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RESEARCH ARTICLE

Influence of oral hormonal contraception on the concentration of anti-Müllerian and reproductive hormones in patients with polycystic ovary syndrome

Klara Dumanić[1],
Jelena Marušić[1, 2, 3],
Ivana Mudnić[4]

[1] University of Split School of Medicine, Split, Croatia

[2] Department of Obstetrics and Gynaecology, University Hospital Center Split, Croatia

[3] Department of Health Studies University of Split, Split, Croatia

[4] Department of Basic and Clinical Pharmacology, University of Split School of Medicine, Split, Croatia

Correspondence to:
Ivana Mudnić
Department of Pharmacology, University of Split School of Medicine, Šoltanska 2, 21000 Split, Croatia
imudnic@mefst.hr

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Aim: To investigate the effects of three-month use of oral hormonal contraception (OHC) on hormonal status and ovarian reserve indicator (anti-Müllerian hormone, AMH) in patients with polycystic ovary syndrome (PCOS).

Methods: 19 patients with diagnosed PCOS and clinical and laboratory signs of hyperandrogenism without additional comorbidities and co-medication were included in the study. All participants received therapy with the same oral hormonal contraceptive (fixed combination of 0.035 mg ethinyl estradiol and 2 mg cyproterone acetate). The main outcomes were the concentrations of reproductive hormones measured before starting therapy and in the first cycle following therapy. Hormone concentrations were analysed using the immunochemical electrochemiluminescence (ECLIA) method.

Results: Initial concentrations of total and free testosterone and AMH were elevated, while initial concentrations of other reproductive hormones were within reference values. By applying the therapy, the concentrations of AMH, luteinizing hormone (LH) and estradiol decreased by more than 20% and those of free testosterone by 85%. The concentration of sex hormone binding globulin (SHBG) increased by 44%.

Conclusions: Three months of oral hormonal contraception with 35 μg ethinyl estradiol and 2 mg cyproterone acetate reduced elevated concentrations of AMH and free testosterone in PCOS patients. The decrease in serum AMH concentration indicates a temporary interruption of folliculogenesis as well as the selection of follicles from preantral to antral, and the decrease in androgens has a positive effect on the clinical condition and symptoms of patients with PCOS.

Keywords: anti-Müllerian hormone; health; oral hormonal contraception; ovarian reserve; polycystic ovary syndrome

Introduction

It is estimated that several hundred million healthy women of reproductive age worldwide use oral hormonal contraceptives (OHC) for family planning [1]. OHC is a therapy for several pathological conditions of the reproductive system, including polycystic ovary syndrome (PCOS), a dominant endocrinopathy in women of reproductive age with an assumed worldwide prevalence of 3% to 20% [2].

Modern OHC is safe and does not alter the likelihood of subsequent spontaneous pregnancies in most users. A smaller number of women (1-10%) develop premature ovarian insufficiency (POI), which can have serious consequences for a woman's health, including infertility. POI may go undetected during OHC due to breakthrough bleeding caused by pharmacotherapy [3]. Therefore, there is growing interest among OHC users to assess the quality of their reproductive health by evaluating ovarian reserve before, during and immediately after cessation of OHC use and before the planned date of achieving motherhood. The assessment of ovarian reserve is even more necessary in women with PCOS who use OHC, as the clinical picture of these patients includes several symptoms that correlate negatively with the possibility of conception (e.g., anovulatory cycles and hyperandrogenism).

A simple and readily available laboratory marker for ovarian reserve is anti-Müllerian hormone (AMH). This glycoprotein is considered the "guardian" of ovarian reserve because it limits the number of recruited oocytes and growing follicles and selects the dominant follicle for ovulation. It is considered the most reliable marker of ovarian reserve in clinical diagnostics [4]. Its synthesis occurs in the granulosa cells of the preantral and small antral follicles [5]. Concentrations are stable (10 to 20 pmol/L) during most of reproductive life, and gradually decrease before menopause, after which they are no longer measurable [6, 7]. The AMH concentration varies due to lifestyle habits (smoking, alcoholic beverage consumption) and body mass index [4]. Due to the increased number of antral follicles in women with PCOS, the basal concentration of AMH is significantly elevated, which, although not indicative of increased ovarian reserve, is a negative prognostic sign. Anovulation occurs more frequently in these women [5, 6].

In the treatment of patients with PCOS and marked hyperandrogenism, preparations containing cyproterone acetate are used due to their strong antiandrogenic effect [8]. This progesterone component of OHC blocks androgen receptors and the enzyme 5-α-reductase and, in addition, increases androgen clearance by inducing liver enzymes, thus decreasing the concentrations of androstenedione, total testosterone and free testosterone, while increasing the concentration of sex hormone binding globulin (SHBG) [9, 10]. The use of all types of OHC in patients with PCOS (but also in healthy users) further lowers the concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E2).

Data from the literature on the effect of OHC on AMH are not consistent [4]. Most studies have shown that AMH concentrations do not change in healthy women and patients with PCOS after taking OHC for several months [11-15], while other studies have shown a significant decrease in AMH concentrations [16-20]. The heterogeneity of the inclusion criteria,

the type and duration of use of the different OHC preparations and the design of the studies contribute to the fact that the results of the studies conducted are contradictory. It is still not clear how AMH concentrations change, how they relate to reproductive hormone concentrations and whether AMH can be used as an indicator of ovarian reserve in PCOS patients during OHC.

Our prospective study included women with PCOS who received a fixed combination of 0.035 mg ethinyl estradiol and 2 mg cyproterone acetate for three months. This is thought to be exactly the time needed for a complete cycle of folliculogenesis [21]. We hypothesised that taking OHC would decrease AMH concentrations and alter concentrations of reproductive hormones, especially androgens.

Participants and methods

Study design and outcome measures

19 women with PCOS and clinical and laboratory signs of hyperandrogenism were included in the study. All included participants were healthy, had normal arterial blood pressure values, had no additional comorbidities or concomitant medications, and denied smoking cigarettes or consuming alcoholic beverages. The study was conducted at the Department of Gynaecological Endocrinology, University Hospital Centre Split. We conducted a prospective cross-sectional study on all participants who met the inclusion criteria and who came to the Human Reproduction Clinic for a specialist examination over a period of three months. The participants were prescribed therapy with the OHC preparation containing 0.035 mg ethinyl estradiol and 2 mg cyproterone acetate, after it had previously been determined that there were no contraindications to starting therapy. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Split (Class: 003-08/22-03/003, Reg. No: 2181-198-03-04-22-0067). Before participating in the study, all participants signed an informed consent form and allowed access to data on height, weight, and age data, as well as a statement not to consume alcoholic beverages and tobacco. According to the guidelines of the World Health Organization guidelines, the criterion for overweight was a body mass index (BMI)≥25 kg/m2. Outcome measures were a) anthropometric parameters: body weight and height, body mass index, b) pituitary hormone concentrations: FSH, LH and prolactin, c) concentration of ovarian reserve marker: AMH, d) concentrations of ovarian hormones: estradiol, progesterone, d) concentrations of hormones with androgenic effects: total testosterone, free testosterone, dehydroepiandrostenedione sulphate (DHEAS) and androstenedione, e) concentration of sex hormone binding globulin (SHBG). Reproductive hormones were measured before starting oral hormonal contraceptive therapy and in the first natural cycle after three months of therapy as part of the research protocol.

Methods for the determination of laboratory parameters

Hormone concentrations were analysed using the immunochemical electrochemiluminescence method (ECLIA) on a Roche-Ellecsys Autoanalyzer in the central laboratory of the Institute of Medical Laboratory Diagnostics of KBC Split.

Statistical data processing

Sex hormone concentrations are expressed as arithmetic means±standard deviation. Hypotheses were tested with the t-test for dependent samples with a significance level of $\alpha=0.05$ ($P<0.05$) sing the computer programme SPSS (IBM SPSS Statistics version 24, New York, USA). Anthropometric characteristics of the sample were analysed with descriptive statistics and presented as medians with interquartile range (IQR). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the distribution of the data.

Results

Age, height, weight, and body mass index

The median age of the participants was 29 years (IQR=18 years, 35 years), and 63% of them were younger than 30 years. The median body weight of the participants was 69 kg (IQR=55 kg, 90 kg), the median height was 168 cm (IQR=155 cm, 183 cm) and the median body mass index (BMI) was 24.2 kg/m^2 (IQR=20.2 kg/m^2, 28.7 kg/m^2). 42% of the participants were overweight.

Comparison of the measured parameters before and after therapy

Baseline concentrations of FSH, LH, prolactin, estradiol, progesterone, androstenedione, DHEAS and SHBG were in accordance with the standards of the laboratory where the test was performed. On the contrary, the concentrations of total and free testosterone were elevated, as was the concentration of AMH. Taking OHC resulted in significant changes in the concentration of LH, estradiol, SHBG, free testosterone and AMH. The SHBG concentration increased by 44% and the concentrations of the above hormones decreased: AMH by 21%, LH and estradiol by 22% and free testosterone by 85% (**Table 1**). The above concentration differences were statistically significant.

Discussion

This study showed the expected increase in the basal concentration of AMH in patients with PCOS and a statistically significant decrease in concentration after three months of OHC therapy (35 μg ethinyl estradiol and 2 mg cyproterone acetate). The decrease in AMH concentrations could be the result of a decrease in circulating androgen concentration and the resulting suppression of the hypothalamic-pituitary-ovarian axis [17]. The key role of the potent antiandrogen cyproterone acetate as a progestogenic component of OHC, which in this study had significant effects on AMH in PCOS patients after a relatively short

Table 1. Concentrations of AMH, LH, FSH, prolactin, estradiol, free and total testosterone, progesterone, androstenedione, DHEAS and SHBG in study participants (n=19) before and after OHC*

Measured parameter	Mean concentration before therapy (mean±SD)	Mean concentration after therapy (mean±SD)	*t*	*P*†
AMH (pmol/L)	46.70±19.01	36.82±15.49	9.201	0.001
LH (IU/L)	6.79±3.22	5.33±2.10	3.112	0.006
FSH‡ (IU/L)	4.87±1.14	4.89±1.15	-0.087	0.932
Prolactin (mIU/L)	412.47±189.16	395.35±174.81	0.469	0.646
Estradiol (pmol/L)	153.75±69.48	119.38±53.67	3.193	0.006
Free testosterone (nmol/L)	0.20±0.25	0.03±0.03	3.084	0.008
Total testosterone (nmol/L)	1.83±0.52	1.65±0.44	2.038	0.057
Progesterone (nmol/L)	2.67±0.99	2.27±0.92	1.553	0.140
Androstendione (nmol/L)	7.47±3.78	7.66±2.93	-0.289	0.777
DHEAS (µmol/L)	6.87±1.77	6.13±1.23	1.979	0.068
SHBG (nmol/L)	69.94±22.88	124.35±61.71	3.805	0.002

* Abbreviations: AMH – anti-Müllerian hormone, LH – luteinizing hormone, FSH – follicle-stimulating hormone, DHEAS – dehydroepiandrostenedione sulphate, SHBG – sex hormone binding globulin, SD – standard deviation.
† t-test for dependent samples.

course of use, was also demonstrated in the study by Panidis et al. [17]. According to previous findings, when comparing treatment with metformin alone, OHC with cyproterone acetate and OHC with drospirenone, the most significant reduction in AMH concentrations was achieved when OHC was used with cyproterone acetate [17].

Our results confirm the anti-androgenic effect of OHC with cyproterone acetate, as we found a statistically significant decrease in free testosterone and an increase in SHBG [22-26]. Since these are hormones that regularly follow the same patterns of concentration changes in various endocrinological diseases and dysfunctions, it can be assumed that similar patterns in the changes in the concentrations of DHEAS and total testosterone after OHC could also be shown in a larger sample.

The increase in SHBG concentration was relatively expected considering the already mentioned inhibition of the hypothalamus-pituitary-ovary feedback loop and is comparable to other studies [24, 25, 27, 28]. The increase in SHBG concentration, which leads to a decrease in free androgens concentration and a drop in testosterone concentration, is a consequence of the estrogenic component of OHC. On the other hand, the choice of the progesterone component of OHC can have an additive, but also an opposite effect on the increase of SHBG [25]. Moreover, cyproterone acetate, as a progesterone component that has an antiandrogenic effect, additionally increases the clearance of androgens by inducing liver enzymes and blocks androgen receptors in the target organs. Therefore, in combination with ethinyl estradiol, it is the optimal therapy in the long-term treatment of patients with pronounced symptoms of hyperandrogenism [25].

The decrease in LH and estradiol concentrations compared to baseline concentrations was relatively expected given the inhibition of the hypothalamic-pituitary-ovarian feedback loop and is consistent with other studies [11, 12, 15-18]. In addition to the absolute concen-

trations of the hormones themselves, an important prognostic parameter is the ratio of LH and FSH, hormones whose concentrations are similar in healthy women. In women with PCOS, the concentration of LH is higher, and the ratio of LH and FSH increases [29, 30]. As expected, OHC therapy decreases the concentration of LH, bringing the LH and FSH ratio closer to physiological values (in this study, the decrease was 1.4 to 1.1).

In healthy women, the basal concentrations of AMH were lower than in women with PCOS, and several studies showed that neither short-term [13], mid-term [15], nor long-term [11] OHC caused a decrease in the AMH concentration. More recent cross-sectional studies, involving many times healthier participants than the previously studies, have shown that the use of any type of OHC decreases AMH concentrations [31, 32]. The common conclusion of the conducted studies is that the decrease in AMH concentration associated with the use of OHC is reversible and does not lead to permanent changes in ovarian reserve. Therefore, the decrease in AMH concentration should be interpreted with great caution, considering the changes in the concentrations of other reproductive hormones in both healthy women and women with PCOS.

The main limitation of our study was the lack of follow-up of the participants after discontinuing OHC therapy. Another limitation was the small number of participants included, which was only partially compensated by the prospective study design in which each subject was her own control. Given the study design, it was not possible to determine the potential predictive value of AMH in assessing ovarian reserve in women with PCOS. A decrease in serum AMH concentration indicates a temporary interruption of folliculogenesis, as well as the selection of follicles from preantral to antral, which does not mean that the ovarian reserve decreases. After discontinuation of OHC, folliculogenesis starts again, including AMH production, but not necessarily the maturation of the dominant follicle. The time to establishment of normal ovulatory cycles may follow an entire cycle of follicular maturation, from primordial to ovulatory follicle, of 72 days. However, extending this study in this way was not possible because most of the participants wanted to become pregnant immediately after stopping OHC.

Monitoring AMH levels in healthy women and women with PCOS is useful because it provides useful data on changes in the representation of antral and preantral follicles and the response to hormone therapy, i.e., assessing the dose of gonadotropin during controlled stimulation of ovulation in medically assisted fertilisation procedures.

The results of this study show that by using OHC with 35 μg ethinyl estradiol and 2 mg cyproterone acetate over a three-month period in PCOS patients, the serum concentrations of AMH, luteinizing hormone, estradiol and especially free testosterone decrease, while the concentration of globulin, which binds sex hormones, increases. The changed concentrations of AMH and reproductive hormones are still within the reference values. Changes in androgen concentration have a positive effect on the condition of PCOS patients.

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ORCID

Ivana Mudnić https://orcid.org/0000-0003-4169-2886

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