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## How to treat acne in women with polycystic ovary syndrome (PCOS)? Review of the available literature

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### Abstract

Acne vulgaris is one of the most common chronic skin diseases among people between 15 and 40 years of age.<sup>1</sup> It would seem that it is a typical disease of adolescence. However, it also very often affects adults. One of the most common causes of acne vulgaris in adult women is polycystic ovary syndrome (PCOS). The hyperandrogenism and metabolic disorders present in this syndrome may contribute to the formation of blackheads, pimples, and cysts on the face, chest and back. This article focuses on a review of current acne treatments associated with polycystic ovary syndrome.

Key words: acne vulgaris, polycystic ovary syndrome, hyperandrogenism, hormone replacement therapy, combined oral contraceptive pill

### **Epidemiology of acne and polycystic ovary syndrome (PCOS)**

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of childbearing age. According to estimates, it affects from 8 to even 13% of them.<sup>2</sup> Acne in adult women is often one of the first manifestations of polycystic ovary syndrome. However, this does not mean that every woman suffering in this endocrine disorder faces acne. Acne is one of the most common chronic skin diseases. Usually associated with adolescence. Then, heightened levels of adrenal androgens responsible for its creation. In adolescent girls diagnosed with PCOS, acne is often more severe than in their peers. More than 50% of them deal with its moderate or severe form.<sup>3</sup> After puberty is over, the problem of acne frequently persists and may impact 10 to 34% of them.<sup>4</sup>

### **Pathophysiology of acne and polycystic ovary syndrome (PCOS)**

Acne vulgaris is a chronic disease of the follicular unit. He is accompanied by seborrhea, abnormal keratinization of the hair follicles, creating biofilms and colonies of *P. acnes*, and finally the release of pro-inflammatory mediators to the skin.<sup>5</sup>

The first stage of acne development is the formation of microcomedones. Then, as a result of overproduction of sebum and abnormal keratinization of the hair follicles, they are enlarged. This, in turn, leads to plugging of the follicular units with the pathogenic *P. Acnes* leading to an engaged inflammatory response. The consequence of which is the formation of inflammatory lumps, bumps, pimples, and cysts.

Women with polycystic ovary syndrome very often face acne in adulthood. It is associated with accompanying hyperandrogenism as well as elevated insulin levels. It is known that androgens affect the hair follicles, contributing to the formation of acne lesions in areas with a high accumulation of sebaceous glands – face, chest and back. In polycystic ovary syndrome, the ovaries and the adrenal glands are the source of excess androgens. 60-80% of these patients have elevated levels of androgens in the blood.<sup>6</sup> The most important factor is the value of free testosterone circulating in the blood. In contrast to plasma protein bound testosterone, it exhibits metabolic activity. In diagnostics, both the determination of free testosterone and the calculation of its value based on the concentration of total testosterone and sex hormone binding globulin (SHBG) are used. However, not all women with polycystic ovary syndrome and acne vulgaris show an increased level of free testosterone in the blood.

Interestingly, some women with high levels of it may not have acne lesions. It is currently postulated that the level of androgens in the skin is a more important mediator of acne than those circulating in the blood. We are talking about dihydrotestosterone (DHT) – the strongest androgen that is formed in the hair follicles under the influence of 5- $\alpha$ -reductase from free testosterone. This enzyme has two isoforms: type 1 is found in the sebaceous glands and the pubic skin, and type 2 is found mainly in the hair follicles, genital skin and scalp of adults. The relative activity of these isoenzymes in the hair follicles may account for the variable clinical picture observed in women with hyperandrogenism. In addition, the increased activity of the 5- $\alpha$ -reductase enzyme is additionally stimulated by excess insulin and insulin-like growth factor. Their level in women with polycystic ovary syndrome is very often elevated.

### **Criteria for the diagnosis of polycystic ovary syndrome (PCOS)**

Polycystic ovary syndrome can be diagnosed when a woman meets 2 out of 3 Rotterdam criteria:<sup>7</sup>

- oligoovulation or anovulation,
- clinical symptoms of hyperandrogenism or hyperandrogenemia,
- polycystic ovarian morphology on ultrasound examination (at least 12 follicles, diameter 2–9 mm, ovarian volume > 10 ml).

The diagnosis of PCO syndrome requires the exclusion of other causes of hyperandrogenism (hormonally active tumors, hypothyroidism, hyperprolactinaemia, congenital adrenal hyperplasia, Cushing's syndrome, acromegaly).

The main clinical symptoms of polycystic ovary syndrome are irregular periods, symptoms of hyperandrogenism (acne, hirsutism, androgenetic alopecia) and being overweight. Coexisting insulin resistance in some women is associated with an increased risk of developing type II diabetes. In contrast, irregular menstrual cycles stimulate abnormal endometrial hyperplasia, as a result of that increasing the risk of developing endometrial cancer. However, polycystic ovary syndrome is not always typical. Some patients with polycystic ovarian morphology and symptoms of hyperandrogenism maintain regular periods. However, in others, irregular menstruation and polycystic ovarian morphology need not be accompanied by hyperandrogenism. Importantly, some PCOS patients have a normal body weight, yet some of them have insulin resistance.<sup>8</sup>

### **Treatment's methods of acne in polycystic ovary syndrome**

The main goal of the treatment of polycystic ovary syndrome is to regulate the occurrence of menstrual cycles, reduce the level and negative effects of androgens, as well as reduce insulin

resistance. Targeted non-pharmacological action and pharmacological treatment can significantly reduce the symptoms of PCOS, including acne.

### **Nonpharmacological Approaches**

Every woman diagnosed with polycystic ovary syndrome should undergo a dietary consultation. The main goal of dietary treatment is:

- weight reduction in women with BMI > 25 kg / m<sup>2</sup>,
- control of the lipid profile and carbohydrate metabolism,
- introduction of regular physical activity, adapted to the abilities.

It demonstrated that a diet with a low glycemic index in women with diagnosed insulin resistance has a positive effect on the reduction of PCOS symptoms, including acne. In addition, weight reduction plays an extremely important role in overweight or obese women. As a result, the levels of androgens and luteinizing hormone are lowered and the tissue sensitivity to insulin increases. In some women, weight reduction by as little as 5% can restore regular menstruation and therefore reduce the symptoms of hyperandrogenism. The Endocrine Society guidelines suggest exercise therapy with dietary modification as first-line treatment for obesity in adolescents and women with PCOS.<sup>9</sup> Recent rodent research has shown that a healthier lifestyle is associated with the normalization of hypothalamic neuropeptides (cocaine and amphetamine regulated transcript (CART) and Kisspeptin) and sex hormone binding globulin (SHBG) in plasma.<sup>10</sup>

### **Pharmacological Treatment**

The treatment of acne in the course of PCOS relies on oral hormonal contraception, anti-androgens, metformin and isotretinoin.

#### **Combined oral contraceptive pill**

Oral combined contraception (COC) is a combination of estrogens and gestagens. In the treatment of acne in the course of PCOS, one should choose preparations containing gestagens with low androgenic activity (norgestimate and desogestrel), or those that have an anti-androgenic effect (cyproteroni acetate, chlormadinone and drospirenone). The estrogen component is typically ethinylestradiol.<sup>11</sup>

The mechanism of action of COCs is to inhibit the release of LH and FSH by the pituitary gland through a negative feedback effect. Thanks to this, the ovaries are not stimulated and the level of androgens produced by them is reduced. In addition, estrogen in COCs increases the production of sex hormone binding protein (SHBG) by the liver, which lowers the level of active androgens in the blood.

On the other hand, the gestagen component reduces the formation of strong androgens in the skin by inhibiting 5-alpha reductase. The aforementioned activities have a positive effect on the condition of the skin, reducing acne lesions.<sup>12</sup>

### **Metformin**

PCOS very often coexists with insulin resistance and hyperinsulinemia. Excess insulin stimulates the ovarian and adrenal androgen production. It is for this reason that metformin, a preparation that increases the sensitivity of cells to insulin, is used in the treatment of acne in the course of PCOS. Treatment with metformin should be started with a low dose (250 mg) and gradually increased to 2 g. The purpose of this action is to avoid side effects of the medicine, such as gas and abdominal pain.<sup>13</sup>

### **Antiandrogenic Therapy**

Antiandrogens such as spironolactone or flutamide are chemical compounds that reduce the effect of androgens on the body. Spironolactone has been used for over 30 years in the treatment of acne. Its main mechanism of action is to block the androgen receptor. In addition, it blocks the enzyme 5-alpha reductase and increases the production of SHBG by the liver. Women who taking spironolactone should remember about regular check potassium levels in their blood. Sexually active women of childbearing potential should use an effective method of contraception, as spironolactan is teratogenic in the fetus.<sup>14</sup>

Flutamide is a drug approved for the treatment of prostate cancer. Due to its side effects, it is of limited use in the treatment of acne. These include the pseudoephedrine state, the risk of feminization of male fetuses, and even fatal hepatitis.<sup>15</sup>

### **Isotretinoin**

The mechanism of action of isotretinoin is to inhibit seborrhea, reduce the multiplication of *Propionibacterium acnes*, control the formation of micro-blackheads, reduce the formation of lesions and existing comedones, and normalize epithelial exfoliation. It can also show anti-inflammatory properties.<sup>16</sup> Numerous studies have shown that isotretinoin may be helpful in the treatment of acne in patients with PCOS.

In one study by Karadag et al. investigated the effect of isotretinoin therapy on the levels of fT4, fT3, TSH, FSH, LH, and E2 and found that tT levels decreased after treatment. However, the levels of FSH and LH did not change significantly. However, this study was conducted in a female and male volunteer with acne.<sup>17</sup>

In contrast, the observations by Acmez et al. showed that isotretinoin reduces the expression and transactivation of the androgen receptor gene and reduces the level of insulin-like growth factor in the serum. In addition, they observed a decrease in the volume of the ovaries and the number of follicles in the antral phase.<sup>18</sup>

## Conclusion

Hormone therapy, metformin as well as the use of isotretinoin is indicated in patients with PCOS who suffer from acne unresponsive to local treatment. Additionally, hormonal treatment can be combined with topical antibiotics, benzoyl peroxide, azelaic acid, and even retinoids. Usually, at least 3 months is needed to see significant effects of the introduced therapy. Patients diagnosed with polycystic ovary syndrome should be made aware of the benefits of reducing excess body weight, a healthy and balanced diet and regular physical activity.

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