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Anti-androgenic therapy in young patients and its impact on intensity of hirsutism, acne, menstrual pain intensity and sexuality — a preliminary study

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ABSTRACT

Objectives: Using anti-androgenic contraception is one of the methods of birth control. It also has a significant, non-contraceptive impact on women's body. These drugs can be used in various endocrinological disorders, because of their ability to reduce the level of male hormones.

The aim of our study is to establish a correlation between taking different types of anti-androgenic drugs and intensity of hirsutism, acne, menstrual pain intensity and sexuality .

Material and methods: 570 women in childbearing age that had been using oral contraception for at least three months took part in our research. We examined women and asked them about quality of life, health, direct causes and effects of that treatment, intensity of acne and menstrual pain before and after. Our research group has been divided according to the type of gestagen contained in the contraceptive pill: dienogest, cyproterone, chlormadynone and drospirenone. Additionally, the control group consisted of women taking oral contraceptives without antiandrogenic component.

Results: The mean age of the studied group was 23 years ± 3.23. 225 of 570 women complained of hirsutism.

The mean score for acne intensity before the use of contraception was 2.7 ± 1.34. The mean score for acne intensity after 3 months of using contraception was 1.85 ± 1.02 ($p < 0.001$). 192 women reported excess hairiness in one or more area before treatment. Mean value based on Ferriman-Gallway scale before the treatment was 6.23 ± 6.21 and 5.39 ± 5.6 after the treatment ($p < 0.001$).

Conclusions: All groups of drugs effectively reduced pain and acne severity. Cyproterone and drospirenone turned out as the most effective drugs in treating hirsutism. Surprisingly, according to our research, dienogest does not have any impact on body hairiness.

Key words: anti-androgenic therapy; oral contraceptives; acne; hirsutism; menstrual pain; young patients

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INTRODUCTION

Hyperandrogenaemia is a very frequent endocrinopathy. It concerns about 7% of women in childbearing age. Its clinical symptoms can be pretty troublesome and often affect our patients' self-esteem. Oral contraceptives, many times viewed only as a method of contraception, turn out to be very useful in those conditions and offer a variety of non-contraceptive health benefits. They are becoming more and more popular in women with higher levels of androgens. Additionally, they reduce menstrual pain and the amount of blood loss during the menstruation. Moreover, taking hormonal contraceptives regulates the menstrual cycle [1].

Hyperandrogenaemia can be caused by different disease entities, for example polycystic ovary syndrome, obesity, Cushing syndrome, ovarian secreting androgens, adrenal tumors, adrenal hyperplasia, liver insufficiency. The most common symptoms connected with higher levels of androgens are hirsutism and acne. Hirsutism affects about 5–15% and acne about 6–55% of women, according to epidemiological data [1].

Physiologically, androgens are responsible for hair growth regulation, production and secretion of gonadotropins, wound healing and cutaneous barrier formation. The pathogenesis of acne and hirsutism in hyperandroge-

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naemia is connected with sebaceous glands, hair follicles and enzymatic reactions in them. Androgens are converted into the dihydrotestosterone (DHT) which has 5 to 10 times higher affinity to androgen receptor than testosterone [1].

The involvement of androgens in acne vulgaris is supported by different evidences such as lack of acne in men with androgen insensitivity or responding in reduced sebum production in women with acne using antiandrogenic drugs. It is also known, that androgens are responsible for the replacement of vellus hair, which are slight and unpigmented, by thicker and darker terminal hair. That is observed in androgen-sensitive areas and happens in hyperandrogenic entities. Therefore, it seems to be justified to use drugs that decrease the level of male hormones, to help with those complaints [2, 3].

For now, two types of oral contraceptives are known: combined and progestin-only. Combined hormonal contraceptives are very effective in skin changes, whereas progestin-only contraception may even worsen the condition of the skin [1].

One of the types of oral contraceptives are antiandrogenic oral contraceptive pills. They are combined hormonal contraceptives that consist of two components: estrogen and progestogen. The mechanism of action of those drugs concentrates on decreasing the level of androgens in four ways. Firstly, inhibition of secretion of gonadotropins, mostly the luteinizing hormone (LH). This mechanism is the main reason for using antiandrogenic pills in ovarian hyperandrogeneamia, especially hyperthecosis. Then, those drugs increase the liver synthesis of sex hormone binding globuline (SHBG), which ends up with a higher level of bounded androgens and reduced level of biologically active male hormones. Moreover, they decrease the adrenal androgens synthesis, and finally, reduce the activity of androgen receptors.

Antiandrogenic hormonal pills can be divided into four groups depending on the type of progestogen: drospirenone, chlormadynone, cyproterone and dienogest.

Drospirenone

Drospirenone is a derived form of 17 alfa-spironolactone and has a similar chemical structure to spironolactone. It is mostly bounded to albumin, so that the free blood amount is about 3–5%. Despite having anti-mineralocorticoid and anti-androgenic activity, which is almost 30% of the anti-androgenic activity of cyproterone acetate, drospirenone has diverse metabolic effects such as potential to reduce blood pressure and weight loss. The overall pearl index of the combined ethinylestradiol/drospirenone contraceptive is 0.64 [4, 5].

Chlormadyinone

Chlormadyinone acetate is one of derived form of progesterone. Studies have shown its high efficiency in treatment of acne, comparing to other anti-androgenic hormonal pills. This contraceptive is well tolerated and shows a reliable contraceptive effect. The overall pearl index of the combined ethinylestradiol/chlormadinone contraceptive is 0.34 [6, 7].

Cyproterone acetate (CPA)

Cyproterone acetate (CPA) is the most common anti-androgenic drug prescribed to patients with PCOS. According to researches, there are no significant differences in mechanism of action between types of those drugs, but CPA seems to play a significant role in women with high LH/FSH ratio. On the other hand, cyproterone acetate should be prescribed wisely, because of its side effects. According to different studies, CPA should not be used only as a contraceptive. It can be prescribed in specific complaints like moderate to severe acne and hirsutism in women in reproductive age, but only if alternative treatments, such as topical therapy and systemic antibiotic treatment, have failed [4, 8].

Dienogest

Dienogest is the only nortestosterone derivative with antiandrogenic potency. Its antiandrogenic activity is measured as about 30% of cyproterone acetate activity. Only 10% of dienogest is bond to SHBG or CBG so that high serum levels are achieved. Moreover, dienogest is known as a proven way to treat endometriosis, as it has tolerable profile, minimal side effects, it is safe for long-term use and lowers the risk of recurrence of endometriosis. The overall pearl index of the combined ethinylestradiol/dienogest contraceptive is 0.21 [5, 9, 10].

Despite many positive aspects of oral contraception, it should be avoided in women suffering from migraine headache, systemic lupus erythematosus, cholecystic diseases, crescent cell anemia, mitral valve prolapse and item in patients who smokes cigarettes, hyperlipidemiae, arterial hypertension, who had in past gestational diabetes and mechanical jaundice during pregnancy. The contraindications to that treatment are as follows: pregnancy, breast feeding, birth canal bleeding with unknown etiology, estrogen-dependent cancers, circulatory system and hepatic diseases, migraine treated by ergotamine, significant hypercholesterolemia or hypertriglyceridemia and smoking after age of 35 years [1, 11].

Of course, the possible harmful effects of oral contraception should also be considered. Other side effects reported with hormonal contraception is breast tension, headaches, nausea, irregular menses, weight growth, diminished libido and depression [12]. Therefore, prescribing oral contraceptives to the patient should always be carefully thought out.

The aim of the study was to establish the correlation between the type of active progestogen ingredient in oral antiandrogenic contraception and reducing hirsutism in specific areas, reducing intensity of pain and acnes in womens body for 3-month follow-up period.

MATERIAL AND METHODS

This prospective, observational, non-interventional study was carried out at the Department of Pregnancy Pathology, Department of Woman's Health, School of Health Sciences in Katowice, Medical University of Silesia, Poland between March 2018 and March 2019. Patients were recruited personally while waiting for their routine medical check-ups. Women above eighteen years old, in childbearing age and non-pregnant were enrolled to our study. Patients with indications for use of oral contraception, who had given permission for the beginning of hormonal therapy took part in our research. Exclusion criteria were using oral hormonal contraception or another drug with antiandrogenic component, for example finasteride and flutamide, for at least three past months and lack of patient's consent. Finally, 570 patients were included into the study. The university Ethics Committee waived the requirement for informed consent due to the anonymous and non-interventional nature of the study (KNW/0022/KB/68/19). Patients gave informed consent to the study.

The completely self-administered questionnaire was provided to the patients twice. At the first visit we asked about gynecological, endocrinological and general medical conditions, menorrhea disorders, used medicaments and intensity of menstrual pain. Information about relationship, habitation, education and quality of life were also collected. Physical examination contained weight and height measurement, evaluation of intensity of acne and hairiness in 9 androgen sensitive areas — upper lip, chin, chest, upper and lower back, upper and lower abdomen, upper arms and thighs. Based on results of examination hirsutism assessment with Ferriman-Gallwey (FG) scoring were done. Hair growth was marked in all of those areas on scale from 0 (no terminal hair) to 4 (maximal growth). The maximum score is 36. Women with a score of 8 and more were diagnosed with hirsutism [13]. During three weeks before evaluation patients were requested not to use shaving or other mode of hair removal. Patients were prescribed oral contraception. According to the type of active ingredient women were divided into five groups: control group (patients using oral contraceptives without anti-androgenic component) and four research groups, depending on active progestogen substance (Fig. 1).

After three months patients were asked to visit the outpatient clinic again in order to re-evaluate the score in the Ferriman-Gallwey scale. Rules of not shaving for three weeks before the evaluation were persistent. The intensity of acne was marked. Questions about the intensity of menstrual pain were also asked.

All data analyses were conducted using StatSoft Statistica version 13.0 PL software and P value of < 0.05 was considered as significant. Quantitative variables are presented as mean and standard deviation (SD) or a median and interquartile range (IQR). The qualitative variables are presented as an absolute value and/or percentage. Between-group differences for quantitative variables were verified using parametric (t-test or ANOVA) or non-parametric tests (Mann-Whitney U or Kruskal-Wallis), with previous verification of their distribution by the Shapiro-Wilk or Kolmogorov-Smirnov test. In the case of qualitative variables, the chi-square test or Fisher's exact test were used.

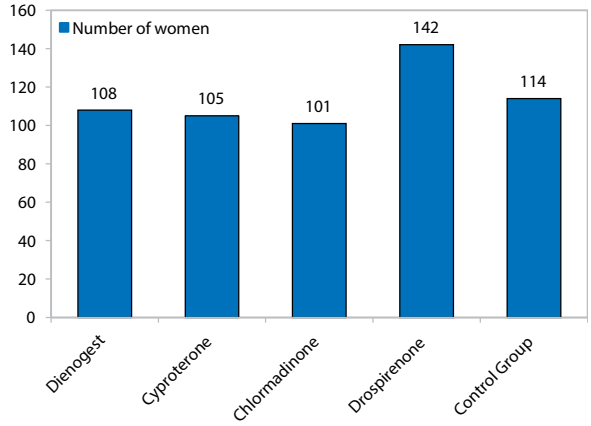

Figure 1. Patients' oral contraception intake divided by type of gestagen

Table 1. Subjects' characteristics.

	Research group	Control group	p
Age [years]	23 ± 3.04	23 ± 3.9	> 0.05
Martial status			
Married	66 (14.5%)	15 (13.15%)	> 0.05
Informal relationship	294 (64.5%)	89 (78.1%)	
Single	96 (21%)	10 (8.8%)	
Education			
University degree	171 (37.5%)	44 (38.6%)	
High school	280 (61.4%)	68 (59.7%)	> 0.05
Vocational	5 (1.1%)	2 (1.7%)	
No education	1 (0.02%)	0 (0%)	
Place of residence			
City above 200,000 residents	222 (48.7%)	67 (58.8%)	
City 50,000–200,000 residents	77 (16.9%)	24 (21.1%)	> 0.05
Town below 50,000 residents	59 (12.9%)	11 (9.7%)	
Village	98 (21.5%)	12 (10.5%)	
Living conditions			
Very good	199 (43.6%)	53 (46.5%)	
Good	202 (44.3%)	48 (42.1%)	> 0.05
Average	54 (11.8%)	13 (11.4%)	
Below the average	1 (0.2%)	0 (0%)	
Growth [cm]	167 ± 7.14	167 ± 6.01	> 0.05
Weight [kg]	62 ± 12.2	59 ± 8.54	> 0.05

Data are presented as number (%) or mean SD

RESULTS

The mean age of the patients was 23 years ± 3.23. Their average age in both of groups was similar. Table 1 presents general characteristics of the studied group (Tab. 1).

Pain and acne

The mean score for acne intensity before the use of contraception was 2.7 ± 1.34. The mean score for acne intensity after 3 months of using contraception was 1.85 ± 1.02 ($p < 0.001$). The intensity of acne before and after the use of contraception in each group is presented in Figure 2. The reduction of acne intensity was statistically important in all five groups ($p < 0.001$).

The mean score of menstruation pain intensity before the use of contraception was 6.15 ± 2.55. The mean score of pain intensity after 3 months of using contraception was 2.96 ± 1.92 ($p < 0.001$). The intensity of pain before and after the use of contraception in each group is presented in Figure 3. All of anti-androgenic groups and control group reduce the intensity of menstrual pain in three months period ($p < 0.001$).

Hirsutism

The mean score based on Ferriman-Gallway scale in the studied group was 2.1 ± 4.65 before the treatment and 1.83 ± 4. 12 after the treatment ($p < 0.001$).

378 women (66.32%) did not report excess hairiness in any part of the body before the treatment (0 points). 386 patients (67.72%) didn't report excess hairiness after the treatment (0 points).

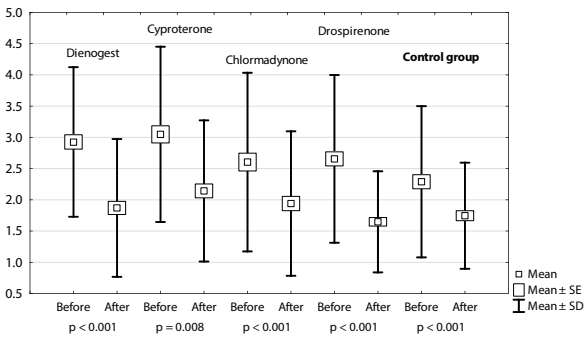

Figure 2. The intensification of acne before and after treatment

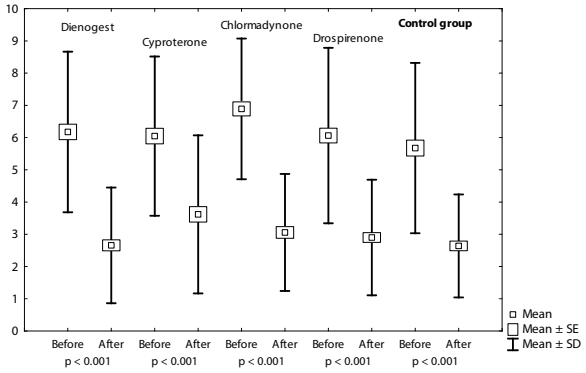

Figure 3. The intensification of the menstrual pain before and after treatment

Table 2. Mean value of excessive hairiness in the group of 192 women who reported excessive hairiness in one or more parts of the body before the treatment

	Before	After	p
Dienogest	2.43 ± 5.38	2.06 ± 4.88	< 0.001
Cyproterone	3.71 ± 5.5	3.48 ± 4.88	< 0.001
Chlormadynone	1.96 ± 4.93	1.73 ± 4.55	< 0.001
Drospirenone	1.7 ± 4.25	1.35 ± 3.34	< 0.001
Control group	0.91 ± 2.36	0.79 ± 2.19	< 0.001

Data are presented as mean ± SD

192 women reported excess hairiness in one or more area before treatment. Mean value based on Ferriman-Gallway scale before the treatment was 6.23 ± 6.21 and 5.39 ± 5.6 after the treatment ($p < 0.001$). In this group, 59 of women had a score of 8 or more, in a scale Ferriman-Gallway this result is regarded as hirsutism.

Table 2 presents the intensity of excessive hairiness in the group of 192 women who reported excessive hairiness in one or more parts of the body before the treatment, depending on the type of contraception.

Effects of the treatment on hirsutism in different parts of the body are shown in Table 3. Cyproterone reduces hairiness on chin ($p = 0.04$), thighs ($p = 0.05$) and buttocks ($p = 0.04$). Drospirenone has the effect of reducing excessive hair on upper lip ($p = 0.01$), thighs ($p = 0.04$) and buttocks ($p = 0.04$). Chlormadinone has statistically important impact on underbelly and thighs ($p = 0.01$) hirsutism. After three months of using control group the p value is important for upper lip ($p = 0.04$). On the other hand, dienogest does not contribute to decrease body hairiness in any of the chosen areas ($p > 0.05$ for each part of the body).

DISCUSSION

Hyperandrogenism is a complex condition that can manifest in different clinical symptoms such as hirsutism, acne and others, which often result in lower self-esteem. For now, we know that oral antiandrogenic pills are helpful, but are prescribed rather randomly because the main differences between ways and places of action are still not known [14].

Although it is unclear how the biochemical markers of hyperandrogenism affect the quality of patients' life, study shows that the clinical manifestations play the main role in worsening it. That is probably because the severity of symptoms in hyperandrogenism correlate poorly with the androgen excess and some of the patients with clinical symptoms of hyperandrogenism have androgen levels in normal ranges. That is why it is important to choose the treatment that can help with patients' complaint, not only the biochemical markers [15].

Table 3. The intensification of the hirsutism before and after treatment

Part of the body	Dienogest			Cyproterone			Chlormadynone			Drospirenone			Control group		
	Before	After	p-value	Before	After	p-value	Before	After	p-value	Before	After	p-value	Before	After	p-value
Upper lip	2.22	1.815	> 0.05	1.571	1.375	> 0.05	1.773	1.55	> 0.05	1.931	1.625	**0.01**	1.444	1.125	0.04
Chin	1.294	1.200	> 0.05	1.667	1.571	**0.04**	2.286	2.444	> 0.05	1.182	1.182	> 0.05	1.143	1.00	> 0.05
Chest	2.200	1.667	> 0.05	1.000	1.00	> 0.05	1.000	0	> 0.05	1.500	1.556	> 0.05	1.250	1.00	> 0.05
Stomach	1.529	1.467	> 0.05	1.500	1.667	> 0.05	1.733	1.600	> 0.05	1.563	1.375	> 0.05	1.222	1.300	> 0.05
Underbelly	2.083	2.000	> 0.05	1.667	1.556	> 0.05	2.316	1.895	**0.01**	1.778	1.444	> 0.05	1.389	1.400	> 0.05
Arms	1.833	2.000	> 0.05	1.667	1.667	> 0.05	2.571	2.571	> 0.05	1.667	1.400	> 0.05	1.667	1.667	> 0.05
Thighs	1.857	1.650	> 0.05	2.500	2.167	**0.05**	2.235	1.765	**0.01**	2.214	1.857	**0.04**	1.875	1.625	> 0.05
Back	2.000	2.000	> 0.05	1.500	1.500	> 0.05	0	0	0	1.400	1.000	> 0.05	1.000	1.000	> 0.05
Buttocks	3.182	2.818	> 0.05	2.400	2.500	**0.04**	2.800	2.800	> 0.05	2.667	2.429	**0.04**	2.333	1.750	>0.05

Data are presented as mean ± SD

Polycystic ovarian syndrome (PCOS) is a common gynecologycal problem that affects about 5–9 % of women in reproductive age. Rotterdam criteria ESHRE/ASRM are used to define that condition. They include clinical or biochemical hyperandrogenism, infrequent or absence of ovulation and polycystic ovaries on ultrasound [17]. It is necessary to exclude other disorders with androgen excess. Ovaries and adrenals are responsible for increased androgen level in PCOS. The excess of testosterone (T), total, unbound and free form can be found. Also, that disorder can be related to high level of Δ4-Androstendione (Δ4-A), dehydroepiandrosterone (DHEA), and DHEAsulfate (DHEAS). It turned out that testosterone is a superior marker of hyperadnogenemia. Free testosterone and Δ4-Androstendione are also important, but less than testosterone. Many women who are suffering from PCOS had increased level of testosterone and normal free testoserone and Δ4-Androstendione. Increased Δ4-A level can be associated with more severe phenotype of PCOS [16–19].

One of the studies, examined the effects of different physical training protocols on the sexual function of women with PCOS. This research revealed that continuous aerobic training as well as intermittent aerobic training increased the quality of sexual life and reduced the anxiety and depression of women with polycystic ovary syndrome [20]. According to that study, women suffering from hyperandrogenism and its clinical symptoms are less satisfied with their sexual life. It turned out that choosing oral antiandrogenic contraception containing chlormadinone acetate cause the change in sexual behavior during the treatment. Patients found themselves to be more sexually attractive and as well their partners found them more sexually attractive than before. That is probably because of the aesthetic improvement obtained by the pill intake. More researches are needed to be done to find out if other groups of antiandrogenic pills have similar impact on women's sexual behavior [21, 22].

One of the studies analyzed the influence of genotype and hyperandrogenism on sexual function, gender identification, and partner preference in women with congenital adrenal hyperplasia (CAH) who present symptoms of hyperandrogenism [23]. This study is pointing to importance of early beginning of antiandrogenic treatment in women with congenital adrenal hyperplasia [23].

This study is only a prototype for comparison between the four groups of antiandrogenic drugs. It is focused on searching the differences between place of action in hirsutism. That means the treatment probably can be matched to specific problems more precisely, limiting the side effects to the minimum for every woman's case.

According to our research the most effective in hirsutism are drospirenone and cyproterone so that they would be the best for patients with polycystic ovary syndrome. A systematic review is pointing to similar effectiveness of these two drugs [24]. They reduce hairiness mostly on thighs, buttock and accordingly on upper lip and chin. Additionally, dienogest statistically does not have any impact on body hairiness. Other study confirms that dienogest is worse in reducing hirsutism than cyproterone [25]. That can suggest withdrawal of prescribing it to women with those complaints. Chlormadinone has impact only on underbelly and thighs excessive hair. According to study these antiandrogenic drug is effective in hirsutism, but less than drospirenone [1].

It is important to remember that the most common symptom of polycystic ovary syndrome is moderate and severe acne. There, gyneacologist should always take into consideration all of the symptoms that patient complaints of and try to find a solution to all of them. However, this research did not indicate any important differences in reducing intensity of menstrual pain and acne. All of the antiandrogenic groups and control group seem to have similar impact on those complaints. That is why matching

the specific group of drug to specific hirsutism area probably can be independent of other popular factors, excluding the side effects [16].

Polycystic ovary-related hyperandrogenic symptoms can by effectively treated by cyproterone acetate and ethinylestradiol (CPA/EE). Besides all the over obvious effects such as improvement in hirsutism, acne, seborrhea, alopecia, irregular bleeding and decrease in hyperandrogenemia and hyperinsulinemia, this treatment may result in reduction in risk of ovarian, colon and endometrial cancer. There are also researches, which indicate that short-term pre-treatment CPA/EE could potentially increase fertility in female patients and improve pregnancy outcomes, however more studies are needed [26].

Considering lipid and glucose metabolism cyproterone acetate and ethinylestradiol seems to be better choice for patient with polycystic ovary syndrome, because this condition is associated with multitude of metabolic disorders. Androgenic progestogens such as levonorgestrel may have negative influence on metabolism parameters [26, 27].

The side effects or hormonal contraception should be always taken into consideration, prudent usage of medicaments with cyproterone is justified and the balance between profits and side effects needs to be kept [12, 28].

CONCLUSIONS

The main finding from this study was different impact on reducing hirsutism in specific areas depending on used drug: dienogest, cyproterone, chlormadinone or drospirenone. It means that the treatment can be precisely matched to specific woman's problem. The biggest impact on chin hair had cyproterone. To reduce hirsute intensity on upper lip prime choice could be drospirenone and oral contraception without antiandrogen component. If thigh area is the most problematic for the patient, she should take cyproterone, drospirenone or chlormadinone. The best treatment for buttocks hairiness is cyproterone or drospirenone and for lower abdomen — chlormadinone. According to this research, dienogest does not have important influence on hirsutism.

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