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FEATURES OF HORMONAL CHANGES DURING PUBERTY IN GIRLS BORN TO WOMEN WITH GESTATIONAL DIABETES

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With the purpose to assess the features of hormonal changes in girls born to mothers with gestational diabetes, the 25 pubertal girls born to mothers with gestational diabetes and 30 practically healthy girls. The sexual development, indicators of carbohydrate metabolism and the levels of follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, prolactin, cortisol, triiodothyronine, thyroxine, dehydroepiandrosterone sulfate, 17-hydroxyprogesteron, estradiol, and testosterone were determined. In the girls from mother with gestational diabetes the hirsutism index was significantly higher (P<0.05), than in healthy girls (15.3±0.06 and 8.3±1.8, respectively). The indicators of secondary sexual characteristics in girls from mothers with gestational diabetes were lower than in healthy girls (P<0.05). In pubertal girls born to women with gestational diabetes, follicle-stimulating hormone, thyroid-stimulating hormone and estradiol were significantly lower than in practically healthy girls (P<0.05). A statistically significant increase in luteinizing hormone, prolactin, triiodothyronine and thyroxine, dehydroepiandrosterone sulfate, 17-hydroxyprogesteron, and testosterone was observed (P<0.05).

Key words: gestational diabetes mellitus, puberty, hypoestrogenism, hyperprolactinemia, adrenal-ovarian hyperandrogenism.

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ОСОБЛИВОСТІ ГОРМОНАЛЬНИХ ЗМІН У ПЕРІОД СТАТЕВОГО ДОЗРІВАННЯ У ДІВЧАТОК, НАРОДЖЕНИХ ВІД МАТЕРІВ ІЗ ГЕСТАЦІЙНИМ ДІАБЕТОМ

З метою оцінки особливостей гормональних змін у дівчаток, народжених від матерів з гестаційним діабетом, обстежено 25 дівчаток пубертатного віку, народжених від матерів з гестаційним діабетом, і 30 практично здорових дівчаток. Визначали статевий розвиток, показники вуглеводного обміну, рівні фолікулостимулюючого гормону, лютеїнізуючого гормону, тиреотропного гормону, пролактину, кортизолу, трийодтироніну, тироксину, дегідроепіандростеронсульфату, 17-гідроксипрогестерону, естрадіолу, тестостерону. У дівчаток від матерів із гестаційним цукровим діабетом індекс гірсутизму був достовірно вищим (P<0,05), ніж у здорових дівчаток (15,3±0,06 і 8,3±1,8 відповідно). Показники вторинних статевих ознак у дівчаток від матерів із гестаційним цукровим діабетом були нижчими, ніж у здорових дівчаток (P<0,05). У дівчаток пубертатного віку, народжених жінками з гестаційним цукровим діабетом, фолікулостимулюючий гормон, тиреотропний гормон і естрадіол були достовірно нижчими, ніж у практично здорових дівчаток (P<0,05). Спостерігалося статистично значуще підвищення лютеїнізуючого гормону, пролактину, трийодтироніну і тироксину, дегідроепіандростерону сульфату, 17-гідроксипрогестерону і тестостерону (P<0,05).

Ключові слова: гестаційний цукровий діабет, статеве дозрівання, гіпоестрогенія, гіперпролактинемія, наднирково-яєчникова гіперандрогенія.

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia. This condition arises due to impaired insulin secretion or reduced insulin action (insulin resistance) [6].

According to the classification adopted by the World Health Organization (WHO) in 1999, gestational diabetes mellitus (GDM) is recognized as an independent nosological entity [4].

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study established new diagnostic criteria for GDM, emphasizing its significance as a serious medical and social problem. GDM is associated with adverse outcomes for both the mother and the newborn, including:

An increased risk of future obesity, type 2 diabetesand cardiovascular disease in both the mother and the child; Pregnancy being a state of physiological insulin resistance, which predisposes to carbohydrate metabolism disorders; The necessity for accurate clinical and laboratory differentiation between “diabetes mellitus”, “manifest diabetes”, “diabetes first detected during pregnancy”, and “gestational diabetes mellitus”; The need for uniform diagnostic and treatment standards for carbohydrate metabolism disorders during pregnancy [2, 5].

An increase in fasting venous plasma glucose levels from 5 mmol/L to 7 mmol/L is considered diagnostic for gestational diabetes mellitus. If carbohydrate metabolism disorders are not detected early in pregnancy, a fasting glucose test and an oral glucose tolerance test (OGTT) with 75 g of glucose are recommended between 24 and 28 weeks of gestation [4].

The development of gestational diabetes mellitus is influenced by various factors, including hormonal changes. Studies have shown that hyperprolactinemia and hyperestrogenemia are commonly observed in women with GDM [3, 11].

Newborns of women with gestational diabetes mellitus often exhibit macrosomia and disproportionate body structure, characterized by a long, faty trunk, short and thin extremities, wide chest, relatively small head, and excessive body hair. These infants are also at higher risk for complications such as prematurity (53.3 %), birth asphyxia (33.3 %), intrauterine infections (26.67 %), cerebral ischemia (93.3 %), neonatal hyperbilirubinemia (20 %), and congenital malformations or dysembryogenesis stigmata (13.3 %). Children born to women with GDM are more likely to develop viral-infectious diseases (34.5 %), cardiovascular disorders (40.4 % in preschool age and 37.5 % in school age), and symptoms of autonomic dysfunction. Common manifestations include excessive weakness and fatigue (38 %), irritability (16.1 %), emotional lability (11.1 %), regular headaches (16.1 %), pain in epigastric area (27.7 %), and weather sensitivity (27.7 %) [9, 14]. Notably, the characteristics of puberty in girls born to women with gestational diabetes mellitus remain understudied. There is a lack of scientific data on hormonal changes during their physical and sexual development.

The purpose of the study was to investigate the feutures of hormonal changes during puberty in girls born to women with gestational diabetes mellitus.

Materials and methods. The study was conducted on the basis of Department of Obstetrics and Gynecology I, Azerbaijan Medical University, in the period of 2023–2024.

In accordance with the study's objectives, 25 pubertal girls born to women with gestational diabetes mellitus were examined.

The comparison group included 30 healthy girls in puberty.

The average age of the examined girls was 15.29±0.27 (14–17) years. Physical and sexual development characteristics of the examined girls, including anthropometric measurements, hirsutism index, external pelvic dimensions, and secondary sexual characteristics were assessed.

The examination of the girls was carried out with the presence of the mother. All data about course of pregnancy, condition of newborn, physical development and psycho-emotional state of the girls and their achievements in education were studied. Clinical, functional, hormonal, biochemical studies were conducted in all examined girls. According to the scale of J.Tanner, secondary sexual characteristics were evaluated. For the assessment of the severity of hirsutism in all of the examined included in the study, the Ferriman-Galway scale was used.

Carbohydrate metabolism was evaluated using fasting serum glucose, insulin levels, and the HOMA-IR and CARO indices to measure insulin resistance. The calculated indices HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) and CARO were used as additional laboratory tests. In the group of people with glucose levels below 7 mmol/L, they are more informative than fasting glucose and insulin alone.

The hypothalamic-pituitary-ovarian axis and thyroid function were also analyzed.Hormonal profiles, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), prolactin (Prl), cortisol (K), triiodothyronine (T_3), thyroxine (T_4), dehydroepiandrosterone sulfate (DHEA-S), 17-hydroxyprogesterone (17-OHP), estradiol (E_2), and testosterone (T), were measured using chemiluminescence immunoassay on the Abbott Architect-1000 system (USA).

Statistical analysis was performed using the “Statgraph” program. Data were organized in a variation series, and group indicators were calculated, including mean values (M), standard deviation (σ^2), standard error (Se), and minimum (min) and maximum (max) values.

Results of the study and their discussion. The study found that pubertal girls born to women with gestational diabetes mellitus had a height of 150.0±0.4 cm (range: 140–165 cm), a weight of 49.19±1.56 kg (range: 35.5–94 kg), an arm span of 153.1±0.02 cm (range: 130–160 cm), a shoulder width (SW) of was 31.9±0.06 cm (range: 29–42 cm), the length of the lower extremities (LE) was 73.5±0.11 cm (range: 68–90 cm), and the chest circumference (CRC) was 63.7±0.2 cm (range: 46–74 cm) and the external dimensions of the pelvis were statistically significantly lower than those of healthy girls ($P<0.05$). The hirsutism index in the study group was 15.3±0.06 (range: 11–17), significantly higher ($P<0.05$) than in healthy girls (8.3±1.8).

It was determined by studying the formation of secondary sexual characteristics in girls during puberty that development of mammary glands (Ma) was scored at 2.0±0.01 (range: 1–3), axillary hair (Ax) at 1.5±0.02 (range: 1–2), and pubic hair (Pb) at 1.5±0.05 (range: 1–2), all of which were lower than in healthy girls ($P<0.05$).

Girls born to women with gestational diabetes mellitus exhibited statistically significant increases in fasting glucose (88.81±1.47 mg/dL; range: 44–110.9 mg/dL), fasting insulin (29.92±1.73 μIU/mL; range: 12.7–70.3 μIU/mL), and HOMA index compared to healthy girls (P<0.05). The results of hormones in the examined girls are presented in Table 1.

Table 1

Characteristics of hormonal changes during puberty in girls born to women with GDM (M±Se)

Parameters/ Hormones	Review groups		P
	Girls born to women with GDM (n=25)	Practical healthy girls (n=30)	
FSH, mLU/ml	4.7±0.11 (0.5–6.4)	5.21±0.09 (35–8.9)	<0.05
LH, mLU/ml	7.42±0.15 (1.6–16)	5.13±0.12 (3.0–8.9)	<0.05
Prl, ng/ml	11.83±0.05 (4–8.6)	4.46±0.19 (1.6–16.9)	<0.05
TSH, mLU/ml	1.85±0.13 (0.6–45)	2.1±0.09 (0.7–3.26)	>0.05
Cortisol, ng/ml 8.00-10.00	261.27±49.8 (47–514)	121.33±23.1 (75–190)	>0.05
T_3free, ng/dl	4.97±0.06 (1.5–10.2	2.9±0.03 (1.1–4.5)	<0.05
T_4free, ng/dl	4.16±0.9 (0.67–12.6)	0.48±0.22 (0.12–1.60)	<0.05
DHEAS, ng,ml	2.95±0.15 (1.02–7.7)	1.97±0.25 (0.6–3.5)	<0.05
17-OHP, ng/ml	0.73±0.02 (0.3–1.8)	0.31±0.01 (0.07–3.0)	<0.05
E_2, pg/ml	59.51±2.5 (70–100)	135.31±27.1 (100–170.3)	<0.05
T total, ng/ml	1.4±0.03 (0.21–4.3)	0.11±0.03 (0.06–1.6)	<0.05

As can be seen from the table, in pubertal girls born to women with gestational diabetes mellitus, FSH (5.21±0.09 mLU/ml), TSH (2.1±0.09 mLU/ml) and E2 (135.31±27.1 pg/ml) were significantly lower than in practically healthy girls (P<0.05). At the same time, a statistically significant increase in LH (5.13±0.12 mLU/ml), Prl (4.46±0.19 ng/ml), T_3 (2.9±0.03 ng/dl) and T_4 (0.48±0.22 ng/dl), DHEA-S (1.97±0.25 ng/ml), 17-OHP (0.31±0.01 ng/ml), and T (0.11±0.03 ng/ml) was observed (P<0.05).

GDM affects approximately 16.5 % of pregnancies worldwide, and this number is set to increase with the escalating obesity epidemic. While several management strategies exist-including insulin and lifestyle interventions-there is not yet a cure or an efficacious prevention strategy. One reason for this is that the molecular mechanisms underlying GDM are poorly defined [9].

M. Agarwal highlights that the etiology of GDM is primarily characterized by dysfunction of pancreatic β-cells, leading to alterations in glycemic levels and insulin resistance [1].

Risk factors for GDM include excess body weight, obesity, excessive weight gain during pregnancy, a “Western diet”, ethnicity, genetic polymorphisms, advanced maternal age, intrauterine developmental factors, personal or family history of gestational diabetes mellitus, and endocrine disorders such as polycystic ovary syndrome [8, 12].

Literature indicates that the consumption of foods high in saturated fats, refined sugars, and processed red meat during pregnancy significantly increases the risk of gestational diabetes mellitus [10].

Kauzskiy-Willer A, et al. report that GDM is diagnosed in 3–4 % of pregnancies with male fetuses during the first pregnancy, compared to female fetuses, and in 7 % of women with multiple pregnancies [6].

The likelihood of GDM in pregnancies achieved through assisted reproductive technology (ART) is significantly higher, reaching 18 %. Additionally, the use of hydroxyprogesterone caproate during pregnancy increases the risk of gestational diabetes mellitus. Conversely, the incidence of GDM is lower in women receiving intravaginal progesterone. Women with arterial hypertension have a threefold increased risk of gestational diabetes mellitus [13].

Harrison J., et al (2022) revealed that the odds of neonatal hypoglycaemia in children who were born in mothers with GDM showed a dose-response pattern. Higher odds of neonatal hypothermia were seen across all groups (the four groups were: women without GDM, women with GDM attending non-dedicated GDM clinics, women with GDM attending dedicated clinic 1 and women with GDM attending dedicated clinic 2). Increased odds of neonatal respiratory distress were limited to the non-dedicated clinics. Increased odds of NICU/SCN admission were seen in both the non-dedicated clinics and the dedicated clinic 2 group [5]. We did not collect the information about neonatal period of girls involved in study, but it should be taken into account on future studies.

Kowalcze K, et al (2024) conducted study aimed of the current study was to assess the hormonal profile and the size of sexual organs in daughters of mothers with gestational diabetes mellitus. The authors

included three matched groups of newborn girls: daughters of healthy women with no metabolic disorders during pregnancy, daughters of women with poorly controlled gestational diabetes mellitus, and daughters of women with gestational diabetes mellitus adequately controlled during pregnancy. The results showed that FSH, LH, and estradiol were higher, while progesterone concentrations were lower in daughters of women with poorly controlled gestational diabetes mellitus than in the other groups. There were no between-group differences in testosterone and DHEA-S concentrations. LH, FSH, estradiol, and progesterone levels correlated with maternal whole blood glycated hemoglobin levels. The results suggest that poorly controlled, but not completely controlled, gestational diabetes mellitus affects the course of female minipuberty [7].

In our study, we did not compare the difference between controlled and uncontrolled gestational diabetes, and the results in the above-mentioned work did not quite match the direction of our data. From this standpoint, further work in this direction will be of undoubted value.

Conclusions

1. In the girls from mother with GDM the hirsutism index was significantly higher ($P<0.05$), than in healthy girls (15.3±0.06 and 8.3±1.8, respectively).

2. The indicies of secondary sexual characteristics in girls from mothers with GDM were lower than in healthy girls ($P<0.05$).

3. In pubertal girls born to women with gestational diabetes mellitus, FSH, TSH and E2 were significantly lower than in practically healthy girls ($P<0.05$).

4. A statistically significant increase in LH, Prl, T_3 and T_4, DHEA-S, 17-OHP, and T was observed ($P<0.05$).

Girls born to women with gestational diabetes mellitus exhibit delayed physical and sexual development during puberty, central hypoestrogenism, hyperprolactinemia, adrenal and ovarian hyperandrogenism, and thyroid activity disturbance, all of which occur against a backdrop of altered carbohydrate metabolism.

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