

АКУШЕРСТВО ГИНЕКОЛОГИЯ РЕПРОДУКЦИЯ

Включен в перечень ведущих
рецензируемых журналов и изданий ВАК

2014 • Том 8 • № 4

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**КЛИНИКА, ДИАГНОСТИКА
И ПРОФИЛАКТИКА ВЕНОЗНЫХ
ТРОМБОЭМБОЛИЧЕСКИХ ОСЛОЖНЕНИЙ
ВО ВРЕМЯ БЕРЕМЕННОСТИ**

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OVARIAN RESERVE IN THE WOMEN OF LATE REPRODUCTIVE AGE AFTER CONSERVATIVE TREATMENT OF POLYCYSTIC OVARIAN SYNDROME (PCOS) IN ADOLESCENCE

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Abstract. Background: the aim of the present study was to assess of the ovarian reserve of the women of late reproductive age after the conservative treatment of polycystic ovarian syndrome in adolescence. *Design:* the study was a longitudinal retrospective by purposive sampling. *Methods:* a total of 67 women of late reproductive age with confirmed primary PCOS in adolescence and 70 healthy age-matched controls were included in the study. The patients with PCOS underwent clinical investigation and conservative treatment with antiandrogens and oral contraceptive pills (OCPs) between 1984 and 1990y. and at the time of original diagnosis they were 13-18 y. *Main outcome measures:* the patients were collected via analysis of histories at primary diagnosis of PCOS in adolescence and at the time of the follow-up investigation of reproductive hormones was conducted. Data were compared between the study and control groups. *Results:* after conservative treatment PCOS patients had higher levels of anti-Müllerian hormone and greater number of antral follicles than controls ($p < 0.01$ and $p < 0.05$ respectively). *Conclusions:* our data suggest that PCOS patients who underwent conservative treatment in adolescence have the better ovarian reserve in late reproductive age than control women.

Key words: Polycystic Ovarian Syndrome, Ovarian Reserve, Anti-Müllerian Hormone, Adolescents, OCPs

Introduction

Ovarian reserve is the ability of the ovary to provide egg cells that are capable of fertilization. Ovarian reserve is an important factor to predict the outcome of assisted reproductive techniques [3,16]. Variables used to estimate the ovarian reserve include age, basal or stimulated levels of follicle-stimulating hormone (FSH), estradiol (E2), anti-Müllerian hormone (AMH), inhibin B and the number of antral follicles and ovarian volume, assessed by transvaginal ultrasound [15]. Last years, serum AMH measure-

ment has been introduced as one of the best markers of ovarian reserve [9]. AMH is secreted by the granulosa cells from pre-antral and antral follicles. Its main function is the inhibition of primordial follicle growth that is important in dominant follicle selection [2]. The higher the antral follicle count, the higher the AMH levels.

In Georgia, as well as around the world polycystic ovarian syndrome (PCOS) is thought to be one of the leading causes of female infertility and represents an actual problem in gynecology. It affects 4% to 12% of women of reproductive age and is the major factor of anovulatory infertility [14]. Its prevalence particularly is increased in adolescents [11]. This population deserves attention considering the future fecundity and long term reproductive results [8]. Because women with PCOS have high numbers of antral follicles, high AMH levels are often seen as well. Besides being used as a potential diagnostic marker for PCOS, AMH is used as an indicator of ovarian reserve as a predictor of ovarian response to stimulation during In Vitro Fertilization (IVF), that is especially important in women of late reproductive age [13,16].

Very few longitudinal follow-up studies for assessment of ovarian reserve in women of late reproductive age with previously confirmed PCOS have been conducted, especially after the diagnosis and treatment of PCOS in adolescence. There is absence of longitudinal follow-up studies also after a course of OCPs in adolescence [8].

Hence, the aim of the present study was to assess the ovarian reserve in women of late reproductive age after the conservative treatment of PCOS with antiandrogens and OCPs in adolescence compared with age-matched controls.

Materials and Methods

A total of 67 women of late reproductive age with confirmed primary PCOS who underwent conservative treatment with antiandrogens and OCPs in adolescence and 70 healthy controls were included in the study. All subjects consenting to participate attended a health examination at

the Zhordania Institute of Human Reproduction. Inclusion criteria for the study were diagnosis of PCOS between 1984-1990 and at the time of original diagnosis subjects were 13-18 years of age, at the follow-up from 35 to 45 years. Only patients with a diagnosis of PCOS according to the Rotterdam criteria were included [7]. In addition to the ultrasound criteria the following two features had to be present for the PCOS diagnosis: 1. oligomenorrhoea or amenorrhoea; 2. clinical and/or biochemical signs of hyperandrogenism such as testosterone 2.7 nmol/l, elevated dehydroepiandrosterone sulfate or hirsutism (8 on the Ferriman and Gallway scale). The exclusion criteria were thyroid dysfunction (normal s-TSH), adrenocortical dysfunction (normal 17-hydroxyprogesterone) or hyperprolactinaemia (prolactin <30 mg/l). Subjects without ultrasound examination were not included also.

The ultrasound examination

Transvaginal ultrasound examination was undertaken on third day of the cycle. It was performed with a 7 MHz transvaginal probe. Ovarian volume was calculated in the largest ovary according to a simplified formula for an ellipsoid ($0.523 \times \text{length} \times \text{width} \times \text{thickness}$). All follicles, antral and growing, were counted. The presence of 12 or more follicles in each ovary measuring 2-9mm in diameter and/or increased ovarian volume (>10ml) was considered as polycystic ovary (PCO). Only one ovary fitting this definition was sufficient to define PCO and a dominant follicle (>10mm) or a corpus luteum should not be present.

Assays

Serum concentrations of FSH, LH, estradiol were analysed by competitive immunoenzymatic colorimetric method for quantitative determination, using commercial NovaTec kits obtained from DiaMetra, Italy. Detection limits for the estradiol assays was 8,7 pg/mL, for FSH 0.17 mIU/ml, for LH 0.22 mIU/ml. Total coefficients of variation varied between 7.91 and 10% for these analyses. The serum concentrations of AMH were determined using enzymelinked immunoassay kits, from Immunotech Beckman Coulter Company, France. The detection limit for AMH was 0.01 ng/ml and levels below this limit were considered undetectable. Total coefficient of variation was 12.3% for the AMH analyses.

Statistical methods

For comparison between groups, independent t-tests or Mann-Whitney U-tests were performed, depending on whether the variable was normally distributed or not. Frequencies were compared between groups by the χ^2 test. The SPSS statistical package was used for all analyses (SPSS Inc. version 17.0, Chicago, IL, USA). A p-value of <0.05 was considered significant.

Results

A total of 137 women of late reproductive age underwent clinical examination. From these 67 patients underwent conservative treatment with antiandrogens and OCPs in adolescence and 70 women were age – matched

	After conservative treatment n=67	Control women n=70	P-value
Age (years)	42.7±2.8	40.8±4.3	ns
Ovarian volume (ml)	7.4±2.1	5.4±2.8	P<0.01
Antral follicle count (n)	10.5±1.4	6.1±2.7	P<0.05
Estradiol (pg/ml)	131± 16	138±24	ns
FSH (IU/l)	7.8±1.4	9.7±3.2	ns
LH (IU/l)	5.8±1.8	6.3±2.7	ns
AMH (pmol/l)	3.8±2.1	2.1±1.8	P<0.01

Table 1. Mean±SD of ovarian volume, number of antral follicles, ovarian steroids and gonadotropins in women of advanced reproductive age with a history of polycystic ovary syndrome (Mann-Whitney U-test).

controls. Exclusion criteria for controls was a history of anovulatory diseases.

Mean ovarian volume and number of antral follicles in women of late reproductive age with history of PCOS after conservative treatment with antiandrogens and OCPs were significantly higher than controls, 7.4±2.1 ml compared with 5.4±2.8 ml (P <0.01) and 10.5±1.4 compared with 6.1±2.7 (P <0.05 respectively) (Table 1).

AMH serum concentrations were significantly higher in women of late reproductive age with PCOS after conservative treatment than controls 3.8±2.1 compared with 2.1±1.8 (P <0.01). There was no statistically significant difference between the groups in estradiol, FSH and LH levels (Table 1).

Discussion

The previous studies showed that women with PCOS have 2 to 3 times higher level of the serum AMH concentration which is related to increased number of small follicles [4]. Some clinical researches suggest improved fertility in ageing women with PCOS. The follicle loss through the process of ovarian ageing could explain the occurrence of more regular cycles in older patients with PCOS [9]. The AMH levels in women of late reproductive age decrease [15]. Adolescent girls with PCOS have high number of antral follicles. The question is whether early treatment with antiandrogens and OCPs of PCOS in adolescence affects ovarian reserve in advanced age. Hudecova showed that PCOS patients have an ovarian reserve possibly superior to women with normal ovaries, but it was unselected population [12]. The previous research showed that after laparoscopic ovarian drilling significantly decrease AFC and AMH levels [6]. This may be explained by possible damage ovarian blood vessels and ovarian tissue after electrocoagulation. In our study women of late reproductive age had significantly better ovarian reserve after conservative treatment in adolescence, emphasizing the importance of treatment of PCOS with antiandrogens and OCPs in this age.

Results for basal levels of FSH in PCOS have been less conclusive, which may be due to the high variability of this hormone [1]. Women with PCOS have lower basal FSH levels in the early follicular phase than women with normal ovaries. The mechanism, that may partly explain a lack of follicular growth, is probably increased production of inhibin B and high AMH levels from the increased number

of antral follicles in polycystic ovaries. As we mentioned above, ovarian ageing results in diminution of the follicular cohort in both normal women and PCOS patients, and is associated with decreased inhibin B and AMH levels [16,17]. It will permit FSH enhancement and lead to full follicle maturation, more regular menstrual cycles and the appearance of ovulatory cycles in polycystic ovaries. Our study showed that there was no statistically significant difference in FSH levels between the groups, that may be explained by similar reduction of follicular cohort.

The major limitation of the present study was the low overall response rate among PCOS patients, especially among

subjects living outside the Tbilisi area. Generally a lack of retrospective research for the evaluation of ovarian reserve especially in adolescence emphasizes the importance of the present research, which is distinguished from the previous studies also by significant amounts of research subjects. Moreover, further controlled researches are needed in order to analyze the remote results for the assessment of ovarian reserve.

In conclusion, the analysis of our material indicates that women of late reproductive age with history of PCOS after treatment of antiandrogens and COCs in adolescence have the better ovarian reserve and possibly a good fecundity than women with normal ovaries.

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ОВАРИАЛЬНЫЙ РЕЗЕРВ У ЖЕНЩИН СТАРШЕГО РЕПРОДУКТИВНОГО ВОЗРАСТА ПОСЛЕ КОНСЕРВАТИВНОГО ЛЕЧЕНИЯ СИНДРОМА ПОЛИКИСТОЗНЫХ ЯИЧНИКОВ (СПКЯ) В ПОДРОСТКОВОМ ВОЗРАСТЕ

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Резюме. *Цель исследования* – оценка овариального резерва у женщин старшего репродуктивного возраста после консервативного лечения синдрома поликистозных яичников в подростковом возрасте. *Дизайн.* Исследование было ретроспективным, с использованием преднамеренной выборки. *Методы.* В исследование были включены 67 пациенток позднего репродуктивного возраста с диагнозом СПКЯ в подростковом возрасте; контрольную группу составляли 70 здоровых женщин того же возраста. У пациенток с СПКЯ исследование и консервативное лечение антиандрогенами и комбинированными оральными контрацептивами (КОК) проводились в 1984-1990 гг. Возраст пациенток колебался от 13 до 18 лет. *Основные критерии оценки.* Исследование было построено на анализе историй с СПКЯ пациенток в подростковом возрасте. В дальнейшем проводился анализ крови на репродуктивные гормоны. Данные были сопоставлены между группами. *Результаты.* После консервативного лечения СПКЯ в подростковом возрасте пациентки старшего репродуктивного возраста имели высшее содержание антимюллерового гормона; количество антральных фолликулов было значительно выше, чем у женщин контрольных групп ($P < 0,01$ и $P < 0,05$ соответственно). *Выводы:* наши данные показывают, что пациентки с СПКЯ, которые прошли консервативное лечение в подростковом возрасте, в старшем репродуктивном возрасте имеют лучший резерв яичников, чем здоровые женщины соответствующего возраста.

Ключевые слова: синдром поликистозных яичников, овариальный резерв, антимюллеров гормон, подростки, КОК.