosis of GDM during pregnancy is made on the basis of fasting glucose $\geq$126 mg/dL; glucose $\geq$200 mg/dL, measured 2 h after a 75 g glucose oral load; or a random blood glucose level $\geq$200 mg/dL, associated with clinical symptoms.

Fasting glucose values of 92–125 mg/dL or glucose levels of 153–199 mg/dL, measured 2 h after a 75 g glucose load, were used to confirm the diagnosis of GDM [9].

CONTACT P. B. Tsyvian pavel.tsyvian@gmail.com Department of fetal antenatal care, Ural Scientific Research Institute of Maternity and Child Care, Head Dep of Physiology, Ural State Medical University, Repin str.3, 620028 Yekaterinburg, Russia

Exclusion criteria for this study were: type-1 and type-2 diabetes, autoimmune and inflammatory diseases, maternal or fetal infections and fetal congenital anomaly.

All women were treated with diet control alone throughout the pregnancy. All newborn infants were consulted by pediatric neurologist within 3 days after birth and brain ultrasound investigations were performed using Philips HD 15 (Philips Medical Systems, USA) ultrasound machine with 5 MHz probe.

Women with GDM were divided into two groups depending on existence of cerebral ischemia (CI) in newborn infants. First (main) group contains 31 women delivered infants with CI, 2d (control) group contains 39 women who delivered infants without CI.

Standard coagulation tests were monitored for each patient before the labor or cesarean delivery. Whole venous blood specimens (3.0 ml) were collected into vials containing 0.3 ml of 3.2% sodium citrate. One milliliter of blood was removed for thrombolastography (TEG) analysis while the reminder was used for clinically indicated PTT and fibrinogen assays. TEG determinations were performed on Helena AC-4 analyzer (Helena Bioscience Europe, UK) according to the manufacturer's instruction.

The four variables directly measured were: (1) Clotting Time (R): the time of latency until initial fibrin formation, (2) Clot Kinetics (K): the speed at which a specific level of clot strength is achieved (20 mm amplitude), (3) Angle (α): the rapidity of clot strengthening and (4) Maximum Amplitude (MA): the ultimate strength of the clot. Additionally, a coagulation index (CI) was derived from the four directly measured variables. Finally, the LY30 measures the rate at which amplitude decreases 30 min after MA is achieved and is representative of clot breakdown or fibrinolysis. Also standard tests, including partial thromboplastin time (PTT), international normalized ratio (INR), thrombin time (TB), fibrinogen concentration and fibrinolytic activity (FA) to assess the coagulation cascade effectiveness were performed. Maternal buccal epithelium samples were genotyped using real-time PCR by DT-96 equipment, kits and manuals of DNA Technology (DNA Technology, Russia).

Statistical analysis

The agreement of the genotype distribution with the Hardy–Weinberg equilibrium was assessed using the exact test. A chi-square test was used to compare genotype and allele distribution between groups. Coagulation parameters were compared between genotype groups using the Mann-Whitney test. Statistical significance was assessed at the value of $p < .05$.

Table 1. Clinical and demographic characteristics of study population.

Parameters	Group 1 (*MTHFR*: 1298/C) ($n = 31$)	Group 2 (*MTHFR*: 1298AA) ($n = 39$)
Maternal age (years)	31.8 ± 1.3	32.1 ± 1.4
Parity	2.0 ± 1.2	1.9 ± 1.1
BMI before pregnancy	23.5 ± 1.3	24.6 ± 0.9
BMI at pregnancy	27.2 ± 1.2	28.2 ± 0.8
Neonatal birth weight	2432.6 ± 458.8*	3521.7 ± 352.1
Gestational age (wk)	37.2 ± 1.1	38.3 ± 1.3
Cesarian delivery (n,%)	15 (48%)	18 (46%)
Apgar at 1st min	5.3 ± 0.6*	7.8 ± 0.4
Apgar at 5th min	6.3 ± 0.7*	8.4 ± 0.5

*Statistical significance $p < .05$.

Results

Maternal and neonatal clinical parameters for both studied groups are shown in Table 1. The two groups were not different for maternal age, parity, maternal BMI and incidence of cesarean delivery. However, mean neonatal birth weight was significantly less in 1st group than in 2d group. Also significant difference was demonstrated for 1 min and 5 min Apgar scores between two groups.

We have analyzed the frequency of determination of the genotype which contain the 'risk' alleles according to the polymorphous locuses of genes which are coding the coagulation cascade proteins *F5*:1691 G > A, *F2*: 20210 G > A, *FGB*: 455 G > A, *PAI-1*: 5 G > 4 G, I*TGA2*: 807 C ≫ T, *ITGB3* 1565 T ≪ C, *MTR* 2756 A > G, *MTRR* 66 A > G, *MTHFR* 677C>T и *MTHFR* 1298 A > C.

We observed that there was an increased frequency (74.2%) of genotype MTHFR with polymorphism 1298 A > C. Variant allele 1298 C in homo- and heterozygote state was found in all women of the first group. In all women of 2d group the genotype *MTHFR* 1298AA was determined.

The coagulation data in women of both studied groups presented in Table 2.

Clotting tests reveal the state of hypercoagulation in women of the 1st group with allele 1298C *MTHFR* gene in comparison with women of group 2. The increase in fibrinogen content (6.09 ± 0.11 g/l vs 5.77 ± 0.19 g/l) was shown in women of group 1. In these women the activation of the internal coagulation cascade was determined (PTT was 28.4 ± 0.4 s. vs. 31.0 ± 0.5 s in group 2). There was also a significant inhibition of serum fibrinolitic activity in women of 1st group (Table 2).

The structural and kinetic characteristics of clot formation according to TEG results were increased in women of 1st group. Both R and K indexes were significantly decreased in women of this group (Table 2) which means the increase the clot formation speed in women with polymorphous allele 1298C *MTHFR* gene. Also both α angle and clot maximal amplitude were increased in women of 1st group. These changes in TEG parameters resulted in the significant increase in coagulation index (3.4 ± 0.2 in women of 1st group versus 2.5 ± 0.2 in women of 2d group).

Discussion

Production and activation of prothrombotic and fibrinolytic factors are balanced very well in normal pregnancy. It was shown

Table 2. Parameters of TEG and coagulation cascade in women of studied groups.

Parameters	Group 1 (*MTHFR*: 1298/C) ($n = 31$)	Group 2 (*MTHFR*: 1298AA) ($n = 39$)
Coagulation cascade		
Fibrinogen, g/l	6.09 ± 0.11	5.77 ± 0.19
FA, min	32.72 ± 1.28	34.31 ± 3.83
TB, sec	15.4 ± 0.2	15.5 ± 0.2
PTT, sec	28.4 ± 0.4*	31.0 ± 0.5
INR, %	0.99 ± 0.01	0.99 ± 0.01
Thrombolastography		
R, min	7.40 ± 0.19	7.75 ± 0.23
K, min	1.2 ± 0.1*	1.8 ± 0.1
α, deg	67.5 ± 0.9*	64.9 ± 1.2
MA, mm	69.3 ± 1.0*	66.2 ± 1.1
E	234.2 ± 7.4*	201.8 ± 10.9
CI	3.4 ± 0.2*	2.5 ± 0.2
LY30, %	0.9 ± 0.2	0.9 ± 0.5

*Statistical significance $p < .05$.

that plasma levels of clotting factors, such as fibrinogen and some other factors, increase while fibrinolysis is inhibited due to the compact structure and innate resistance of the fibrin molecule to lysis in diabetes mellitus [10]. GDM may be quite similar to a milder form of the metabolic syndrome. Since body mass is higher in women with GDM compared to healthy women, insulin resistance may be triggered in pregnant subjects leading to gestational diabetes.

One of the most important measures in assessing the coagulation cascade is PTT. There are studies showing that decreased PTT support hypercoagulability status in both normal pregnancy and GDM [11]. It was determined that PTT and platelet counts were significantly lower in the 3rd trimester of normal pregnancy [12]. However, another group reported that both parameters were unchanged in women with GDM [13]. In our findings, PTT was lower in 1st group than in 2d. We think that this data support hypercoagulable state in GDM. Moreover, there was no compensatory increase in fibrinolitic activity in women of the first group with allele 1298C *MTHFR* gene.

We found that mean birth weight of infants born to GDM mothers with polymorphous MTHFR gene was less than in neonates of 2d group women. One could suggest some degree of placental dysfunction as a result of coagulation disturbances in women of the first group.

In this study, we examined the association between *MTHFR* gene polymorphism in GDM women and cerebral ischemia of their newborn infants. Our results have indicated increased frequency of CI and 1298C *MTHFR* allele genotype among women with GDM. Maternal *MTHFR* gene mutation has a significant impact on offspring. It was reported that homozygosity mutation in the *MTHFR* gene was associated with increased frequency of fetal growth retardation and neonatal brain injuries [14].

There is a hypothesis that neonatal cerebral injuries are secondary to the interaction of the epigenetic stimuli and genome [15]. The epigenetic programing is active during pregnancy, and epigenetic processes respond to environmental stimuli ranging from maternal nutritional restriction to hypoxia and hyperglycemia [16].

Therefore, the genetic predisposition (polymorphous allele 1298C *MTHFR* gene) may represents a potential risk factor for cerebral ischemia in newborn infants born to mothers with gestational diabetes mellitus.

Disclosure statement

The authors report no conflicts of interest.

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