СОСТОЯНИЕ ОВАРИАЛЬНОГО РЕЗЕРВА У ЖЕНЩИН С САХАРНЫМ ДИАБЕТОМ 1 ТИПА В РЕПРОДУКТИВНОМ ПЕРИОДЕ

© О.Р. Григорян[1]*, Н.С. Красновская[2], Р.К. Михеев[3], Е.Н. Андреева[1,3], И.И. Дедов[1]

[1]Национальный медицинский исследовательский центр эндокринологии, Москва
[2]Городская поликлиника № 9, Москва
[3]Московский государственный медико-стоматологический университет им. А.И. Евдокимова, Москва

ОБОСНОВАНИЕ. Для женщин с сахарным диабетом 1 типа (СД1) характерно ускоренное старение, что проявляется в повышении частоты сердечно-сосудистых событий, нарушениях овариально-менструальной функции, в раннем наступлении менопаузы. Показано, что нарушение репродуктивной функции у женщин с СД1 может быть связано, в частности, со снижением овариального резерва.

ЦЕЛЬ. Сравнить овариальный резерв у женщин репродуктивного возраста с СД1 и без СД1.

МЕТОДЫ. В исследование включены больные СД1 и здоровые женщины репродуктивного возраста (от 18 до 37 лет). У всех больных на 2–3 день менструального цикла определяли следующие маркеры овариального резерва: сывороточные уровни антимюллерова гормона (АМГ), ингибина В, фолликулостимулирующего гормона (ФСГ), лютеинизирующего гормона (ЛГ), эстрадиола, тестостерона, а также ультразвуковые параметры – когорту антральных фолликулов и объем яичников. Дополнительно исследовали уровень гликированного гемоглобина (HbA_{1c}, %).

РЕЗУЛЬТАТЫ. Обследовано 224 больных СД1 и 230 здоровых женщин. Статистически значимо у женщин с СД1 и без СД1 различались уровень АМГ, когорта антральных фолликулов, в то же время параметры оставались в референтных пределах. Отмечалась выраженная отрицательная зависимость между уровнями HbA_{1c} и АМГ.

ЗАКЛЮЧЕНИЕ. Для больных СД1 репродуктивного возраста характерно снижение показателей овариального резерва по сравнению со здоровыми женщинами. Указанные изменения наряду с данными о более высокой частоте неблагоприятных исходов беременности у больных СД1 следует учитывать при консультировании больных СД1 гинекологом и эндокринологом (рекомендации по более раннему планированию беременности для сохранения возможности применения вспомогательных репродуктивных технологий при длительных безуспешных попытках естественного зачатия).

КЛЮЧЕВЫЕ СЛОВА: антимюллеров гормон; антральные фолликулы; объем яичников; овариальный резерв; сахарный диабет 1 типа

OVARIAN RESERVE IN REPRODUCTIVE AGE WOMEN WITH TYPE 1 DIABETES

© Olga R. Grigoryan[1]*, Natalia S. Krasnovskaya[2], Robert K. Mikheev[3], Elena N. Andreeva[1,3], Ivan I. Dedov[1]

[1]Endocrinology Research Centre, Moscow, Russia
[2]City clinic №9, Moscow, Russia
[3]Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, Moscow, Russia

BACKGROUND: Premature aging are frequently observed among individuals with type 1 diabetes. Decrease of ovarian reserve may be one of the characteristics of such process.

AIMS: To evaluate the ovarian reserve function in female patients of reproductive age with type 1 diabetes in comparison with healthy women.

MATERIALS AND METHODS: This study evaluated 224 Caucasian women, age 18–37 years with type 1 diabetes and 230 healthy women of comparable age. Serum concentrations of anti-Mullerian hormone (AMH), inhibin B, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone and testosterone were compared on the 2–3 day of menstrual cycle as ovarian volume and antral follicle count (AFC). In addition, glycated hemoglobin level (HbA_{1c}%) was evaluated.

RESULTS: We reveal statistically significant difference in following parameters in diabetic women in comparison with healthy women: AMH, AFC. But even in diabetic patients parameters remained within reference ranges. There was a pronounced negative relationship between the levels of HbA_{1c}% and AMG.

CONCLUSIONS: Ovarian reserve function parameters decrease in young women with type 1 diabetes in comparison with healthy women, but ovarian reserve parameters are in normal reference range. These findings are important in pregnancy planning consulting by gynecologists and endocrinologists. We must recommend to women with type 1 diabetes more early planning of natural pregnancy for treatment with reproductive technology in cases of prolog absence of nature pregnancy.

KEYWORDS: anti-Mullerian hormone; antral follicles; ovarian reserve; type 1 diabetes

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Despite the significant improvement in the prognosis for patients with type 1 diabetes mellitus (DM1) in recent decades, such patients are still at risk of early formation of micro- and macrovascular complications, leading to peripheral artery lesions, development of cardiovascular and cerebrovascular diseases and progression of chronic kidney disease [1]. It is obvious that in many respects, the increase in risk is associated with metabolic disorders typical of DM1 (hyperglycemia, hyperlipidemia, etc.), but the extent of its increase cannot be explained by these factors alone. Moreover, the known gender differences in the incidence of cardiovascular diseases (significantly higher in men) in DM1 patients are much less pronounced than in the general population. Early development of cardiovascular diseases is not the only manifestation of accelerated ageing in DM1 patients; other manifestations include thinning and increased stiffness of the basic membrane of the muscular capillaries. This is observed in individuals without DM1 only after the age of 50 years, but in DM1 patients, it is noted at a much younger age, especially with the long course of the disease. In addition, cataracts often develop in DM1 patients, and the rate of cell renewal is reduced as compared with that in healthy individuals [2].

Clearly, other manifestations that cause discrepancies between the biological and calender ages of DM1 patients are underestimated. It is known that menarche appears later in DM1 patients as compared with healthy women, and an irregular menstrual cycle is noted more often in the reproductive period, with the presence of amenorrhea, polymenorrhea, or oligomenorrhea in 30% of female DM1 patients; menopause also occurs earlier [3]. In female DM1 patients, polycystic ovary syndrome often develops, and reduced fertility is characteristic [3, 4, 5]. Late DM1 complications and high levels of glycated haemoglobin (HbA1c) may contribute to a reduction in ovarian reserve in DM1 patients; however, it appears that the basis of pathogenesis in such patients is a cascade of autoimmune processes.

Ovarian reserve is the number of antral follicles in both ovaries. To determine ovarian reserve, it is customary to evaluate the serum levels of follicle-stimulating hormone (FSH) and anti-Mullerian hormone (AMH) on day 2–3 of the menstrual cycle. A reduction in ovarian reserve is associated with a decrease in the number of eggs and loss of quality, indicating a poor prognosis for in vitro fertilisation outcomes. The evaluation of AMH levels is especially important in young women, since the reduction in ovarian reserve is often overlooked by clinicians, and as a result, the infertility diagnosis remains incomplete, meaning that all possible interventions are not exploited [6].

A study by Soto et al. (2009) revealed that premature ovarian ageing occurs in DM1 patients, which is manifested as a decrease in the levels of AMH and inhibin B. This indicates an earlier decrease in the number of follicles in the ovaries as compared with healthy women [7]. The present study aimed to perform a comparative assessment of the ovarian reserve in female DM1 patients and healthy women of reproductive age.

AIM

The present study aimed to compare the ovarian reserve between female DM1 patients of reproductive age and their healthy counterparts.

METHODS

Study design

Prospective observational single-centre parallel group study.

Acceptance criteria

To minimise the impact of additional factors that modify ovarian reserve, Caucasian women of reproductive age (18–37 years inclusive) were included in the present study. The study group included patients with a DM1 diagnosis verified for at least two years, and the reference group included women without DM. Exclusion criteria were previous pelvic surgery, chemotherapy, or radiation therapy, the presence of ovarian tumours, polycystic ovary syndrome (PCOS), endometriosis, a previous diagnosis of infertility, menstrual irregularities, pregnancy, menopause, intake of hormonal medications (with the exception of insulin in the study group) at the time of enrolment and within three months prior to enrolment, endocrine diseases (with the exception of DM1 in the study group), cigarette smoking at the time of enrolment or in the history, alcohol abuse, drug addiction, or toxic substance addiction. All participants referred to the information regarding the study, received answers to any questions, and signed an informed consent form to participate in the study.

Implementation conditions

The present study was conducted in a single centre: the National Medical Research Centre of Endocrinology, Moscow.

Study duration

The duration of enrolment of female participants in the study according to the plan was 10 months; each participant was examined twice each month, on days 2–3 and 21–23 of the menstrual cycle. The study was conducted during 2017.

Description of medical intervention

All participants were examined according to a single protocol, such as venous blood sampling in the fasting state on days 2–3 and 21–23 of the menstrual cycle to determine serum levels of AMH, inhibin B, FSH, LH (lutenising hormone), estradiol, testosterone (on days 2–3 of the cycle) and progesterone (on days 21–23 of the cycle) by enhanced luminescence; on day 2, the levels of glycated haemoglobin (HbA1c) was also determined. The age of menarche and the manifestation of DM1 (for patients in the study group) were recorded in the Case Report Form. On days 2–3 of the menstrual cycle, a transvaginal ultrasound (US) examination was performed using a Hewlett Packard Image Point supersonic apparatus (USA) with a 3.5-MHz vaginal sensor, in accordance with a conventional method, to estimate the volume of the ovaries and the number of antral follicles.

PRIMARY STUDY OUTCOME

The primary parameters evaluated in the present study were AMH levels and the cohort of antral follicles on days 2–3 of the menstrual cycle.

Table 1. Results of the examination of female DM1 patients (group A) and healthy women (group B)

Characteristics	Group A (n = 224)	Group B (n = 230)	Reference range
Age, years	26.7±5.3	25.8±4.2	n/a
Age of menarche, years	13.4±0.8*	11.8±0.45	n/a
Single childbirth	53%	56%	n/a
Repeated childbirth	21%	23%	n/a
BMI, kg/m2	22.7±3.3	23.6±3.9	18-24.9
Waist circumference, cm	72.3±3.8	76±5.3	≤ 80
AMH, ng/mL	2.9±1.3*	4.7±1.5	1-12.6
Inhibin B, pg/mL	92.1±18.6	100±22.3	<273
FSH, mMU/mL	5.4±2.6	5.8±2.3	1.37-9.9
LH, mMU/mL	8.7±3.4	9.2±3.8	1.68-15
Estradiol, pmol/L	176±35	204±42	68-1269
Testosterone, nmol/L	0.65±0.15	0.68±0.13	0.52-1.72
Progesterone, nmol/L	1.4±0.5	1.6±0.6	0.3-2.2
HbA1c, %	8.2±2.5*	4.9±0.52*	<6
Ovarian volume, cm3	8.4±2.2	8.2±1.4	≤10
Number of antral follicles	16.4±7.2*	20.4±5.2*	Min 3-10

Note: *p < 0.05 when comparing the parameter between DM1 patients and healthy women

Additional study outcomes

Additional estimated parameters were the levels of inhibin B, FSH, LH, estradiol and testosterone and the volume of the ovaries on days 2–3 of the menstrual cycle, the levels of progesterone on days 21–23 of the menstrual cycle and the levels of HbA1c upon enrolment in the study.

Subgroups analysis

The patients were divided into two groups:

- Group A (study)–DM1 patients;
- Group B (reference)–healthy women without DM.

Registration methods of outcomes

The levels of AMH, inhibin B, FSH, LH, estradiol, testosterone and progesterone were determined by the enhanced luminescence method. HbA1c levels were determined by high-performance liquid chromatography. To assess the volume of the ovaries and the number of antral follicles, transvaginal ultrasound (US) was performed using a Hewlett Packard Image Point supersonic apparatus (USA) with a 3.5-MHz vaginal sensor, in accordance with a conventional method. The reference values were determined on the basis of data from the local laboratory, and also taking into account the 2015 recommendations of the American College of Obstetricians and Gynecologists regarding the definition of ovarian reserve [8] and the Rotterdam criteria of PCOS (for determining the normal volume of the ovary) [9].

Statistical analysis

Principles of calculating the sample size: the sample size was not preliminarily calculated.

Methods of statistical data analysis: Statistical analysis was performed using the Statistica 6.0 software package (StatSoftInc, USA). The normality of the distribution of characteristics was estimated using the Shapiro–Wilk test. When describing normally distributed variables, the mean and standard deviation (M ± SD) are indicated. The quantitative indicators were compared between the two groups using the Mann–Whitney test. Qualitative indicators are presented in the form of an absolute number of observations. Differences are considered statistically significant at $p < 0.05$. Using the Spearman coefficient, the relationship force between the variables (r) was estimated. For $r < 0.3$, the relationship is considered weak and insignificant; at $r = 0.3–0.7$, average or moderate and at $r > 0.7$, significant and strong.

Ethical expertise

The study protocol was approved at the meeting of the Ethical Committee of the National Medical Research Centre of Endocrinology on 19 October 2016 (Protocol No. 12).

RESULTS

Key study results

The study group included 224 women, and the reference group included 230 women.

The results of the examination are presented in Table 1.

Due to the strict inclusion/exclusion criteria, participants from both groups were comparable in age and major factors affecting ovarian reserve. There were no differences in parameters such as age, body mass index, waist circumference, levels of FSH, LH, estradiol, testosterone, progesterone, or inhibin B, or ovary volume. Table 2 presents the parameters that were statistically significantly different between DM1 patients and healthy women.

Attention is drawn to the significant differences in such parameters of ovarian reserve between DM1 patients and

Table 2. Significant differences in parameters between DM1 patients (group A) and healthy women of reproductive age (group B)

Characteristics	Group A (n = 224)	Group B (n = 230)
Age of menarche, years	13.4±0.8	11.8±0.45
Number of antral follicles, n	16.4±7.2	20.4±5.2
HbA1c, %	8.2±2.5	4.9±0.52
AMH, ng/mL	2.9±1.3	4.7±1.5

healthy women, such as the level of AMH (2.9 ± 1.3 ng/mL in DM1 patients versus 4.7 ± 1.5 ng/mL in the group of healthy women, $p < 0.05$) and cohorts of antral follicles (16.4 ± 7.2 in DM1 patients versus 20.4 ± 5.2 in healthy women). The significant difference in the levels of HbA1c was expected (8.2 ± 2.5% in DM1 patients versus 4.9 ± 0.52% in healthy women). Menarche in DM1 patients occurred significantly later as compared with women without DM (13.4 ± 0.8 years versus 11.8 ± 0.45 years, $p < 0.05$).

When analysing the correlation between HbA1c levels and the parameters of ovarian reserve, there was a strong negative association with AMH levels ($r = -0.92$, $p < 0.05$) and the number of antral follicles ($r = -0.76$, $p < 0.05$). The levels of ovarian reserve markers, such as the size of the ovaries and the levels of FSH, LH, inhibin B, estradiol and progesterone, did not differ significantly.

When analysing the dependence of ovarian reserve on the time of DM1 manifestation, interesting results were obtained; in patients with DM1 manifestation before puberty, the ovarian reserve estimated by the levels of AMH was lower than that in patients with DM1 manifestation after puberty (Figure 1).

When analysing the subgroups of DM1 patients, depending on the degree of disease compensation (HbA1c levels), no relationship between the level of diabetes control and ovarian reserve in a one-stage study could be revealed (Figure 2).

Adverse events

During the study period, no adverse events were recorded.

Discussion

The state of reproductive health in DM1 patients has been the subject of serious study in recent years. In 2016, the work of Yarde et al. [10] was published. These researchers aimed to establish the relationship between the factors of cardiovascular risk in DM1 patients and the reduction in ovarian reserve as a parameter characterising age-related ovarian changes. This cross-sectional case-control study included data analysis of 150 DM1 patients (mean age 33.8 ± 8.4 years) and 177 healthy women with preserved reproductive function. Parameters such as the cohort of antral follicles, lipid profile, plasma levels of AMH, C-reactive protein, HbA1c, as well as systolic blood pressure, blood flow-induced arterial dilatation, pulse-wave velocity and thickness of the intima-media complex were evaluated. The authors concluded that there were no significant differences in the parameters of ovarian reserve between DM1 patients and healthy women; a negative correlation was found only between the values of systolic blood pressure and the levels of AMH and the number of antral follicles. In comparison with the present study, the difference in methodology is notable, which is retrospective with historical control.

In addition, in the present study, significantly younger women participated in accordance with the inclusion criteria. The prospective nature of our study enabled the control of all known factors that affect ovarian reserve, ensuring high comparability of groups with respect to all parameters. Moreover, the sample size of the present study is significantly larger, which increases the statistical power of the study and the reliability of the findings. Thus, the differences in the results obtained can be explained. Nevertheless, the results of the study by Yarde et al. are of great value for understanding the pathogenesis of ovarian reserve reduction in DM1 patients. In the present study, we did not compare the parameters of ovarian reserve with the severity of risk factors for cardiovascular diseases; only a correlation with the levels of HbA1c was found. The absence of correlations between the parameters of ovarian reserve and those of the lipid profile and the characteristics of the vascular wall in the study by Yarde et al. indicates the absence of at least a direct causal relationship between a decrease in ovarian reserve in DM1 patients and macrovascular lesions.

Soto et al. studied ovarian function in DM1 patients (n = 66) as compared with healthy women (n = 58) younger than 45 years of age. Among the DM1 patients, there were more frequent cases of lowered AMH levels to those typically seen in menopause, while in DM1 patients older than 33 years of age, the levels of AMH were significantly

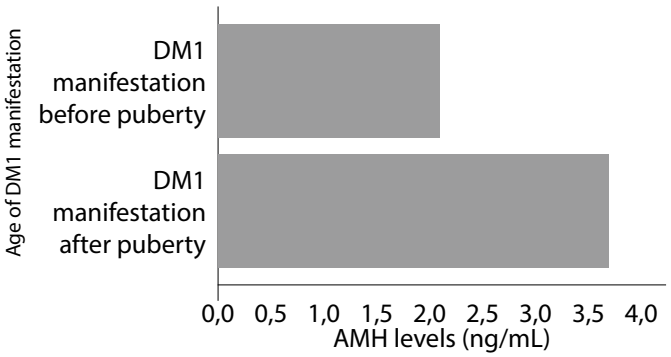

Fig. 1. Dependence of the levels of AMH (ng/mL) on the time of DM1 manifestation.

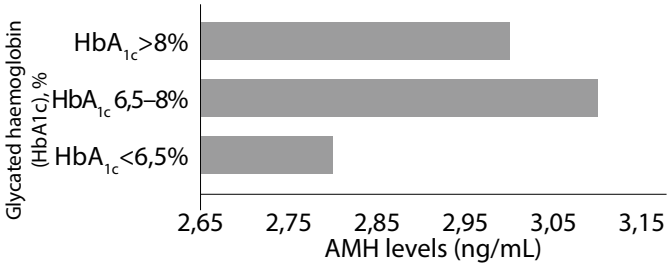

Fig. 2. Dependence of AMH levels (ng/mL) on the HbA1c percentage in DM1 patients. There were no statistically significant differences between the patient subgroups.

lower than in healthy women. The authors concluded that the decrease in AMH levels in DM1 patients in the fourth decade of life indicates an accelerated decrease in the cohort of primordial follicles. These data are consistent with the results obtained in the present study; even in young women of reproductive age, the presence of DM1 led to a decrease in ovarian reserve (lower values of AMH and cohort of antral follicles) [7].

Kim et al., in a study involving women aged 30–45 years with preserved reproductive function, revealed that in DM1 patients, the log concentrations of AMH were significantly lower as compared with women without DM (β-coefficient: 1.27, 95% confidence interval [– 2.18, – 0.36]) [11].

Relatively recently, a study by Al Khafajia et al. [12] analysed the parameters of ovarian reserve in 60 young female DM1 patients and 80 healthy young women (mean age: 24.87 ± 8.47 years versus 25.91 ± 8.29 years, respectively). The authors revealed significantly lower levels of AMH (2.82 ± 1.27 ng/mL versus 3.79 ± 1.91 ng/mL) and higher levels of HbA1c (8.73 ± 2.8% versus 4.82 ± 0.39%) in DM1 patients as compared with healthy women ($p < 0.00$ for both comparisons). There was a strong negative correlation between the levels of AMH and the content of HbA1c ($r = – 0.931$, $p = 0.2$). Thus, the data reported by Al Khafajia is in accordance with the results of the present study.

According to Codner et al., ovarian changes associated with DM1 start prior to the onset of puberty [13]. The study evaluated the hormonal status and pelvic organs in girls with DM1 (n = 73) and healthy girls (n = 86). At pre-pubertal age, in DM1 patients, the AMH levels were significantly higher in comparison with healthy peers (4.07 ng/mL versus 4.19 ng/mL, respectively); however, during the pubertal period, a significant reduction in AMH levels was observed in DM1 patients, which was not noted in healthy girls (1.41 ng/mL versus 2.20 ng/mL, respectively). Thus, by the onset of puberty, there were more follicles in the ovaries of DM1 patients as compared with healthy peers, which the authors attribute to the influence of exogenous insulin as a growth factor. This increase in the number of follicles increases the risk of PCOS in DM1 patients. Accordingly, folliculogenesis in the ovaries changes after reaching puberty, with an increase in the levels of gonadotropins and a progressive decrease in the AMH levels as compared with healthy girls.

Thus, the results of the present study, which show a reduction in ovarian reserve in DM1 patients as compared with healthy women of reproductive age, are consistent with the results of most other studies in which ovarian reserve was assessed in DM1 patients. The mechanisms of ovarian reserve reduction in DM1 remain unclear. These girls are born with a pool of follicles in the ovaries, very few of which enter the maturation process when puberty is reached, while the rest represent 'resting' follicles. Cells of granulosis are in close interaction with surrounding cells, which is necessary for survival and adequate maturation of the egg. In animal models of induced diabetes, it has been shown that these cells are damaged in hyperglycemia, the metabolic pathways are altered, follicle maturation is impaired and apoptosis is increased [14–17]. In addition, during physiological ageing, the glycosylation of proteins is involved, which is significantly increased in diabetes. Accordingly, Diamanti-Kandarakis et al. showed a significant increase in the levels of advanced glycation end products, even in the ovaries of healthy young women [18]. It is logical to assume that the content of such toxic substances in the ovaries of DM1 patients is increased to a greater extent, which will negatively affect ovarian reserve. Finally, a number of studies have revealed the association of autoimmune diseases, including DM1, with the development of premature ovarian insufficiency, which is assumed to be associated with the involvement of autoimmune mechanisms in the earlier reduction of ovarian reserve in DM1 patients [19, 20].

In the Russian literature, it was possible to find single publications on the evaluation of ovarian reserve in DM1 patients. A study by Tolopygina et al. evaluated ovarian function in DM1 patients; an analysis of the examination results of 180 female DM1 patients of reproductive age showed that 62.2% had ovarian insufficiency. There was a correlation between ovarian insufficiency (evaluation criteria were the levels of FSH, LH, prolactin, estradiol, total and free testosterone, progesterone in peripheral blood and parameters of pelvic organ ultrasounds) and the levels of glycemia and HbA1c and the dose of insulin administered. There was no correlation between the insufficiency of ovarian function and the severity of microvascular diabetic complications or insulin therapy regimens. In DM1 patients, there was an increase in the ovarian volume and the number of antral follicles as compared with those in healthy women. In these patients, there was an increase in the levels of LH, estradiol and free testosterone in the blood. The increase in ovarian volume correlated with the presence and severity of diabetic microvascular complications and the dose of insulin administered. Autoimmune ovarian lesions (assessed by the presence of antibodies against ovarian tissue) in female DM1 patients were detected in only 3.6% [21]. In our 2015 study, we showed that among female DM2 patients aged 20–49 years, as compared with the reference group, the levels of FSH were increased and the total number of follicles was reduced [22].

Limitations of the study

In the present study, a formal calculation of sample size was not performed, which is permissible within noninterventional studies. Strict criteria for the selection of participants in the present study reduced the likelihood of effects of additional interfering factors, but in actual clinical practice, dysmenorrhoea, hormonal contraceptive intake, gynaecological surgeries in history and obesity can significantly modify ovarian reserve. Thus, extrapolation of the results to the general population of DM1 patients of reproductive age is incorrect.

CONCLUSION

In the present study, a reduction in the parameters of ovarian reserve in young DM1 patients was proven as compared with healthy women of the same age (18–37 years). In combination with previously published data on the violations of menstrual function associated with DM1 and the problems in planning pregnancy, the present

results suggest information transfer to physicians and female patients regarding the potential effect of diabetes on reproductive function. Despite the preservation of the parameters of ovarian reserve within the reference range, taking into account their decrease in DM1 patients in comparison with healthy women, it is reasonable to recommend that such patients plan pregnancy at a younger age.

ADDITIONAL INFORMATION

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

Participation of authors. O.R. Grigoryan, N.S. Krasnovskaya–collection of material, writing the manuscript; E.N. Andreeva, I.I. Dedov–idea, editing the text of the manuscript; R.K. Mikheev–statistical analysis of the data, writing the manuscript.

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ИНФОРМАЦИЯ ОБ АВТОРАХ [AUTHORS INFO]

*__Григорян Ольга Рафаэльевна__, д.м.н. [Olga R. Grigoryan, MD, PhD]; ORCID: http://orcid.org/0000-0003-4979-7420; eLibrary SPIN: 3060-8242; e-mail: iceberg1995@mail.ru

Красновская Наталья Сергеевна, врач-эндокринолог [**Natalia S. Krasnovskaya**, MD]; адрес: 109439, г. Москва, Есенинский бульвар, д. 9, корп. 1 [address: 9b corp. 1 Eseninskiy b-r, Moscow, 109439 Russian Federation]; ORCID: https://orcid.org/0000-0002-2683-9387; eLibrary SPIN: 1087-3117; e-mail: krasnovskayaNS@yandex.ru
Михеев Роберт Константинович, студент [Robert K. Mikheev, medical student]; ORCID: http://orcid.org/0000-0001-5826-3186; eLibrary SPIN: 9767-8468; e-mail: iceberg1995@mail.ru
Андреева Елена Николаевна, д.м.н., профессор [Elena N. Andreeva, MD, PhD, Professor]; ORCID: http://orcid.org/0000-0001-8425-0020; eLibrary SPIN: 1239-2937; e-mail: iceberg1995@mail.ru
Дедов Иван Иванович, д.м.н., профессор, академик РАН [Ivan I. Dedov, MD, PhD, Professor]; ORCID: http://orcid.org/0000-0002-8175-7886; eLibrary SPIN: 5873-2280; e-mail: dedov@endocrincentr.ru

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