

What should be kept in mind when treating acne with oral contraceptives? Narrative review

Co należy mieć na uwadze, lecząc trądzik doustnymi środkami antykoncepcyjnymi? Przegląd narracyjny

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STRESZCZENIE

CO NALEŻY MIEĆ NA UWADZE, LECZĄC TRĄDZIK DOUSTNYMI ŚRODKAMI ANTYKONCEPCYJNYMI? PRZEGLĄD NARRACYJNY

Wprowadzenie. Trądzik pospolity to częsta dermatoza, w której kluczową rolę odgrywają czynniki hormonalne, zwłaszcza androgeny zwiększające produkcję sebum. To hormonalne podłoże sprawia, że terapie o działaniu antyandrogennym, takie jak tabletki antykoncepcyjne, stanowią logiczną i skuteczną strategię leczenia. Niniejszy przegląd ma na celu opisanie skuteczności i mechanizmów działania tabletek antykoncepcyjnych w leczeniu trądziku.

Cel pracy. Celem niniejszego przeglądu jest opisanie skuteczności i efektów stosowania tabletek antykoncepcyjnych w leczeniu trądziku, z uwzględnieniem trądziku jako zmiany wtórnej w przebiegu niżej wymienionych schorzeń.

Materiał i metody. Dokonano przeglądu literatury medycznej w dniu 19 października 2024 roku, korzystając z baz danych PubMed, Scopus oraz Google Scholar. Użyto słów kluczowych: „antykoncepcja hormonalna” (hormonal contraception) oraz „trądzik pospolity” (acne vulgaris). Ramy czasowe wyszukiwania obejmowały okres od 2017 roku do dnia przeprowadzenia analizy. Zidentyfikowano 15 artykułów w bazie Google Scholar, 12 w bazie PubMed oraz 26 w bazie Scopus.

Wyniki. Przegląd piśmiennictwa wskazuje, że tabletki antykoncepcyjne mogą być skuteczne w leczeniu trądziku pospolitego dzięki swoim właściwościom antyandrogennym. Przyjmuje się, że androgeny stymulują wzrost gruczołów łojowych i zwiększają produkcję sebum, przyczyniając się do powstawania trądziku. Tabletki antykoncepcyjne są również stosowane w leczeniu innych zaburzeń hormonalnych związanych z podwyższonym poziomem androgenów, takich jak hirsutyzm i zespół policystycznych jajników (PCOS).

Podsumowanie. Trądzik pospolity pozostaje ważnym problemem medycznym i społecznym. Dermatoza ta dotyka nie tylko osoby młode, ale także pacjentów endokrynologicznych lub osoby w trakcie stałego leczenia. Znajomość mechanizmu powstawania trądziku i roli hormonów w jego patogenezie pozwala na ustalenie odpowiedniego algorytmu leczenia.

Słowa kluczowe: antykoncepcja hormonalna, leczenie trądziku, trądzik pospolity, antyandrogeny

ABSTRACT

WHAT SHOULD BE KEPT IN MIND WHEN TREATING ACNE WITH ORAL CONTRACEPTIVES? NARRATIVE REVIEW

Introduction. Acne vulgaris is a common dermatosis where hormonal factors, particularly androgens that increase sebum production, play a key role. This hormonal basis makes therapies with anti-androgenic effects, such as Combined Oral Contraceptives (COCs), a logical and effective treatment strategy. This review will describe the effectiveness and mechanisms of COCs in managing acne.

Aim. The aim of this review is to describe the effectiveness and effects of COC use in the treatment of acne, taking into account acne as a secondary lesion in the course of the below-mentioned conditions.

Material and methods. The medical literature was reviewed on October 19, 2024 using the PubMed, Scopus and Google Scholar browsers using the keywords: hormonal contraception, acne vulgaris. The time frame for searching the sample was from 2017 to the current date of the search. 15 articles were identified in the Google Scholar database, 12 in the PubMed database and 26 in the Scopus database.

Results. COCs can be effective in treating acne vulgaris due to their antiandrogenic properties. Androgens are believed to stimulate the growth of sebaceous glands and increase sebum production, contributing to acne formation. COCs are also used to manage other endocrine disorders associated with elevated androgen levels, such as hirsutism and polycystic ovary syndrome.

Conclusions. Acne vulgaris continues to be an important medical and social problem. This dermatosis affects not only young people, but also endocrinological patients or patients receiving permanent treatment. Knowledge of the mechanism of its formation and the role of hormones in its pathogenesis may allow it to determine the appropriate treatment algorithm.

Key words: contraceptives, treating acne, acne vulgaris, antiandrogens

INTRODUCTION

Acne vulgaris as an inflammatory disease of the pilosebaceous unit of the skin affects about 9% of the world's population, occurs in 85% of people aged 12-24 and 50% of people aged 20-29 [1,2]. The presence of the adolescent acne was found in 27.9% boys and 20.8% of the girls, however the adult acne is found in at least 82.1% women [3]. Although it is a common dermatosis, it negatively affects the patient's quality of life and body image, and it is also associated with an increased incidence of anxiety and depression [4]. For this reason, the thorough understanding of the etiology of acne vulgaris is extremely important.

Four pathogenic processes are responsible for the formation of acne lesions - keratosis of hair follicle openings leading to the formation of blackheads, excessive production of sebum stimulated by androgens, colonization of sebaceous gland openings by anaerobic bacteria *Propionibacterium acnes* and complex inflammatory mechanisms involving both innate and acquired immunity [5]. Genetic factors and diet are important in the pathogenesis of acne and its course. Consumption of chocolate, milk and foods with a high glycemic index has been shown to exacerbate the course of acne, while a diet rich in omega-3 fatty acids and consumption of probiotics improves the results of acne vulgaris treatment [6].

It is impossible to ignore the role of hormones in the formation and course of acne lesions, because androgens increase the size of the sebaceous glands and increase the secretion of sebum, thus aggravating the course of acne. In particular, the strong androgen 5 α -dihydrotestosterone plays a role in the pathogenesis of acne, acting through the nuclear androgen receptor with cofactors such as peroxisome proliferator-activated receptor (PPAR) ligands and leukotrienes B₄ [7]. Estrogens, on the other hand, exhibit a local anti-androgenic effect, as well as inhibit androgen production and influence gene regulation [8]. Estrogens have been shown to have anti-inflammatory effects through complex interactions with insulin-like growth factor 1 (IGF-1) [9].

An increase in the incidence of acne has been observed in diseases coexisting with hyperandrogenism, such as polycystic ovary syndrome (PCOS) [5,10]. In PCOS, the increased concentration of androgens results from their overproduction by the ovaries (androstenedione and testosterone) and the adrenal glands (dehydroepiandrosterone sulfate). Acne in the course of PCOS is characterized by a severe course, the presence of cystic lesions and resistance to treatment [11]. Studies show that the development of acne depends mainly on local concentrations

of androgens and the sensitivity of androgen receptors of the sebaceous glands to androgens, and the severity of the disease is not directly related to the increase in plasma androgen concentration [10].

Hormonal contraceptives

Hormonal contraceptives (HC) are a type of method or device (the intrauterine device) that is used to prevent pregnancy, although they can sometimes also be used to treat acne. There are different types of contraceptives on the market, including the pill, implants, hormonal intrauterine device (IUD), and many others. There are two types of HC pills: combination pills that contain estrogen and progestin, and single-component pills that contain only progestin [12]. When treating acne, combined birth control pills are chosen because they reduce androgen levels, thus affecting reduced sebum production [13]. They are used as an alternative treatment for acne when other methods fail. Treatment with combined oral contraceptives (COCs) leads to a significant reduction in the number of all lesions (papules, pustules, nodules, cysts) that result in acne [3,14]. Acne after discontinuation of contraception has a predisposition to recurrence, due to the increase in the level of androgens in the body [15].

AIM

The purpose of this article is to review scientific publications from 2017-2022, which demonstrated the effectiveness, effects and side effects of COC use in the treatment of acne, taking into account acne as a secondary lesion in the course of endocrine-related diseases or in the course of treatment with other drugs, e.g. in transgender people.

METHODS

The medical literature was reviewed on October 19, 2024 using the PubMed, Scopus and Google Scholar browsers using the keywords: hormonal contraception, acne vulgaris. The time frame for searching the sample was from 2017 to the current date of the search. There were 15 articles identified in the Google Scholar database, 12 in the PubMed database and 26 in the Scopus database. The results of the search were examined for relevant articles using defined criteria. Articles were classified as relevant if they contained information on acne and/or hormonal contraception. Because of the limited number of studies available, clinical studies and review articles were included if they contained information relevant to the review topic. After exclusion of outdated, non-essential articles, duplicates, and papers in a language other than English,

a total of 13 papers were identified and used for the reported narrative review.

Isotretinoin and contraception

Isotretinoin is a highly effective retinoid in the treatment of acne vulgaris, the use of which can lead to remission of the disease. It is the only anti-acne drug with long-term disease-modifying potential [16]. However, it should be remembered that isotretinoin, as a strong teratogen, leads to retinoid embryopathy as a result of systemic exposure of the fetus [2,16-20]. Other side effects include hypertriglyceridemia, depressive disorders, emotional lability, anxiety disorders and alopecia [21].

Due to the teratogenic effect of isotretinoin, effective contraception is essential during its use in women of childbearing potential. The Food and Drug Administration requires women treated with isotretinoin to be enrolled in the iPLEDGE pregnancy prevention program, which requires women of childbearing age to use two methods of contraception simultaneously (primary and secondary) or to commit to sexual abstinence during the course of therapy [16]. It is estimated that about 20% of people who reported abstinence under the iPLEDGE program are sexually active during isotretinoin therapy [22]. Due to the multitude forms of contraception, the effectiveness of its various forms was tested during the first 6 months of its use, where it was proved that the contraceptive options from level 2 in combination with barrier methods give effectiveness at the level of over 99% [16].

In a retrospective analysis by Albogani et al. on the basis of insurance claims data from 2006-2015 in the United States, contraceptive use during acne treatment was <50% in women using isotretinoin and <30% in other study groups, and in women treated with isotretinoin and of those using contraception, only 1% of them chose long-acting forms of contraception [18]. This means that nearly 50% of women using isotretinoin have a significant risk of fetal exposure to retinoids. The table shows pregnancy outcomes among conceptions during exposure to acne treatments (Tab. 1).

■ Tab. 1. Pregnancy outcomes among conceptions during acne treatment

	iPLEDGE	Label Warning	Unknown Risk
Abortion	40%	25%	20%
Live Birth	40%	60%	65%
Pregnancy	12%	10%	10%
Ectopic Pregnancy	7%	3%	3%
Stillbirth	1%	2%	2%

Despite the implementation of the iPLEDGE program, fetal exposure to isotretinoin still occurs. Giving patients the opportunity to simplify iPLEDGE requirements by using a single method of highly effective contraception, such as implants or the IUD, can help to reduce the burden of multiple forms of contraception and frequent pregnancy diagnostics, but both strict contraceptive guidelines and logistical difficulties of complying with iPLEDGE program are barriers to the application of

appropriate acne treatment [21]. Focusing on the choice of effective contraceptives and their consistent use, even with limited sexual activity, is important during the counseling of patients initiating teratogenic drugs [18].

The use of hormonal contraception in acne

Hormonal treatment for acne is being used as an alternative method for women [3]. Hormonal anti-androgens in combination with systemic antibiotic and topicals or hormonal anti-androgens in combination with a topical treatment can be considered for females as the alternative treatment in severe papulopustular/moderate nodular acne and severe nodular/conglobate acne [23]. Moreover, oral spironolactone at the dose of 50-200mg can be also used off-label for the treatment of adult acne [23]. However, hormonal anti-androgens are not recommended in case of comedonal acne and mild to moderate papulopustular acne [24].

Male contraception, in addition to the use of condoms and vasectomy, also includes the use of hormonal contraception. However, as noted by the British Health Service, contraception for men has not changed much over the last fifty years. Condoms and a vasectomy are the most common available means. Men often turn to hormonal contraception to treat acne [24]. One of the causes of acne is an excess of androgens, which is why the use of drugs that lower their levels is the best method of treatment. Previous research on male contraception has focused mainly on the administration of androgens. They inhibit the action of male hormones, thereby treating acne. In addition, a decrease in the amount of semen after about 3-4 months was noted in the treatment. After discontinuation of treatment, the sperm count returns to its previous state. The low acceptability of weekly injections prompted the search for tablets [25].

In the years 2008-2012, in 10 research units was analysed the effect of contraception containing 1000 mg of testosterone undecanoate and 200 mg of norethisterone enanthate [26]. The failure rate was 1.57 per 100 users (95% CI, 0.59-4.14). The contraceptive mentioned above effectively and reversibly inhibited spermatogenesis in 95% of the participants.

The study by Abbe et al. analysed the side effects associated with the five most common female hormonal methods of contraception between 2006 and 2010: the combined oral contraceptive (COC), the levonorgestrel-releasing intrauterine device, progesterone injections, the transdermal patch and the vaginal ring. Contraceptive-related adverse events were analyzed in both genders. Mood swings were the most frequently mentioned. In women, it is a worse mood or its fluctuations. In men, however, hostility, aggression or depression. In male patients, side effects in the form of mood changes occurred significantly more often than in female patients.

Men participating in the study reported acne significantly more often than women. This fact seems logical, since estrogen-containing birth control pills reduce acne. Therefore, they are recommended for treatment. Acne is a side effect of androgens. 1% to 8% of study participants (depending on the amount) who used 1% testosterone gel

(AndroGel) developed acne as a side effect of the treatment [26].

The above-mentioned studies emphasise that male hormonal contraception plays an important role in the treatment of acne. However, despite the positive effects, this treatment is still moderately available and not used very often. The reason for this may be e.g. the fact that men more often than women give up contraceptive therapy [27]. This may be the cause of choosing a different type of therapy in men struggling with this condition.

Among the examined male patients, it was shown that men reach for hormonal contraception when their partner cannot use similar drugs for medical reasons [28].

Another study by Abbe et al. showed a significant need for contraception in men. This analysis showed that the potential side effects of the subcutaneous injection method are less than the benefits, and in the light of current research, it is a new promising method. Modern research suggests that the combination of androgen and progestin to improve tolerance may become an effective long-acting male contraceptive [29].

Limited research has examined how hormonal long-acting reversible contraception (LARC) affects acne in adolescents and young adults. Among those who received progestin-only LARC, 28.5% reported a worsening of acne [30]. Moreover, data reveal that the occurrence of acne among LNG-IUD users varies, particularly showing a higher prevalence in younger women. Research indicates variability in acne incidence among LNG-IUD users, with younger women experiencing it more frequently [31].

The use of hormonal contraception in the treatment of acne in the course of polycystic ovary syndrome

Polycystic ovary syndrome (PCOs) is a disease of the endocrine gland that affects approximately 5–18% of women [10,32]. PCOS is associated with high levels of adrenal hormones and ovarian androgen hormones, and abnormal secretion of gonadotropins. The skin manifestation of PCOS is acne and occurs in about 85% of people aged 12–24. It is mainly located on the face, 50% on the neck, chest and upper back. One of the causes of acne is excessive secretion of androgens. The drugs of first choice for treating this type of skin lesions in people with PCOS are COCs. They are used both during monotherapy and as an addition to local therapy. The most commonly used COCs are desogestrel/ethinylestradiol, drospirenone/ethinylestradiol, cyproterone acetate/ethinylestradiol [33].

In people with PCOS, cyprothreone acetate/ethinylestradiol should be avoided as the drug of first choice when treating acne, as there may be a risk of venous thromboembolism.

The most effective androgenic agent is spironolactone. Studies conducted by the Department of Clinical Pharmacy and Therapeutics in Amman-Jordan showed that spironolactone administered at the dose of 50 mg twice daily from the 5th to 25th day of the female cycle in combination with triphasic oral contraceptive pills for a period of 9 months improved the condition of patients with acne by 50% [34].

Isotretinoin is used for patients who cannot use COCs and is also used for patients with severe cystic acne. During the treatment of patients with PCOS, vitamin D supplementation should be considered due to its ability to increase insulin sensitivity and stabilize hormonal balance: androgens, adrenal hormones, gonadotropins [35].

The use of hormonal contraception in the treatment of acne in transgender people

Acne is one of the most common side effects of exogenous testosterone therapy in transgender men, who take masculinizing hormone therapy. Acne in these patients is most often located on the face, back and chest. This secondary change may occur up to 2 years after the start of testosterone therapy with a peak at 6 months after the start of treatment [36,37].

Feminising hormone therapy, which involves estrogen or spironolactone may, in turn, improve acne in trans women due to a negative feedback mechanism in gonadotropin release and/or modulation of genes that are responsible for sebum production. [38]. Contraception should be initiated when oral antibiotics and/or oral isotretinoin are administered to reduce the severity of acne lesions. Transgender men rarely decide to use COCs for reasons other than contraception due to their feminising effect or the risk of spontaneous bleeding [19,39]. Therefore, treatment with this method should be implemented when the maximum masculinising effect of testosterone therapy is achieved, i.e. within about 2 years from the beginning of hormone therapy [39,40].

Safety of cyproterone acetate in combination with ethinylestradiol (CPA/EE) in the treatment of acne

Cyproterone acetate/ethinylestradiol (CPA/EE) is a synthetic derivative of progesterone with multidirectional action, i.e. gestagenic, antigonadotropic and antiandrogenic. CPA/EE was first introduced for medical use in 1973. Indications for use in men are excessive sexual excitability, in women it is hirsutism, androgenetic alopecia, acne, seborrhea. Since the introduction of the drug, many side effects have been reported in both sexes. According to men, the most frequently reported side effects were: gynecomastia, decreased libido and depressive moods. In case of women, respectively: thromboembolic events, shortness of breath, weight gain.

Despite the above-mentioned symptoms, the drug is still used. The reason for this is the benefit gained in the treatment of conditions such as hirsutism (excessive hair growth), acne and seborrhea. CPA is used to treat such conditions both in low doses as a birth control pill and alone in higher doses [41]. The contraceptive pill containing a low dose of CPA in combination with ethinylestradiol for the treatment of acne has been found to improve 75 to 90% of women [42]. It has also been shown that discontinuation of CPA causes a significant recurrence of symptoms in up to 70% of women [41,42].

In the study by Penning-van Beest et al. conducted in the years 2011–2017 in the Netherlands, Great Britain and Italy, the impact of undertaken interventions to reduce the

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■ Tab. 2. Summary of the literature used in the article

Authors, Title, Year of publication	Group of subjects	What was assessed/ Country of origin	Methods of assessment	Main result
Rajaa Daghash, Ayah Daghash, May Abu-Taha, The Clinical Practice of Acne Treatment in Polycystic Ovary Syndrome, 2021	-	Research showing range of options for treating acne in women with PCOS	-	COCs are considered as the therapy of first choice in the treatment of acne in PCOS. Spironolactone, oral antibiotics and metformin can be added as second choice drugs. The choice of treatment mainly depends on various factors
John S. Barbieri, Nandita Mitra, David J. Margolis, Cynthia C Harper, Arash Mostaghimi, and Katrina Abuabara, Influence of Contraception Class on Incidence and Severity of Acne Vulgaris, 2021	n=336 738 -no acne in previous years n=21 178 - acne in medical history	Evaluation of the association of different contraceptive methods on the incidence and severity of acne/USA	Retrospective cohort study	Oral contraceptives have a modest protective effect on acne onset and treatment efficacy of acne compared to other methods of contraceptives
M.K. Trivedi BS, BA K. Shinkai MD, PhD J.E. Murase MD, A Review of hormone-based therapies to treat adult acne vulgaris in women, 2017	n=236 total articles n=36 relevant studies	Overview of most the types of hormonal therapy that are available for the treatment of acne	Systematic search of the PubMed Database	Combined oral contraceptives and spironolactone as an adjuvant and monotherapy are safe and effective in the treatment of women with acne. It is also important to carry out preliminary tests before administering the medication
Bosanac, Suzana S Trivedi, Megha Clark, Ashley K, Progestins and acne vulgaris: a review, 2018	n=2147 having acne with different types of contraceptives	Research conducted to find if the usage of different types of contraception has impact on the acne/USA	Review	The causes and the effects of progestogens are difficult to determine and more research is needed in this area
Radi, R., Gold, S., Acosta, J.P. et al. Treating Acne in Transgender Persons Receiving Testosterone: A Practical Guide.	-	A practical guide for the treatment of testosterone-induced acne in transmen patients, USA.	Review of the literature	Multidisciplinary approach to acne care, involving mental health, reproductive health, gender-affirming hormone therapy and surgeries.
Eichenfield D.Z., Sprague J., Eichenfield L.F.; Management of Acne Vulgaris: A Review; 2021.	-	Evaluation of the effectiveness of acne vulgaris treatment methods according to the severity of the disease; USA	Review of the literature	First-line therapies are topical retinoids, benzoyl peroxide, azelaic acid, or combinations of topicals. For more severe types of the disease, oral antibiotics and hormonal therapies are most effective.
Tan A.U., Schlosser B.J., Paller A.S.; A review of diagnosis and treatment of acne in adult female patients; 2017.	-	Evaluation of the treatment options for adult female patients with acne; USA.	Review of the literature	Many treatment choices are available to treat adult female patients with acne. Treatment options should be tailored to the individual patient with considerations for the patient's preferences, tolerability of the medication, and psychosocial factors.
DeGrazia T.M., Rolader R., Thiboutot D.M., Yeung H.; Eligibility Criteria Related to Hormone Therapy in Acne Clinical Trials: A Systematic Review; 2021.	-	Assessment of the inclusion and exclusion criteria of acne clinical trials to identify potential barriers to the enrollment of patients receiving hormone therapy; USA.	A systematic review	Many trials on acne have included patients, who has been receiving stable hormone therapy, but there is lack of clearly reported data on the inclusion of those receiving hormone therapy.
Albogami Y., Sarayani A., Hincapie-Castillo J.M., Winterstein A.G.; Real-World Fetal Exposure to Acne Treatments in the United States: A Retrospective Analysis from 2006 to 2015; 2021.	The insurance claims data of > 100,000 acne treatment users between 2006 and 2015.	To quantify fetal exposure rates during the use of common acne treatments; USA.	A retrospective analysis.	Fetal exposure to acne treatments varied according to levels of teratogenicity, with reduced rates among users of isotretinoin and to a lesser extent doxycycline/minocycline. Adolescents had low pregnancy rates but less pronounced differences in fetal exposure across acne treatments.
Han J.J., Faletsky A., Barbieri J.S., Mostaghimi A.; New Acne Therapies and Updates on Use of Spironolactone and Isotretinoin: A Narrative Review; 2021.	-	To highlight new therapeutic developments and updates on the use of spironolactone and isotretinoin in acne; USA.	A literature review.	Significant improvements in acne treatments have been developed with the goals of improving efficacy and tolerability. Recent data supported reduced lab monitoring and warrant changes in guidelines for patients taking spironolactone and isotretinoin.
Penning-van Beest FJA, Bezemer ID, Smits E, García Rodríguez LA, Cea Soriano L, Lapi F, Simonetti M, Asimwe A, Herings RMC. Reduction in use of cyproterone/ethinylestradiol (Diane-35 and generics) after risk minimization measures in the Netherlands, UK and Italy.	-	Study of the effect of risk minimization measures for CPA/EE, contaminant of HC and indications.	Retrospective study	The initiation rate of CPA/EE decreased by 44%–91% between 2011 and 2017.
Bezemer ID, Smits E, Penning-van Beest FJA, Asimwe A, Herings RMC. Thrombotic risk minimization for Diane-35 and generics. Pharmacoepidemiol Drug Saf. Abbe C., Roxby A.C.; Assessing safety in hormonal male contraception: a critical appraisal of adverse events reported in a male contraceptive trial; 2020.	n= 7876 of new CPE/EE users in 2011 n=7562 of new CPE/EE users in 2012 n=1401 of new CPE/EE users in 2014	Evaluation of the risk of minimization on CPA/EE in the Netherlands.	Retrospective drug utilization study	Similar proportions of CPA/EE users examined with acne or with recent acne treatment before and after referral procedure. Strong overall reduction of CPA/EE in the Netherlands.
Abbe C., Roxby A.C.; Assessing safety in hormonal male contraception: a critical appraisal of adverse events reported in a male contraceptive trial; 2020.	Data on AEs associated with the five most commonly used female, reversible, and hormonal contraceptive methods from 2006-2010	Investigation of adverse events of male contraceptive options; USA.	The original study	Female hormonal methods of contraception generally have similar rates of AEs to those reported in a recent male hormonal contraceptive trial, and male patients who used these methods had lower rates of discontinuation due to AEs.

risk of side effects during the use of cyproterone/ethinyl estradiol (CPA/EE) was analyzed [43]. Moreover, simultaneous use of other hormonal contraceptives (HC) was reviewed [43].

A side effect of cyproterone acetate therapy is venous thromboembolism [44-46]. The relationship between the use of CPA/EE and the occurrence of the above-mentioned ailment has been proven in many clinical studies [44-48]. Therapy with cyproterone is popular among people struggling with acne. The percentage of patients diagnosed with this ailment and treated with CPA/EE was: 55% in 2011, 52% in 2012 and 47% in 2014 [47]. This shows a downward trend in the use of this substance.

In the Penning-van Beest study, the CPA/EE initiation rate decreased by 44%-91%. In summary, the study showed a downward trend in the use of cyproterone/ethinyl estradiol to reduce the risk of complications. No changes were observed in the concomitant use of other HCs [43].

A study conducted in the United Kingdom of Great Britain in 2013 analysed the indications for the use of CPA/EE. The study involved women who used this active substance in 2011-2014. Hyperandrogenism was diagnosed in 61% of new drug users in 2011, 62% in 2012 and 63% in 2014. Acne was reported in 51%, 54% and 55%, respectively. The majority of patients taking CPA/EE had previously diagnosed acne (76% (n=2091) in 2011, 79% (n=2296) in 2012 and 78% (n=1834) in 2014) [45]. In conclusion, the majority of women surveyed who treated acne with CPA/EE had a condition that was consistent with the approved indication for cyproterone/ethinylestradiol and had received acne treatment in the past according to the guidelines [45].

In study by Gourbil et al. [47] analysed the treatment of women in age between 15-49 who used CPA/EE due to acne and were hospitalized for thromboembolism, venous thrombosis, ischemic stroke and myocardial infarction in 30 hospitals in France.

Among the 2,966 identified patients, were 803 (27.1%) women, who used a hormonal contraceptive and 56 women, who used cyproterone acetate. A total of 452 of these patients experienced venous thromboembolic events (VTE) and in 351 occurred arterial thromboembolic events (ATE).

Significant risk factors for VTE were age ≥ 40 years and thrombophilia, while smoking and age ≥ 40 years were the main risk factors for the development of ATE.

The study showed insufficient control and reporting of the above-mentioned side effects during treatment with contraceptives and cyproterone acetate. The above-mentioned studies highlight the role of CPA/EE in the treatment of acne. Despite a slight decrease in use in recent years, it is still one of the most popular substances available on the market. It is extremely important to strengthen the knowledge of healthcare professionals about the risk factor for the occurrence of a thromboembolic episode when first prescribing and subsequent use of hormonal contraceptives containing the active substance cyproterone/ethinyl estradiol [49].

DISCUSSION

Despite the numerous available methods of treatment, acne vulgaris remains a prevalent dermatosis that affects individuals across all age groups. This chronic condition has a multifactorial etiology and can significantly impact a patient's emotional well-being and daily functioning in society [50,51].

Effective management of acne involves maintaining proper facial hygiene and a balanced diet. When these measures are insufficient, patients often turn to topical treatments, including antibiotics, retinoids, benzoyl peroxide, salicylic acid, or azelaic acid. If these options do not prove effective, the next step may involve systemic treatments such as retinoids, antibiotics, or oral combined hormonal contraceptives (COCs) [52,53].

COCs can be effective in treating acne vulgaris due to their antiandrogenic properties. Androgens are believed to stimulate the growth of sebaceous glands and increase sebum production, contributing to acne formation. COCs are also used to manage other endocrine disorders associated with elevated androgen levels, such as hirsutism and polycystic ovary syndrome (PCOS). These contraceptives can reduce both inflammatory and non-inflammatory acne by inhibiting luteinizing hormone and follicle-stimulating hormone, which lowers androgen production. This process decreases the activity of 5 α -reductase and blocks androgen receptors, ultimately reducing sebum secretion [54-56].

Given the broad application of COCs and their significant antiandrogenic role, their beneficial use in the treatment of acne vulgaris, often as secondary to various endocrine disorders, should be emphasized.

However, isotretinoin, a potent teratogen, poses risks of retinoid embryopathy with systemic fetal exposure. Nearly 50% of women on isotretinoin face substantial risks of fetal exposure. The iPLEDGE dual birth control program can be burdensome for patients, and despite its implementation, there remains a risk of fetal exposure to isotretinoin. Strict contraceptive guidelines may deter patients from adhering to treatment. Thus, careful selection of COCs is essential, as they can complement isotretinoin therapy effectively while minimizing side effects. The triphasic combination of ethinylestradiol (EE) and norgestimate (NGM) is particularly effective and user-friendly, making it a safe option for managing acne vulgaris, either alone or in combination with other treatments [57]. Ensuring effective contraception within the iPLEDGE program is crucial, even for those with limited sexual activity.

One primary cause of acne is an excess of androgens, making medications that lower androgen levels to the preferred treatment approach. While COCs can lead to side effects, particularly in men, such as aggression and mood swings, hormonal contraception remains vital for the treatment of acne vulgaris. However, due to a higher incidence of side effects in men, they may be more likely to discontinue the treatment when compared to women. Therefore, it is important for patients to be informed about the potential risks associated with COCs before initiating acne treatment.

Acne is also a common skin manifestation of PCOS, characterised by elevated plasma androgen levels. COCs are the preferred treatment for this type of acne, often used in combination with topical therapies like desogestrel/ethinylestradiol, drospirenone/ethinylestradiol, or cyproterone acetate/ethinylestradiol, with spironolactone being the most effective androgen-lowering agent. However, cyproterone acetate/ethinylestradiol should not be the first-line treatment due to the risk of venous thromboembolism. For PCOS patients, who cannot use COCs, isotretinoin may be an alternative.

The increased prevalence of acne is also a significant concern among male transgender patients. A study by Park et al. found that acne in these individuals was linked to serum testosterone levels exceeding 630 ng/dL. This underscores the necessity of assessing the benefits and risks of testosterone therapy before initiation [50]. Such assessments may help prevent trans men from needing COCs and mitigate potential feminizing effects. The use of COCs in male transgender patients can not only alleviate acne but also regulate fertility.

Cyproterone acetate/ethinylestradiol (CPA/EE) possesses gestagenic, antigonadotropic, and antiandrogenic properties, making it suitable for the treatment of acne, hirsutism, and seborrhea, albeit with various side effects. As a contraceptive in low doses, it is vital for healthcare providers to be aware of the thromboembolic risks associated with CPA/EE when they decide to prescribe these hormonal contraceptives. Additionally, it is important for healthcare providers to inform adolescents and young adults who are considering progestin-only LARC about the possibility of developing new acne or exacerbating existing acne [30].

Future studies should further investigate the effects of the LNG-IUD on acne in younger populations, employing robust study designs and taking into account participants' previous contraceptive use [31].

CONCLUSIONS

Acne vulgaris continues to be an important medical and social problem. This dermatosis affects not only young people, but also endocrinological patients or patients receiving permanent treatment. Knowledge of the mechanism of its formation and the role of hormones in its pathogenesis may allow it to determine the appropriate treatment algorithm.

COCs, in addition to their role in regulating fertility, can be used as a treatment for acne vulgaris. Thanks to the antiandrogenic mechanism, COC has found application in diseases associated with excess secretion of androgens. The use of COCs in the treatment of acne in endocrine patients thus improves the medical and cosmetic situation of the patient. COCs have a beneficial effect on acne when used with other forms of treatment in the absence of contraindications.

Further research should also be conducted on the use of COCs in the treatment of acne vulgaris in transmale patients, in whom this dermatosis is a common side effect of testosterone intake. More randomized trials in more people will allow to determine the potential adverse effects

of COCs in this group of patients. By understanding all the risks and benefits of COCs, dermatologists will be able to become experts in prescribing these drugs (Tab. 2).

Abbreviations:

HC - hormonal contraceptives

COCs - combined oral contraceptives

PCOS - polycystic ovary syndrome

CPA/EE - cyproterone acetate/ethinylestradiol

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