Expert Review of Clinical Pharmacology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierj20

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To cite this article: Edileia Bagatin, Marco Alexandre Dias da Rocha, Thais Helena Proençade Freitas & Caroline Sousa Costa (2021): Treatment challenges in adult female acne and future directions, Expert Review of Clinical Pharmacology, DOI: 10.1080/17512433.2021.1917376

To link to this article: https://doi.org/10.1080/17512433.2021.1917376

Accepted author version posted online: 07 May 2021.

Publisher: Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group

Journal: *Expert Review of Clinical Pharmacology*

DOI: 10.1080/17512433.2021.1917376

Treatment challenges in adult female acne and future directions

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Abstract

Introduction: Acne is a chronic, inflammatory, and immune mediated disease of the pilosebaceous unit, highly prevalent in adolescents. However, an increasing number of adults over 25 years old with facial acne, particularly women, have been observed. It is considered a different disease when compared to acne vulgaris. Face is the mainly involved area with inflammatory lesions and more sensitive skin, pointing out the need of a holistic approach.

Areas covered: We performed a comprehensive literature search on PubMed database, up to January 2021, regarding adult female acne. We synthetized data about: pathogenesis; differences compared to acne vulgaris; and treatment, with focus in the management challenges and perspectives.

Expert opinion: it is essential to value the negative impact on quality of life of adult female acne, independently of severity. The disease has prolonged evolution, and patient might be resilient once the improvement, regardless the treatment option, will just be noticeable after three months. Aggravating factors should be clearly discussed, such as the need of changing many habits, especially lesions manipulation. The therapeutic regimen includes make-up and tailored skin care (considering proneness to sensitivity), while anti-acne drugs should be chosen in accordance with desire to be pregnant, presence of pregnancy or breastfeeding.

Keywords: acne, adult, dermatosis, dermatology, female

Article highlights

- Adult female acne (AFA) has been demonstrating an increasing prevalence all over the world. It is an impacting disease for adult women, in their social, and professional life. Quality of life and patients' suffering should be valued.

- In accordance with the available data from more recent international observational study, lesions may have different distribution from adolescent acne in about 10 % of the cases, when there is predominance of mild to moderate inflammatory papules along mandibular and perioral areas of the face, in a "surgical mask-like" pattern. The presence of comedones and inflammatory papules, with a full-face involvement, is the most commonly clinical picture in AFA; and more than 50% of the affected women have truncal lesions.

- The pathogenesis is similar to acne vulgaris, but additional factors trigger and aggravate the disease chronic evolution, including high level of stress, sleep deprivation, picking habit, sensitive skin, pollution and diet. It seems that peripheral production of androgens, at sebaceous gland level, is responsible for its prolonged duration.

- It is important to treat AFA as early and as effectively as possible to avoid scars and psychological sequelae, taking into account the desire to be pregnant. The majority of patients have normal androgen levels in the serum. However, other signals of hyperandrogenism, mainly hirsutism and menstrual irregularities, should be addressed and hormonal investigation, as well as transvaginal ultrasound, requested

- There are many topical but only three different systemic drugs (antibiotics, antiandrogens and isotretinoin) available for treatment, usually in combination for inflammatory acne.

- For mild acne, topical treatment, always combined with adjuvant measures (gentle cleanser, moisturizer, sunscreen and dermocosmetics), may be sufficient for disease control, in prolonged period of time. For this reason, topical antibiotics should be avoided.

- Oral hormones represent the most important drugs for AFA, especially spironolactone and contraceptives, containing ethinyl estradiol and cyproterone acetate, drospirenone or chlormadinone as progestins

- Oral isotretinoin might be considered in severe and refractory disease as it is highly effective and safe for acne vulgaris. Off label low daily doses and variable duration of the treatment are the best approach, always associated with contraception methods, starting one month before the treatment up to one month after drug interruption This regimen promotes less mucocutaneous side effects, same efficacy and better adherence. Lab tests (lipid profile, transaminases, gama-GT, total blood count) should be requested at baseline and repeated after two months, as well as beta-HCG monthly. Serious adverse events, including depression and inflammatory bowel disease, are rare and individual and do not justify excessive warning and concern.

- Topical clascoterone (androgen blocker) and new anti-inflammatory substances, as well as new use of oral nonsteroidal anti-androgen, such as bicalutamide are interesting perspectives for AFA control.

1. Introduction

Acne of the adult female (AFA) has been observed in the past 30 years in opposite to acne juvenile that is recognized for centuries. It is well known that acne vulgaris is a chronic inflammatory and immune-mediated disease of the pilosebaceous unit with non-inflammatory (comedones) and inflammatory (papules, pustules, nodules) lesions compounding the clinical picture. Regarding the severity, acne may be mild, moderate or severe, with possibility of spontaneous resolution, but with risk of scars and post-inflammatory hyperpigmentation. Lesions are localized in the seborrheic areas on face and trunk. There is some controversy regarding the distribution of lesions in adult female acne (AFA), i.e., similar to acne vulgaris or predominantly in lower one-third of face. In respect to age, it is considered when occurs in patients over 25 years old and there are differences with regard to therapeutic decisions in women ages 25 to 44 from those over 45 years, in the perimenopause [1].

The Global Burden of Disease Study [2] analysed the most prevalent diseases in the world population and revealed a global distribution of acne with a rate of 9.38%. At that time, it was the 8th most prevalent disease, especially among male adolescents and female adults. A further revision of those data identified an increase of 5.1% in the global prevalence of acne, from 2006 to 2016 [3].

In the last 30 years researchers have been observed a crescent number of adults over 25 years old with facial acne, particularly women [4]. One of the first epidemiological studies about this condition in France demonstrated a 41% prevalence of acne in women between 25 to 40 years old [5]. Many authors have been discussing this phenomenon, as well as the decrease of acne with aging, although it can be present in women at menopause period [4-8].

A question had been raised: what is the meaning of this elevated prevalence, in adult women, in the last decades? A major search for medical care related to increasing concern about beauty or perfect skin or it represents a real higher incidence? About the second hypothesis, which are the causes? In 1999, a study pointed out that adult women with acne reported the disease also in relatives after adolescence [9]. The genetic predisposition is involved. In addition, there is an increasing discussion about many other triggering and aggravating factors [10]. One study considered that in the modern life style the women have been accumulating many activities and socioeconomic pressures, leading to high level of stress, tiredness and sleep deprivation [11]. The

occidental diet with high glycaemic level, skimmed cow's milk and derivatives ingestion and oral supplements containing whey proteins and leucine 1 influence lipogenesis pathways [by a decrease in expression of the forkhead fox O1 (FoxO1) and an increase of mammalian or mechanistic target of rapamycin complex (mTORC-1) transcription factors], enhance sebum production and can trigger or worsen adult female acne (AFA) [12-14]. Other triggering and aggravating factors from the environment, known as exposome, includes pollution, smoking, cannabis consumption, excessive sun exposure, occupation and excessive use of cosmetics [15-20].

Hormonal alterations represented by high levels of circulating androgens, usually caused by polycystic ovarian syndrome (PCOS), may cause acne in addition to hirsutism and menstrual irregularities [21-26]. The use of oral androgenic progestin such as levonorgestrel also present in some intrauterine devices or etonogestrel in subcutaneous implants may be worsening factors for acne in susceptible women [27-29].

Some medications, like vitamin B, corticosteroids, isoniazid, cyclosporine and anti-cancer targeted therapies, particularly Human Epidermal Growth Factor Receptor inhibitors (Cetuximab), with incidence of 50-85%, may cause inflammatory acneiform eruptions that may be differentiated from AFA [30].

Acne in adult women is classified as: persistent, when starting in adolescence; late-onset, less common, if it occurs after 25 years old; and recurrent, when developing many years after puberty. The last one is usually related to the interruption of long-term COCs that were effective for acne control. Currently, AFA is considered a different disease when compared to acne vulgaris [8,31,32]. Table 1 shows some factors that relate specifically to AFA pathogenesis [33-35]. However, the main pathogenic factors are similar: quantitative and qualitative alterations of sebaceous secretion, follicular hyperkeratinization, proliferation of a specific strain of *Cutibacterium acnes* that activates the Toll-like receptor (TLR) from innate immunity, resulting in inflammation and epidermal barrier damage [6,36-39]. The inflammation, even subclinical, is considered the key process and responsible for its chronic evolution [37]. Recent findings about the interaction between the host response and microbiome, as well as the less diversity of skin and gut microbiome provide progress into understanding the biology of acne vulgaris [40].

Which are the differences between acne vulgaris and AFA? It is assumed that AFA characterizes by more pronounced stress and prolonged duration, as well as the clinical

presentation has some particular aspects such as: predominance of facial mild or moderate involvement with inflammatory lesions in mandibular area, mentum and neck. In a second form, named retentional, comedones and microcysts are present in the whole face [8, 31,32]. Table 2 summarizes all aspects that distinguish AFA from adolescent acne [33-35].

AFA causes negative impact on quality of life with professional, social, psychological and psychiatric consequences. Therefore, an earlier and holistic management is mandatory [33,41].

This review represents a guide for an appropriated diagnosis, identification of possible triggers, aggravating factors and therapeutic challenges for choosing the best topical and/or systemic drugs, as well adjuvant measures and procedures.

2. Method:

We searched PubMed for systematic reviews, clinical trials and observational studies, using the terms acne, adult, female, women and treatment, up to February 2021. After the selection of the studies addressing critically themes on adult female acne, especially pathogenesis, clinical presentation, quality of life, topical and systemic treatment, focusing hormones, adjuvant measures and new treatments, we reviewed and summarized data from more recent evidence.

3. Quality of life

A systematic review including 35 studies showed a variable prevalence of acne around the world, ranging from 35 to 100%. The authors also analysed additional influencing factors related to its presence and severity. They concluded that the most relevant were familial history and Body Mass index (BMI). However, they also pointed out the possible role of diet, smoking, stress, quality and sleep time [42].

A review published by Chinese researchers selected 80 studies and presented a proposal for a better understanding of influencing factors in acne evolution [18]:

1. Individual socio-economic and biologic: demographic (gender, age, economic level); physiological (genetic predisposition, obesity, menstrual cycle); life style (diet, smoking, sleep) and psychological
2. Natural environment: sun, pollution
3. Social environment: media and social network (internet-addiction)
4. Big cities environment: population density, stress, sedentary lifestyle, pollution, fast food, few green places, etc

The social and psychological repercussion of acne have been well described and associated with negative impact in quality of life (Qol), as well as the presence of psychiatric comorbidities. The high risk of depression and anxiety is very well documented [43]. There is an increasing recognition that just objective clinical measures, like imprecise lesion counting, may be inadequate in assessing the overall impact and effect of acne. This statement has led to the development of disease-specific psychometric instruments to be used in acne clinical trials, since 1989, including: Acne Disability Index (ADI) [44], Cardiff Acne Disability Index (CADI) [45], Assessment of the Psychological and Social Effects of Acne (APSEA) [46], Acne Quality of Life Scale (AQOL) [47], Acne Quality of Life (Acne-QoL) [48-50] and its shorter version – Acne-Q4 [51]. The latter has demonstrated to be reliable, valid, responsive and useful in routine clinical practice.

A useful review about Qol instruments that have been used for acne, describing their validation, purposes, limitations and recommendations was published by the European Academy of Dermatology and Venereology Task Forces on Quality of Life [52].

Recent studies evaluated the impact of different acne forms, regardless age, ethnicity, and severity and confirmed the negative impact in Qol, which is higher in AFA [53-56]. The impairment may not be directly related to acne severity; in adult women, social and psychological distress is also higher than in male patients, and even mild clinical presentations may cause significant impact [6,33,57].

A Brazilian study demonstrated the negative impact on QoL, by using the AcneQol questionnaire, in 38 adult and normoandrogenic women with acne, even mild or moderate, as well as the improvement after just topical (azelaic acid) or systemic (oral contraceptive) treatment [58].

Insomnia, poor sleep quality and sleep interruptions related to urban noises, artificial lights, excessive routine worries, stress and modern life style are worsening factors in different diseases. The mechanism is the release of hormones, which affects the immune system. The sleep quality was investigated in two groups of women and a significant improvement was observed after the acne control, regardless the use of monotherapy with oral (contraceptive) versus topical (azelaic acid) drugs [59].

The mechanism of stress and poor quality of life in acne can be explained by the results of *in vitro* studies, which demonstrated the presence of various receptors for

neuromodulators produced by hypothalamus and hypophysis in the meibocytes membrane [60].

A recent research letter presented the results of a population national study representative of outpatient visits in the United States, regarding the screening for depressive symptoms in acne patients. They observed an extremely low rate, despite the known associations of acne with depression, and it was less common among dermatologists than non-dermatologists. This screening, by using a simple questionnaire such as the PHQ-2 (Patient Health Questionnaire-2) published by Mc Donald, in 2018, would be relevant for a subsequent appropriate referral to better address mental health problems among acne patients [61].

4. Topical treatment

Considering that AFA commonly presents mild or moderate lesions, the topical treatment may be able to control the disease. The most used, in monotherapy or combined products, are:

- Azelaic acid (15% gel or foam or 20% cream): anti-microbial, anti-inflammatory, depigmenting and mild comedolytic action; also useful for post-inflammatory hyperpigmentation.
- Retinoids, such as adapalene gel (0.1%, 0.3%), tretinoin (0.025%, 0.05% cream) and trifarotene (0.005%, just approved in USA): comedolytic and anti-inflammatory activity, as modulators of TLR.
- Benzoyl peroxide (BP) gel (2.5%, 4%, 5%, 8% and 10%): anti-microbial, anti-inflammatory and comedolytic properties.
- Antibiotics: the only still recommended is clindamycin, as it is less associated to bacterial resistance; the mechanism of action is the anti-inflammatory activity; however, it never should be used as monotherapy and combined to oral antibiotic. Considering that acne is not an infectious disease, new options targeting the skin microbiome are under development to replace the antibiotics [40].

Fixed combinations have been demonstrated by high certainty evidence, and are: BP (2.5%) plus adapalene (0.1%, the most used); and clindamycin (1% or 1.2%) plus tretinoin (0.025%) or adapalene (0.1%) or BP (5%) [62-65].

It is important to remember that these substances usually cause skin barrier damage, with consequent irritative dermatitis, characterized by erythema, dryness, scaling and pruritus. In AFA these side effects may be more severe as the patients have sensitive

skin. In order to control them, it is recommended to use topical agents in alternate days and add appropriated moisturizer and mild cleanser in a daily basis routine [66,67].

New compounds that have been recently approved or are in tests:

- Probiotic (*Enterococcus fecalis* and *Lactobacillus plantarum*) [68]
- Dapsone 5% (twice a day), 7.5% (once a day) gel [69]
- Tretinoin 0.05% lotion [70]
- BP 2.5% plus adapalene 0.3% [71,63]
- BP plus adapalene plus clyndamicin (IDP-126) [72,73]
- Ketoconazole 2% cream - anti-inflammatory and antiandrogenic actions [74]
- Minocycline 4% foam [75]
- Trifarotene cream 0.005%, the only topical retinoid that selectively targets RAR-gamma, which is the most common RAR found in the skin [76]
- Tazarotene 0.045% lotion [77]
- Clascoterone (cortexolone 17a-propionate) 1% cream (the first androgen receptor inhibitor) [78,79]

5. Systemic treatment:

5.1 Antibiotics

Oral antibiotics, mainly the tetracyclines, are recommended to treat moderate to severe inflammatory AFA by the inhibition of *C. acnes* proliferation, but mainly due to anti-inflammatory effects [80-82]. According to clinical guidelines and recommendations, with the aim of minimize the risk of emergent antibacterial resistance, their use should be limited to a maximum duration of 12 to 16 weeks; monotherapy or as maintenance treatment are contra-indicated [62,65,82-85]. Therefore, oral antibiotics plus topical agents (except antibiotics) combined or not to systemic anti-androgens hormones (COCs and spironolactone) are useful for AFA when there is no desire to get pregnant. This regimen may be used as a first-line therapy for moderate to severe papular-pustular acne and secondary option for treating nodular-cystic acne when there is contraindication for oral isotretinoin [62,82-83]. It is a well-accepted current physician's consensus, and also an evidence-based approach, to recommend the associated use of BP or BP plus adapalene when prescribing oral antibiotics [62,82,84,86]. This strategy allows either preventing treatment failure due to antibiotic-resistant acne, as rising of resistant *C. acnes* strains in the communities [85-87]. Topical retinoids and azelaic acid may also be the therapeutic choice in association

with oral antibiotics, especially if post-inflammatory hyperpigmentation is a concern [8]. Despite improvement in inflammatory lesions, post-therapy relapses are very frequent in AFA following one oral antibiotic course [88]. Serious adverse events are rare; the common events related to incorrect long-term treatment are gastrointestinal. Cutaneous eruptions, Candida vulvovaginitis and Gram-negative folliculitis of the trunk and face are less frequent [82].

Second-generation tetracyclines - minocycline, doxycycline and lymecycline - are nowadays the mainstay when opting for systemic antibiotic [80]. Macrolides represent a second-line for inflammatory acne due to increasing antimicrobial resistance [87,89]. Trimethoprim/sulfamethoxazole emerges as a third-line, when intolerance to tetracyclines or antibiotic-resistance occurs [82,87]. There is not a definitive and consistent body of evidence pointing out a greater efficacy of minocycline, doxycycline and lymecycline when compared to tetracycline, either a superiority of one of them against the other two [82,90]. Advantages in comparison to tetracycline are chiefly related to the better pharmacokinetics: feeding do not impair their intestinal absorption, so they can be administered during meals; better adherence is related to single daily dose regimen, as these drugs have a longer half-life [91].

Since 2019, sarecycline, labelled exclusively for acne, is available in United States to treat moderate to severe cases. It's still unknown if it has better efficacy and safety in comparison to other antibiotics from tetracycline class, as it has only been tested against placebo in randomized controlled trials [92,93]. However, this fourth-generation tetracycline shows a narrower-spectrum antibacterial activity, with consequent lower potential for raising intestinal dysbiosis, resulting in better tolerability and less gastrointestinal side effects [80]. The bacteriostatic effect is more targeted to *C. acnes*, with a decreased action on Gram-negative bacteria and bacterial resistance may also be reduced [94].

Prescription of any tetracycline for adult women who desire to become pregnant (or pregnant or breastfeeding) is contra-indicated as permanent dental coloration changes and impairment to foetal skeletal growth are possible adverse effects [65,91]. In the particular case of pregnancy or breastfeeding, there will be benefit from the prescription of erythromycin stearate or amoxicillin or cephalexin plus azelaic acid [65,82].

5.2 Isotretinoin

Isotretinoin, the single systemic intervention which can be used as monotherapy for acne, is the first-line drug for severe or moderate nodulocystic and alternative therapy

for severe or moderate papulopustular acne which relapses rapidly after first therapeutic approach, has tendency for scarring or compromises significantly QoL [82-84]. Isotretinoin improves more Qol than any other intervention [95].

Among all other systemic anti-acne therapies, isotretinoin is the only one that acts against all pathogenic mechanisms [96]. Isotretinoin normalise follicular hyperkeratinization by increasing the production of cytokeratin 7, 13 and 19, laminin B1 and interleukin 1 (IL-1); while promotes a decrease in release of cytokeratin 1, 10 and 14, filaggrin and metalloproteinases. The corneal lawyer changes favor cellular proliferation and shedding, with renewal within the follicular units and reduced comedogenesis [97]. There is local immune regulation, with decrease in inflammation, chiefly by down-regulation of gene expression related to TLR-2 and 4 and T helper cells [98,99]. Isotretinoin inactivates the androgen nuclear receptor in sebaceous glands and increases cell apoptosis, explaining the potent sebo-suppressive effect [100]. Finally, the microenvironment within the pilosebaceous follicle changes, regarding sebum quantity and composition, and becomes unfavourable to the hypercolonization by *C. acnes* [101,102].

Conventional dosage is 0.5 to 1.0 mg/kg daily, which must be taken with meals (exception for isotretinoin-lidose that also works under fasting), until a total dose of 120-150 mg/kg. Dermatologists around the globe have been following this paradigm since the drug release in market, almost forty years ago. However, more recent and high-quality evidence has failed to discover that a specific targeted total dose is needed to achieve acne clearance and a predictor of treatment duration [103-105]. There is nowadays an evidence-based tendency to considerate individual clinical aspects when deciding about daily dose and duration of therapy; instead of pursue a cumulative dose, it is better maintaining isotretinoin for one to two months after total resolution of the lesions [96,105,106]. Female gender and PCOS represents risk factors for needing more than one course of isotretinoin and slower response to the drug [107,108]. AFA with hormonal alterations very often are the group of patients who have acne relapse after one course of oral isotretinoin, which corresponds to around one third of those treated for the first time [83,109,105].

Less serious adverse effects are dose-dependent and very common. Dryness of skin and mucosae affects at least 90% of patients and occur as a consequence of the decreased cutaneous sebum production, thickness reduction of stratum corneum and impaired cutaneous barrier. Lip, skin, nasal mucosa and eyes moisturizers and

lubricants can prevent these side effects, if recommended to patients since the beginning of the course. Laboratory alterations - increase in lipid, liver and transaminases blood tests - are seen in 2% of patients [103,110,111]. Both, clinical and laboratory side effects quickly disappear with dose reduction or treatment interruption. Regarding laboratory abnormalities, stopping isotretinoin is only indicated if a minimum elevation upper than three times the normal value occurs in one of the monitoring tests [112,96]. There is high quality evidence supporting the safety of reduced laboratory testing during treatment period; blood cell count, lipid and hepatic panel should be performed at baseline and repeated with 1 to 2 months [113]. Additional screening is recommended only in case of concomitant health conditions that increase the risk of laboratory abnormalities (metabolic syndrome and use of hepatotoxic drugs) or if some change is detected in one of the two blood assessments [96, 112-114].

The most serious adverse event is teratogenicity, which is dose-independent. Therefore, monthly pregnancy blood tests and adequate adherence to efficacious contraception methods (intrauterine device or COCs combined with condoms) are required for adult women with potential childbearing. Women should avoid pregnancy during treatment with oral isotretinoin and up to one-month post-therapy; after this period, there is no more risk of teratogenicity [83,113,115]. Based on the best available evidence today, isotretinoin does not cause any change in female fertility and ovarian reserve [116,117]. Inflammatory bowel disease (IBD) was linked to oral isotretinoin, but recent systematic reviews and meta-analysis could not find any causal association [104,118,119]. This past and controversial association is now imputed to the fact that the majority of patients treated with isotretinoin have history of previous exposition to antibiotics and tetracyclines which may increase the risk of IBD, chiefly Crohn's disease [120,121]. Psychiatric serious adverse events (depression, psychosis and suicide) have also been reported in patients receiving oral isotretinoin, but analysis of data from the FDA database (from 1997 to 2017) suggested that frequency of complete suicide among these patients seems to be lower than rates verified in general population [122]. However, the currently best available evidence does not support any causal relationship between the drug and depression [104,123]. Instead of this, data from prospective controlled trials showed a greater improvement of depression symptoms and Qol in comparison to other anti-acne therapies [104,95]. Due to all this controversy, acne patients with personal or familiar history of depression should receive low daily

dose and close monitoring of changes in humour and behaviour when treated with oral isotretinoin [96].

Lower daily doses (0.1-0.5 mg/kg, up to 5 mg) for moderate acne, with a longer duration of therapy (up to 18 months) are a recent trend in isotretinoin prescription, despite being off-label. Clinical studies have shown reduced frequency of clinical and laboratory side effects, but efficacy and recurrence rates do not seem to be impaired in comparison with conventional dosage regimen [84,105,124,125]. The low daily dosage adds a peculiar benefit for the management of AFA, as there is increased frequency of mucocutaneous side effects among this specific group of patients, who more frequently presents sensitive skin [6]. Pulsed or intermittent and alternate days regimens should be avoided due to the lower efficacy, according to data from a recent Cochrane systematic review [104].

There is a current evidence-based recommendation, in patients taking isotretinoin, not to postpone less-invasive surgical and cosmetic dermatological procedures such as: medium and superficial peeling; microneedling; microdermabrasion; manual dermabrasion; fractional lasers; Q-switched laser and vascular lasers; micro-needled fractional radiofrequency; biopsies and superficial excisions [126-129]. Concerns about an increased risk of abnormal healing associated to isotretinoin, which were raised by old case reports, have not been corroborated by posterior clinical studies [130-136]. This new approach may facilitate either the management of post-inflammatory hyperpigmentation and acne scars as well as signs of photoaging in adult women, achieving a better overall skin appearance and improvement in Qol [83,33].

5.3 Hormonal treatment

The hormonal treatment aims to block or decrease the functioning of the sebaceous gland, interrupting the production of sebum [6].

It is important to highlight that this option is recommended not only for cases of acne associated with hyperandrogenic conditions, as PCOS, the most common cause of hyperandrogenism in women; but also, for normoandrogenic patients, who present excellent results [6].

In women at childbearing age, 50% of androgens are produced in peripheral tissues, including skin, especially in the sebocytes level. Dysfunctions in this system can be caused by increase in intracellular conversion to potent androgens, from hormonal precursors such as dehydroepiandrosterone sulfate (S-DHEA) or cholesterol; or by lower aromatase activity, or even greater sensitivity of androgen receptors [137,138].

Recently research, using advanced technology for laboratory dosages, proved that there is an increase in peripheral androgenic activity in these patients. The analysis revealed that the dosage of androsterone glucuronate (ADT-G), one of the androgen metabolites, was significantly elevated. Its quantification can be an excellent biomarker in patients with acne without other hyperandrogenic clinical manifestations [34].

5.3.1 Inhibitors of androgen synthesis

The most widely used are the COCs, with an estrogenic component, i.e., ethinyl estradiol (EE). Their actions are: blockage of the pulsatile secretion of gonadotrophins, decrease production of testosterone by the ovaries, increase production of sex hormone-binding globulin (SHBG), reduced free plasma testosterone and activation of estrogen receptors in the sebaceous gland with antagonizing androgenic effects [139-142]. Newer estrogens (such as 17-beta-estradiol) used in the combined pills appear to offer additional benefits to women's health, but apparently induce lower production of SHBG by the liver, leading to a lesser anti-androgenic effect [143].

From the 70s to the present, there was a gradual decrease in the doses of estrogen (20 or 35 μg) in the pills, which made them safer, but with less anti-acne action. There are progestins produced from 19-nortestosterone, such as levonorgestrel, with androgenic activity and others, such as drospirenone and chlormadinone which acts as anti-androgen. Thus, the choice of the pill must take into account the synergistic anti-acne effect of the associated components [144].

Progestin-only pills, known as ‘minipill’, long-term hormonal implants and intrauterine systems with levonorgestrel are not effective for treating acne and often lead to worsening [144-46].

Several studies have proven the effectiveness of COCs for acne, reducing inflammatory and non-inflammatory lesions by blocking the androgenic system and interrupting the disease evolution [145].

A meta-analysis has compared the effectiveness of COCs to oral antibiotics to treat acne. After a 6-month treatment, there was no difference in effectiveness; however, it should be considered that there is a worldwide effort to reduce the long-term use of systemic antibiotics to treat immune-inflammatory diseases such as acne [147].

A systematic review on the use of COCs to treat female acne showed that the combination of ethinyl estradiol with an anti-androgen progestin offers better results than any other option of COC [148].

Not all women can use COCs; a detailed medical history and blood pressure measurement are the first steps towards a safe choice. Its use increases the risk of thromboembolic events as well as causes a small increase in the relative risk of breast cancer [149].

The most common side effects are nausea, breast enlargement, headaches and weight gain. Concomitant use with antibiotics may reduce the contraceptive effect, as in the case of rifampicin and griseofulvin. Current studies have proven safety when tetracyclines are used, but if patients experience vomiting or diarrhoea, additional protection should be indicated [149,150].

5.3.2 Blockers of androgen receptor

5.3.2.1 Spironolactone

It is an aldosterone antagonist with anti-androgenic activity, blocking the androgen receptor and inhibiting androgen biosynthesis. The peak action is reached after 2 to 4 hours of oral intake, with half-life of 12 hours, and its active metabolic is canrenone. Administration with food positively influences the absorption of the drug [151,152]. As a potassium-sparing diuretic has several indications approved by regulatory agencies, but its use in the treatment of acne, since the 1980s, although frequent and growing, remains off-label, being based on low quality randomized controlled trials and case series [152].

The dose for acne varies from 50 to 100 mg daily, which may be divided into twice dosing, with a good safety profile, as the side effects are dose-dependent. At higher doses, menorrhagia or another menstrual dysfunction is common, which may resolve after 2 to 3 months of therapy [153]. If menstrual abnormalities do not improve, the recommended approach is to reduce spironolactone dose to 50 to 75 mg daily and add an COC or cycle the spironolactone, giving it for 21 consecutive days, followed by 7 days off [154].

Although the drug is a potassium saver, with theoretical risk for hyperkalaemia, recent studies, considering the mentioned doses, in young women, without hepatic and/or renal abnormalities and who is not using other drugs that increase potassium, do not need laboratory monitoring. The drugs most commonly associated with a higher risk of hyperkalaemia are angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, and other aldosterone inhibitors (eplerenone), as well as heparin and low molecular weight heparin, trimethoprim; nonsteroidal anti-inflammatory drugs such as indomethacin, and selective serotonin reuptake inhibitors [155].

In addition to menstrual irregularity, patients may experience dizziness, oedema, and breast pain, weakness, and headache, symptoms that tend to improve with continued use. Less than 1% of patients have complaints related to libido [156].

The FDA package insert warns that tumours were found in studies about chronic toxicity in rats. However, doses 25 to 250 times higher than the usual human dose, according to bodyweight, were administered. These doses resulted in benign adenomas of the thyroid and tests, malignant mammary tumours, and proliferative changes in the liver. The potential for spironolactone to induce oestrogen-dependent malignancies has been a long debate, but recent studies pointed out the drug safety even with a positive history. Individual cases should be discussed with the oncologist [154].

Spironolactone and its metabolites can cross the placental barrier. Studies demonstrated feminization of the male rat foetus during gestation, but limited reports in humans have not shown adverse pregnancy outcomes. The FDA labelled the drug as a pregnancy category C, because of the potential risk based on animal studies and the anti-androgenic properties. Therefore, it should be avoided in pregnant women and they should be advised of the potential risk to a male foetus [154]. The metabolite canrenone has been detected in the breast milk, but the use during breastfeeding is acceptable [157].

The effectiveness of spironolactone is well documented but varies individually. Complete suppression usually takes 3 to 12 months with a plateau after one year. It may be necessary to add either an adjunctive anti-androgen or an androgen inhibitor, but it is advisable to wait at least 3 months before start any association [154].

A retrospective study of 85 women treated with spironolactone, 50 to 100 mg daily, alone or associated with topical treatment, reported therapeutic success rates of 33% for complete response, 33% for important, 27% for partial improvement, and only 7% presented no result [158]. A study compared spironolactone versus oral antibiotic for acne and concluded that the rate of discontinuation of spironolactone was lower, the efficacy similar, suggesting it as the first line for AFA [159].

A retrospective study, including 110 patients, 92% treated with a dose of 100mg daily, showed 55% of complete improvement, with treatment duration from 4 to 17 months. This result was better than oral minocycline [156].

A recent retrospective study including 395 patients, with moderate acne, from Mayo Clinic, using an average dose of 100 mg daily, reported that 66% of patients had a complete resolution and response greater than 50% was observed in 85% of patients.

The average time for improvement was 3 months and the maximum response occurred after 5 months. Side effects were mild and rare. They highlighted that the spironolactone was effective and safe for treatment of AFA [160].

5.3.2.2 Cyproterone acetate

It is a progestin with anti-androgenic properties, no longer available in some countries, like the United States. Currently it is less used for the treatment of hyperandrogenism caused by PCOs. The main action on sebocytes is the blockage of the androgen receptor by competing with dihydrotestosterone (DHT), produced from free testosterone by the action of the enzyme, 5-alpha-reductase type 2. It also has strong progestin activity thereby suppressing gonadotropin secretion and testosterone production [161].

It can be prescribed in different ways, but in order to not cause menstrual irregularity the reverse sequential scheme is: 50 to 100 mg from 5th to 14th day of the menstrual cycle, associated with oestrogens from 5th to 24th day or smaller doses (10 to 25 mg), when administration should be prolonged (12 to 15 days instead of 10) to maintain the regular cycle [161].

High doses of oral cyproterone acetate have been associated with side effects, such as fatigue, galactorrhea, benign breast nodules, weight gain, anaemia and hepatotoxicity [161]. There is also a 2mg fixed presentation associated with 35 µg EE, similar in use to COCs.

Current European recommendations suggest caution when using doses above 3 mg/day of cyproterone acetate due to the risk of developing meningioma [162].

5.3.3 Associations:

It is well known the possibility of association between COCs with spironolactone for a synergic androgen blocking with superior results. Even when a contraceptive containing drospirenone, a derivative of spironolactone, is used, there is no increase in potassium level above the safety limits. As an additional advantage, there is a reduction in the risk of an unwanted pregnancy, avoiding teratogenicity [163]. Spironolactone associated to low daily dose of oral isotretinoin is an important alternative to antibiotics for AFA, when there is no risk of pregnancy [159,145].

Another interesting combination is the use of spironolactone and levonorgestrel intrauterine system, which often are the choice of the gynaecologists to treat some diseases. A significant reduction in the risk of androgenic side effects as acne, oiliness, and thinning hair is an advantage [164].

6. Adjuvant measures

Adult women presenting acne have special needs because the sensitive and dry skin prone to irritation, picking habit, presence of various degrees of photoaging and exposure to environmental and other aggravating factors. Non-prescription acne products may help to control mild forms and increase the tolerability and efficacy when combined with prescription drugs [165,166]. They are also good options during pregnancy and breastfeeding.

Skincare and dermocosmetics, including make-up, should be part of therapeutic regimen for all clinical forms and severity of AFA [167-170]. A recent guideline about non-prescription acne treatment and skincare for AFA included noncomedogenic and mild cleansers (pH 4 to 6), moisturizers and photoprotection [165]. Their role has become a topic of interest to physicians as they may improve adherence to treatment, reducing skin irritation, and improving patient outcomes [171-174]. The skin barrier damage in AFA is well known [8]. It is not clear if it is a characteristic of acne-prone skin or if the disease and the topical medications are the main causes. The repair of cutaneous barrier is also considered essential for the balance of skin microbiome. Daily use of noncomedogenic moisturizes and avoiding frequent skin exfoliation are relevant measures. The better-evaluated substances are [169]: keratolytic (salicylic acid, lipohydroxyacid, alpha-hydroxyacids, retinol, retinaldehyde); and anti-inflammatory (niacinamide; alfa-linoleic acid, zinc and antioxidants).

With regards to energy-based devices, blue or red light emitting diodes (LEDs) and photodynamic therapy has been recommended in expert's guidelines, and also analysed in randomised clinical trials, as alternative treatments for acne. However, there is still lack of a high-certainty body of evidence to support the use of these interventions [82,84,175].

7. Future Directions

There are two important new options for the treatment of acne, which will be useful, in particular, for AFA: clascoterone (topical androgen blocker) and new oral nonsteroidal anti-androgen.

7.1 Clascoterone

The cortexolone 17α-propionate is an ester derivative of cortexolone, part of a new class of medications, which work as androgenic blockers. Although the exact mechanism of action as topical treatment for acne is unknown, the drug is believed to compete with the androgen DHT for binding to androgen receptors in the sebaceous

gland and hair follicles, attenuating the signalling necessary for acne pathogenesis [78,79].

In August 2020, the cream 1% received its first approval in the USA for patients 12 years of age or older. Two studies for its approval showed reduction of inflammatory and non-inflammatory lesions superior to control group. When compared to other anti-androgens, clascoterone was four times more potent than progesterone, three times than flutamide, approximately two times more effective than finasteride, and approximately as active as cyproterone acetate [176].

In a small comparative study with placebo and 0.05% tretinoin, clascoterone 1% cream was more effective than tretinoin 0.05% cream in reducing total lesion count (mean improvement 65.7% vs 52.5%), inflammatory lesion count (67.3% vs 50.7%) and acne severity (68.4% vs 53.1%), despite not significantly. Its use was safe for men and women, but for the latter they were more important as, in addition to being effective, it showed excellent tolerability, with side effects similar to vehicle group but rapid onset of action [177,178]. Skin reaction on face and trunk such as erythema, scaling, dryness and minimal or mild pruritus occurred in 18.1% (110/607) patients [179]. It has been discussed, although no experience is available, the possible topical and systemic combinations with this new drug.

7.2 Nonsteroidal anti-androgens

Such as other classes of androgenic inhibitors, as finasteride and dutasteride, nonsteroidal anti-androgen drugs were launched to treat tumours or hormone-dependent prostatic dysfunctions. Based in the experience of their clinical use and the observation of the medication's safety, new indications have been proposed, also seeking the androgenic blockage, exactly as what happened with finasteride for androgenetic alopecia.

Few studies are available about bicalutamide, but the excellent safety profile, compared to flutamide, has been the background for its use in patients with hyperandrogenic manifestations caused by PCOS (acne, androgenic alopecia, and hirsutism). The results are very good, even when it is prescribed in low doses and for patients resistant to spironolactone. The researchers believe that these findings may be related to genetic variations in the androgen receptors. In addition, the adverse effects are mild and less frequent, with no menstrual dysfunction [180-182].

However, further randomized, controlled and comparative studies, providing data on effectiveness and safety are need.

New antimicrobials (diallyl disulfide oxide and nitric oxide) and anti-inflammatory (phytochemicals; small molecule inhibitors targeting sebaceous glands and enzymes; probiotics; ammonia-oxidizing bacterial strains, etc) are being studied and assessed in clinical trials [183].

8. Conclusions

AFA is a distinct disease in the "Acne spectrum". As adult women with acne usually are in pregnancy and breastfeeding age, limitations are imposed to treatment. It is frequent the need for contraception, which is an advantage if the women agree and there is no contraindication, as it also has beneficial effect for the disease control. As much as possible, systemic therapy is the choice, and anti-androgens, particularly spironolactone, are the first option in association with topical agents, such as azelaic acid, used twice a day. This is the best topical regimen. Other topical anti-acne drugs can cause irritative dermatitis, as adult women with inflammatory lesions have more sensitive skin and hyperseborrhoea is not always present.

Oral isotretinoin should be considered for moderate or severe acne to accelerate the improvement and can be associated to spironolactone.

As the disease has a prolonged evolution the maintenance treatment is recommended. It is mandatory to add skin care, including photoprotection and make-up in the management schedule. Attention to psychological, habits, life style, lesions manipulation, risk of scars and hyperpigmentation is also essential. Finally, a good patient- doctor relationship with empathy is the key for therapeutic success and positive impact in quality of life.

9. Expert opinion:

Considering literature review and author’s opinion, it is relevant to highlight the following key messages:

- It is essential to consider the negative impact on quality of life of AFA, independently of severity and the doctor should value patients’ suffering and demonstrate interest for her disease. Even when acne severity is mild, this harm might not be misjudged.
- Patients need to understand that the disease has prolonged evolution, and resilience is necessary once the improvement, regardless therapeutic option, will be noticeable after three months.

- Aggravating factors should be clearly discussed; the need of changing lifestyle and habits such as: lesions' manipulation, self-treatment, smoking, stress, and insomnia.
- Well-designed observational studies are still needed to well-elucidate clinical pictures of AFA: age groups between 25 and 45 years old and perimenopausal women; facial involvement, following the adolescent-pattern, or classical presentation with mild or moderate inflammatory lesions in the lower third of face.
- Therapeutic regimen, always including skin care and make-up, may be chosen according to desire to be pregnant or presence of pregnancy or breastfeeding.
- More data from well-designed randomised controlled trials involving exclusively AFA are still necessary to support spironolactone indication, especially regarding the best dosing regimen for acne clearance without side effects. Also, there is a lack of high-certainty evidence regarding the use of isotretinoin to manage AFA and the superiority of COC's containing anti-androgenic progestin when compared to other anti-acne therapies. Another clinical research gap is the true benefit of associated systemic therapies: efficacy and safety of spironolactone plus isotretinoin (important antibiotic-sparing approach for more severe AFA) and COCs plus spironolactone compared with isolated use of these drugs and oral antibiotics has not yet been analysed in randomised controlled trials.
- First therapeutic options are: gentle cleanser, light moisturizer (with niacinamide, ceramides) once a day, at night; tinted sunscreen in the morning and lunch time; 15% azelaic acid gel minutes before sunscreen in the morning and moisturizer at night; spironolactone associated or not to COCs and, in severe or refractory cases, already presenting scars, low daily dose of oral isotretinoin until complete clearance of lesions may be added, always associated with highly effective contraception method. For the retentional form, 0.05% tretinoin for three months is recommended, and if poor or no response, low daily dose of oral isotretinoin constitutes the best option. Topical antibiotics should be avoided, even when in combinations. Oral antibiotics are rarely indicated, as they are less effective for AFA if compared to adolescent acne and should be used at a maximum of three months, what is a very short time for this disease

that has prolonged evolution. In addition, many cycles of oral antibiotics may increase the risk of bacterial resistance.

- Finally, AFA is an increasing prevalent disease, affecting quality of life and should be specifically treated as early as possible to prevent psychological sequels and scarring. It also may be the first sign of hyperandrogenism, when associated to hirsutism, even mild, and menstrual irregularities. The early diagnose of this condition is fundamental to prevent the evolution to metabolic syndrome and its serious consequences.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

One reviewer has declared recieving research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Alvotech, Leo Pharma, BMS, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Ortho Dermatology, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Helsinn, Arena, Forte, Informa, UpToDate and National Psoriasis Foundation. They have also consulted for others through Guidepoint Global, Gerson Lehrman and other consulting organizations. They have also declared employment at www.DrScore.com. and Causa Research, a company dedicated to enhancing patients' adherence to treatment. Another reviewer has declared being involved in clinical research (FDA clinical trials) with many of the agents that are in this review. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

1. Zeichner JA, Baldwin HE, Cook-Bolden FE, et al. Emerging issues in adult female acne. J Clin Aesthet Dermatol. 2017;10(1):37-46.

****Authors pointed out that the distribution of lesions in AFA is similar to acne vulgaris and not predominantly in lower one-third of face, which is usually reported. They also consider that the disease may be different in women ages 25 to 44 from those over 45 years, in the perimenopause, with implications in the therapeutic regimen, and also stated that the adherence to treatment is higher in women than men.**

2. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012;380(9859):2163–2196.
3. Lynn DD, Umari T, Dunnick CA, Dellavalle RP. The epidemiology of acne vulgaris in late adolescence. Adolesc Health Med Ther. 2016;7:13-25.
4. Goulden V, Stables GI, Cunliffe WJ. Prevalence of facial acne in adults. J Am Acad Dermatol. 1999;41(4):577-580.
5. Poli F, Dréno B, Verschoore M. An epidemiological study of acne in female adults: results of a survey conducted in France. J Eur Acad Dermatol Venereol. 2001;15:541-545.
6. Rocha MA, Bagatin E. Adult-onset acne: prevalence, impact, and management challenges. Clin Cosmet Invest Dermatol. 2018;11:59-69.

****The increasing prevalence of persistent acne in adult women, the predominance of patients without endocrinopathy, i.e., normal levels of circulating androgens, the higher impact on quality of life compared to adolescents and the challenges for appropriated treatment were reviewed.**

7. Collier CN, Harper JC, Cafardi JA, et al. The prevalence of acne in adults 20 years and older. J Am Acad Dermatol. 2008;58(1):56-59.
8. Dréno B, Layton A, Zouboulis CC, et al. Adult female acne: a new paradigm. J Eur Acad Dermatol Venereol 2013;27(9):1063-1070.

****A review with focus on specific factors to be considered for the AFA treatment choice is presented. Authors highlighted the predisposition of adult skin to**

irritation, slow response to treatment, the usual good adherence, child-bearing age, and relevant psychosocial impact of the disease.

9. Goulden V, McGeown CH, Cunliffe WJ. The familial risk of adult acne: a comparison between first-degree relatives of affected and unaffected individuals. Br J Dermatol. 1999;141(2):297-300.
10. Dréno B, Thiboutot D, Layton AM, et al. Large-scale international study enhances understanding of an emerging acne population: adult females. J Eur Acad Dermatol Venereol. 2015; 29(6):1096-1106.

****This study presented an objective assessment of facial acne in adult women. Authors detected, in contrast to other observational studies, mixed lesions (inflammatory and non-inflammatory) in multiple facial areas and also in the trunk (48.4% of patients). The ones with mandibular acne were the minority and reported greater stress level, despite presenting mild disease. A study limitation was the inclusion of patients already on treatment, as well as in the initial consultation.**

11. Albuquerque RGR, Rocha MAD, Bagatin E, et al. Could adult female acne be associated with modern life? Arch Dermatol Res. 2014; 306(8):683-688.

****The study had established a connection between AFA and daily stress (insertion in the labour market together with duties of mother and wife), sleep deprivation and variation across the menstrual cycle, as well as the higher risk of anxiety and depression.**

12. Romanska-Gocka K, Wozniak M, Kaczmarek-Skamira E, Zegarska B. The possible role of diet in the pathogenesis of adult female acne. Postepy Dermatol Alergol 2016; 33(6):416-420.
13. Claudel JP, Auffret N, Leccia MT, et al. Acne and nutrition: hypotheses, myths and facts. J Eur Acad Dermatol Veneroel. 2018;32(10):1631-1637.
14. Penso L, Touvier M, Deschasaux M, et a. Association between adult acne and dietary behaviors. Findings from the NutriNet-Santé prospective cohort study. JAMA Dermatol. 2020; 156(8):854-862.

****The presence of acne in adults was associated to consumption of fatty and sugary products, sugary beverages and milk. Despite the adjust for confounding factors, the study limitations were the use of online self-questionnaire about presence or not of past and current acne and questions about dietary behaviour, which is extremely variable.**

15. Di Landro A, Cazzaniga S, Cusano F, et al. Adult female acne and associated risk factors: Results of a multicenter case-control study in Italy. J Am Acad Dermatol. 2016;75(6):1134-1141.e1.

***This is an Italian study, including 248 women over 25 years old with acne. It was observed association with the following risk factors: familial history, acne during adolescence, no previous pregnancies, hirsutism, office working, psychological distress and low weekly intake of fruits, vegetables and fresh fish**

16. Capitanio B, Sinagra JL, Picardo M. Acne and smoking. Dermatoendocrinol. 2009;1(3):129-135.

17. Yang YS, Lim HK, Hong KK, et al. Cigarette smoke-induced interleukin-1 alpha may be involved in the pathogenesis of adult acne. Ann Dermatol. 2014;26(1):11-16.

****By comparing non-smoking and smoking adult acne patients, it was demonstrated a higher level of IL-1 alpha and lipid peroxide in comedones, with no correlation with severity and distribution of lesions. The retentional type of AFA, with multiple comedones is observed in smoking women.**

18. Yang J, Tang H, Xu A, He L. A review of advancement on influencing factors of acne: an emphasis on environment characteristics. Front Public Health. 2020;8:450.

19. Dréno B, Bettoli V, Araviiskaia E, et al. The influence of the exposome on acne. J Eur Acad Dermatol Venereol. 2018;30:1-8.

20. Dréno B, Shourick J, Kerob D, et al. The role of the exposome in acne: results from an international patient survey. J Eur Acad Dermatol Venereol. 2020;34:1057-1064.

****This was an international study, using anonymized internet questionnaire, which compared 2826 acne patients and 3853 controls, 15 to 39 years, i.e., adolescents and adults, investigating exposome factors. It was demonstrated association of acne with sweets, alcohol, whey proteins, pollution, stress, exaggerated skincare, humid or hot climate and excessive sun exposure.**

21. Carmina E, Lobo RA. Evidence for increase androsterone metabolism in some normoandrogenic women with acne. J Clin Endocrinol Metab. 1993; 76(5):1111-1114.

22. Slayden SM, Moran C, Sams WM Jr, et al Hyperandrogenemia in patients presenting with acne. Fertil Steril. 2001;75(5):889-892.

23. Yarak S, Bagatin E, Hassun KM, et al. Hyperandrogenism and skin: polycystic ovary syndrome and insulin peripheral resistance. Brazilian Ann Dermatol. 2005;80(4):395-410.

24. Archer JS, Chang RJ. Hirsutism and acne in polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol. 2004;18(5):737-754.

25. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol. 2014;6:1-13.

26. Bansal P, Sardana K, Vats G, et al. A prospective study examining trigger factors and hormonal abnormalities in adult female acne. Indian Dermatol online 2020;11(4):544-550.

**** The study included just women from a hospital in north India. A wide range of hormones was tested, but just 17-hydroxyprogesterone, dehydroepiandrosterone sulphate and anti-Mullerian hormone presented alterations. The majority of these patients reported moderate to severe stress. Authors concluded that high levels of adrenal androgens should be associated to stress and sleep deprivation.**

27. Lortscher D, Admani S, Satur N, Eichenfield LF. Hormonal contraceptives and acne: a retrospective analysis of 2147 patients. J Drugs Dermatol. 2016;15(6):670-674.

28. Gezginc K, Balci O, Karatayli R, Colakoglu MC. Contraceptive efficacy and side effects of Implanon. Eur J Contracept Reprod Health Care. 2007; 12(4):362-365.

29. Bahamondes L, Brache V, Meirik O, et al. WHO Study Group on Contraceptive Implants for women. A 3-year multicentre randomized controlled trial of etonogestrel- and levonorgestrel-releasing contraceptive implants, with non-randomized matched copper-intrauterine device controls. Hum Reprod. 2015;30(11):2527-2538.

30. Ferreira MN, Ramseier JY, Leventhal JS. Dermatologic conditions in women receiving systemic cancer therapy. Int J Womens Dermatol. 2019;5(5):285–307.

31. Preneau S, Dréno B. Female acne - a different subtype of teenager acne? J Eur Acad Dermatol Venereol. 2012;26(3):277-282.

32. Khunger N, Kumar C. A clinico-epidemiological study of adult acne: is it different from adolescent acne? Indian J Dermatol Venereol Leprol. 2012;78(3): 335-341.

****This is an important study showing that adult acne predominates in women and its presentation is different from adolescent acne vulgaris. It is more**

inflammatory; the lesions are located in the cheeks and lower face and comedones are rare. Scarring are present in the majority of patients and stress is an important trigger and aggravating factor.

33. Dréno B, Bagatin E, Blume-Peytavi U, et al. Female type of adult acne: Physiological and psychological considerations and management. J Deusch Dermatol Ges. 2018:16(10):1185-1194.

****Authors highlighted that the psychological impact of acne in adult women is significant and underestimated; stress during professional and private life, anxiety and sleep quality, have a reciprocal relationship with disease susceptibility and severity. Therefore, the disease management should consider not just medical treatment, but also a holistic approach to the patient as a whole, individual lifestyle and the impact in quality of life.**

34. Rocha M, Cardozo KHM, Carvalho VM, Bagatin E. ADT-G as a promising biomarker for peripheral hyperandrogenism in adult female acne. Dermatoendocrinol. 2017;9(1):e1361571.

**** This unprecedented research developed a method for detection and quantification of androsterone glucuronate (ADT-G), an androgenic metabolite. Authors demonstrated that ADT-G was sensitive in detecting differences between control and acne groups and was reduced after systemic treatment of acne. Therefore, it could be used as a biomarker for the whole peripheral hyperandrogenism in adult female acne.**

35. Rocha MAD, Guadanhim LRS, Sanudo A, Bagatin E. Modulation of Toll Like Receptor-2 on sebaceous gland by the treatment of adult female acne. Dermatoendocrinol. 2017;9(1):e1361570.

36. Antiga E, Verdelli A, Bonciani D, et al. Acne: a new model of imune-mediated chronic inflammatory skin disease. G Ital Dermatol Venereol. 2015;150:247-254.

37. Rocha MA, Costa CS, Bagatin E. Acne vulgaris: an inflammatory disease even before the onset of clinical lesions. Inflamm Allergy Drug Targets. 2014;13(3):162-167.

38. Dréno B, Gollnick HPM, Kang S, et al. Understanding innate immunity and inflammation in acne: implications for management. J Eur Acad Dermatol Venereol. 2015;29:3-11.

39. Kim J. Review of the Innate Immune response in acne vulgaris: activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. Dermatology. 2005;211(3):193-198.
40. O'Neill AM, Gallo RL. Host-microbiome interactions and recent progress into understanding the biology of acne vulgaris. Microbiome. 2018;6:177.
41. Gü A, Colgecen E. Personality traits and common psychiatric conditions in adult patients with acne vulgaris. Ann Dermatol. 2015;27(1):48-52.
42. Heng AHS, Chew FT. Systematic review of the epidemiology of acne vulgaris. Sci Rep. 2020;10:5754.
43. Vallerand IA, Lewinson RT, Parsons LM, et al. Risk of depression among patients with acne in the U.K.: a population-based cohort study. Br J Dermatol. 2018;178(3):e194-e195.
44. Motley RJ, Findlay AY. How much disability is caused by acne? Clin Exp Dermatol. 1989;14:194-198.
45. Motley RJ, Finlay AY. Practical use of a disability index in the routine management of acne. Clin Exp Dermatol. 1992;17:1-3.
46. Layton AM, Seukeran D, Cunliffe WJ. Scarred for life? Dermatology. 1997;195(supp 1):15-21.
47. Gupta M, Johnson AM, Gupta AK. The development of an acne quality of life scale: reliability, validity, and relation to subjective acne severity in mild to moderate acne vulgaris. Acta Derm Venereol 1998; 78:451-456.
48. Girman CJ, Hartmaier S, Thiboutot D, et al. Evaluating health-related quality of life in patients with facial acne: development of a self-administered questionnaire for clinical trials. Qual Life Res 1996;5:481-490.
49. Martin AR, Lookingbill DP, Botek A, et al. Health-related quality of life among patients with facial acne – assessment of a new acne specific questionnaire. Clin Exp Dermatol. 2001;26:380-385.
50. Fehnel SE, McLeod LD, Brandman J, et al. Responsiveness of the acne-specific quality of life questionnaire (Acne- QoL) to treatment for acne vulgaris in placebo-controlled clinical trials. Qual Life Res 2002;11:809-816.
51. Tan J, Fung KY, Khan S. Condensation and validation of a 4-item index of the Acne-QoL. Quality of Life Research. 2006;15:1203-1210.

52. Chernyshov PV, Zouboulis CC, Tomas-Aragones L, et al. Quality of life measurement in acne. Position Paper of the European Academy of Dermatology and Venereology Task Forces on Quality of Life and Patient Oriented Outcomes and Acne, Rosacea and Hidradenitis Suppurativa J Eur Acad Dermatol Venereol 2018;32(2):194-208.

53. Gallitano SM, Berson DS. How acne bumps cause the blues: the influence of acne vulgaris on self-esteem. Int J Womens Dermatol. 2018;4(1):12–17.

54. Davern J, O'Donnell AT. Stigma predicts health-related quality of life impairment, psychological distress, and somatic symptoms in acne sufferers. PLoS One. 2018;13(9):e0205009.

55. Bondade S, Hosthota A, Basavaraju V. Stressful life events and psychiatric comorbidity in a case-control study. Asia Pac Psychiatry. 2019;11(1):e12340.

56. Oztekin C, Oztekin A. The association of depression, loneliness and internet addiction levels in patients with acne vulgaris. Biopsychosoc Med. 2020; 14: 17. doi: 10.1186/s13030-020-00190-y.

57. Richter C, Trojahn C, Hilmann K, et al. Sensitivity to change of the Dermatology Life Quality Index in adult females with facial acne vulgaris: a validation study. J Eur Acad Dermatol Venereol. 2017:169-174.

58. Rocha M, Sanudo A, Bagatin E. The effect on Acne Quality of Life of topical azelaic acid 15% gel versus a combined oral contraceptive in adult female acne: a randomized trial. Dermatoendocrinol. 2017;9(1):e1361572.

****This is a Brazilian study demonstrating at baseline a significant impact of acne on adult women quality of life. The topical azelaic acid 15% gel, as well as combined oral contraceptive, despite being monotherapy resulted in significant improvement in quality of life scores. Comparing the four domains of Acne-QoL, oral contraceptive promoted greater improvement in self-perception and acne symptoms.**

59. Albuquerque RG, Rocha MAD, Hirotsu C, et al. A randomized comparative trial of a combined oral contraceptive and azelaic acid to assess their effect on sleep quality in adult female acne patients. Arch Dermatol Res. 2015;307(10):905-915.

60. Clayton RW, Langan EA, Ansell DM, et al. Neuroendocrinology and neurobiology of sebaceous glands. Biol Rev Camb Philos Soc. 2020;95(3):592-624.

61. Taylor MT, Barbieri JS. Depression screening at visits for acne in the United States, 2005-2016. J Am Acad Dermatol. 2020;83(3)936-938.

62. Thiboutot DM, Dréno B, Abanmi A, et al. Practical management of acne for clinicians: An international consensus from the Global Alliance to Improve Outcomes in Acne. J Am Acad Dermatol. 2018;78(2 Suppl 1):S1-S23.e1.
63. Gold MH, Baldwin H, Lin T. Management of comedonal acne vulgaris with fixed□combination topical therapy. J Cosmet Dermatol. 2018;17(2):227-231.
64. Tan J, Bissonnette R, Gratton D, et al. The safety and efficacy of four different fixed combination regimens of adapalene 0.1%/benzoyl peroxide 2.5% gel for the treatment of acne vulgaris: results from a randomised controlled study. Eur J Dermatol. 2018;28(4):502-508.
65. Bagatin E, Florez-White M, Arias-Gomez MI, Kaminsky A. Algorithm for acne treatment - Iberian-Latin American Consensus. Brazilian Ann Dermatol. 2017;92:689-693.
66. Bershad S, Kranjac Singer G, Parente JE, et al. Successful treatment of acne vulgaris using a new method: results of a randomized vehicle-controlled trial of short-contact therapy with 0.1% tazarotene gel. Arch Dermatol. 2002;138:481-489.
67. Levin J. The relationship of proper skin cleansing to pathophysiology, clinical benefits, and the concomitant use of prescription topical therapies in patients with acne vulgaris. Dermatol Clin. 2016;34(2):133-145.
68. Kober MM, Bowe WP. The effects of probiotics on immune regulation, acne and photoaging. Int J Womens Dermatol. 2015;1(2):85-89.
69. Eichenfield LF, Lain T, Frankel EH, et al. Efficacy and safety of once-daily Dapsone gel, 7.5% for treatment of adolescents and adults with acne vulgaris: second of two identically designed, large, multicenter, randomized, vehicle-controlled trials. J Drugs Dermatol. 2016;15(8):962-969.
70. Tyring SK, Kircik LH, Pariser DM, et al. Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: assessment of efficacy and safety in patients aged 9 years and older. J Drugs Dermatol. 2018;17(10):1084-1091.
71. Kircik LH. Anti-inflammatory dose doxycycline plus adapalene 0.3% and benzoyl peroxide 2.5% gel for severe acne. J Drugs Dermatol. 2019;18(9):924-927.
72. ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; [cited 2020 Feb 14]. Available from: https://clinicaltrials.gov/ct2/show/NCT04214639.

73. ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; [cited 2020 Feb 14]. Available from: https://clinicaltrials.gov/ct2/show/NCT03653403

74. Chottawornsak N, Chongpison Y, Asawanonda P, Kumtornrut C. Topical 2% ketoconazole cream monotherapy significantly improves adult female acne: A double-blind, randomized placebo-controlled trial. J Dermatol. 2019;46(12):1184-1189.

75. Raoof TJ, Hooper D, Moore A, et al. Efficacy and safety of a novel topical minocycline foam for the treatment of moderate to severe acne vulgaris: A phase 3 study. J Am Acad Dermatol. 2020;82(4):832-837.

76. Blume-Peytavi U, Fowler J, Keme´ny L, et al. Longterm safety and efficacy of trifarotene 50 lg/g cream, a first-in-class RAR-c selective topical retinoid, in patients with moderate facial and truncal acne. J Eur Acad Dermatol Venereol. 2020;34(1):166-173.

77. Tanghetti EA, Werschler WP, Lain T, et al. Tazarotene 0.045% lotion for once-daily treatment of moderate-to-severe acne vulgaris: results from two phase 3 trials. J Drugs Dermatol. 2020;19(1):70-77.

78. Hebert A, Thiboutot D, Stein Gold L, et al. Efficacy and safety of topical clascoterone cream, 1%, for treatment in patients with facial acne: two phase 3 randomized clinical trials. JAMA Dermatol. 2020;156(6):621-30.

79. Barbieri JS. A new class of topical acne treatment addressing the hormonal pathogenesis of acne. JAMA Dermatol. 2020;156(6):619-20.

80. Armstrong AW, Hekmatjah J, Kircik LH. Oral Tetracyclines and Acne: A Systematic Review for Dermatologists. J Drugs Dermatol. 2020;19(11):s6-s13.

81. Eady AE, Cove JH, Layton AM. Is antibiotic resistance in cutaneous propionibacteria clinically relevant?: implications of resistance for acne patients and prescribers. Am J Clin Dermatol. 2003;4(12):813-831.

82. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74(5):945-73.e33. Erratum in: J Am Acad Dermatol. 2020;82(6):1576.

83. Bagatin E, Freitas THP, Rivitti-Machado MC, et al. Adult female acne: a guide to clinical practice. Brazilian Ann Dermatol. 2019;94(1):62-75.

****Adult female acne presents specific characteristics, multiple pathogenic and aggravating factors and the possibility of pregnancy. As its management is**

more complex, this guide provided recommendations for the best clinical practices and therapeutic decisions. The algorithm was divided in two situations: desire to be pregnant or presence of pregnancy or breastfeeding and without desire to be pregnant.

84. Nast A, Dréno B, Bettoli V, et al. European evidence-based (S3) guideline for the treatment of acne - update 2016 - short version. J Eur Acad Dermatol Venereol. 2016; 30(8):1261-1268.

85. Ozolins M, Eady EA, Avery AJ, et al. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. Lancet 2004;364: 2188–2195.

86. Tzellos T, Zampeli V, Makrantonaki E, Zouboulis CC. Treating acne with antibiotic-resistant bacterial colonization. Expert Opin Pharmacother. 2011;12(8):1233-47.

87. Bienenfeld A, Nagler AR, Orlow SJ. Oral antibacterial therapy for acne vulgaris: an evidence-based review. Am J Clin Dermatol. 2017;18(4):469-490.

88. Shaw JC, White LE. Persistent acne in adult women. Arch Dermatol. 2001; 137(9):1252–1253.

89. Sardana K, Mathachan SR, Gupta T. Antibiotic resistance in acne an emergent need to recognize resistance to azithromycin and restrict its unapproved use in acne vulgaris. J Eur Acad Dermatol Venereol. 2020 Dec 22. doi: 10.1111/jdv.17099.

90. Garner SE, Eady A, Bennett C, et al. Minocycline for acne vulgaris: efficacy and safety. Cochrane Database Syst Rev. 2012;2012(8):CD002086.

91. Ochsendorf F. Systemic antibiotic therapy of acne vulgaris. J Dtsch Dermatol Ges. 2010;8 Suppl 1:S31-46.

92. Leyden JJ, Sniukiene V, Berk DR, Kaoukhov A. efficacy and safety of sarecycline, a novel, once-daily, narrow spectrum antibiotic for the treatment of moderate to severe facial acne vulgaris: results of a phase 2, dose-ranging study. J Drugs Dermatol. 2018;17(3):333-338.

93. Moore A, Green LJ, Bruce S, et al. Once-daily oral sarecycline 1.5 mg/kg/day is effective for moderate to severe acne vulgaris: results from two identically designed, phase 3, randomized, double-blind clinical trials. J Drugs Dermatol. 2018;17(9):987-996.

94. Kircik LH. ARTICLE: A novel antibiotic just for acne. J Drugs Dermatol. 2020;19(11):s5.

95. Chernyshov PV, Tomas-Aragones L, Manolache L, et al. Which acne treatment has the best influence on health-related quality of life? Literature review by the European Academy of Dermatology and Venereology Task Force on Quality of Life and Patient Oriented Outcomes. J Eur Acad Dermatol Venereol. 2018;32(9):1410-1419.

96. Bagatin E, Costa CS. The use of isotretinoin for acne - an update on optimal dosing, surveillance, and adverse effects. Expert Rev Clin Pharmacol. 2020; 13(8):885-897.

**** This comprehensive review concludes that oral isotretinoin, after 40 years of usage, is highly effective, despite common, controllable, and reversible mucocutaneous side effects may occur. Serious adverse events are rare and represent individual reactions. Teratogenicity is the most severe, requiring rigorous control. There is consensus that no other therapeutic option, even topical agents combined to oral antibiotics, accomplishes same results. Recurrence after treatments other than isotretinoin is the rule, prolonging risk of scars, compromising skin appearance, and causing emotional distress. If there is no absolute contraindication, isotretinoin should be indicated for moderate to severe inflammatory acne. Regarding AFA, recent studies considered that low daily dose of oral isotretinoin combined with spironolactone is an alternative regimen to oral contraceptives and antibiotics.**

97. Törmä H. Regulation of keratin expression by retinoids. Dermatoendocrinol. 2011;3(3):136-140.

98. Chen W, Zhao S, Zhu W, et al. Retinoids as an immunity-modulator in Dermatology disorders. Arch Immunol Ther Exp (Warsz). 2019; 67:355–365.

99. Dispenza MC, Wolpert EB, Gilliland KL, et al. Systemic isotretinoin therapy normalizes exaggerated TLR-2 mediated innate immune responses in acne patients. J Invest Dermatol. 2012;132(9):2198–2205.

100. Melnik BC. Apoptosis may explain the pharmacological mode of action and adverse effects of isotretinoin, including teratogenicity. Acta Derm Venereol. 2017;97(2):173-181.

101. Ganceviciene R, Zouboulis CC. Isotretinoin: state of the art treatment for acne vulgaris. J Dtsch Dermatol Ges. 2010;8 Suppl 1:S47-59.

102. Mccoy WH 4th, Otchere E, Rosa BA, et al. Skin ecology during sebaceous drought-how skin microbes respond to isotretinoin. J Invest Dermatol. 2019;139(3):723-735.

103. Roche. Roacutan (isotretinoína) Produtos Roche Químicos e Farmacêuticos S.A. Available from: http://www.anvisa.gov. br/datavisa/fila bula/frmVisualizarBula.asp?pNuTransacao=14365632016&pIdAnexo=3212245 [accessed 15.01.21].

104. Costa CS, Bagatin E, Martimbianco ALC, et al. Oral isotretinoin for acne. Cochrane Database Syst Rev. 2018;11(11):CD009435. Tan J, Knezevic S, Boyal S, et al. Evaluation of evidence for acne remission with oral isotretinoin cumulative dosing of 120-150mg/kg. J Cutan Med Surg. 2016;20(1):13-20.

105. Tan J, Boyal S, Desai K, Knezevic S. Oral Isotretinoin: new developments relevant to clinical practice. Dermatol Clin. 2016;34:175-184.

106. Rademaker M. Making sense of the effects of the cumulative dose of isotretinoin in acne vulgaris. Int J Dermatol. 2016;

107. Layton A. The use of isotretinoin in acne. Dermatoendocrinol. 2009;1(3):162-169.

108. Fallah H, Rademaker M. Isotretinoin in the management of acne vulgaris: practical prescribing. Int J Dermatol. 2020 Aug 29. doi: 10.1111/ijd.15089.

109. Webster GF, Leyden JJ, Gross JA. Results of a phase 1152 III, double-blind, randomized, parallel-group, non-inferiority 1153 study evaluating the safety and efficacy of isotretinoin-Lidose 1154 in patients with severe recalcitrant nodular acne. J Drugs Dermatol. 2014;13:665-70.

110. Brito MF, Sant'Anna IP, Galindo JC, et al. Evaluation of clinical adverse effects and laboratory alterations in patients with acne vulgaris treated with oral isotretinoin. Brazilian Ann Dermatol. 2010;85(3):331–337.

111. Vallerand IA, Lewinson RT, Farris MS, et al. Efficacy and adverse events of oral isotretinoin for acne: a systematic review. Br J Dermatol. 2018;178(1):76–85.

112. Altman RS, Altman LJ, Altman JS. A proposed set of new guidelines for routine blood tests during isotretinoin therapy for acne vulgaris. Dermatology. 2002;204(3):232-235.

113. Lee YH, Scharnitz TP, Muscat J, et al. Laboratory monitoring during isotretinoin therapy for acne: a systematic review and meta-analysis. JAMA Dermatol. 2016;152(1):35-44. Erratum in: JAMA Dermatol. 2016;152(1):114.

114. Barth JH, Macdonald-Hull SP, Mark J, et al. Isotretinoin therapy for acne vulgaris: a re-evaluation of the need for measurements of plasma lipids and liver function tests. Br J Dermatol. 1993;129(6):704-707.

115. Nau H. Teratogenicity of isotretinoin revisited: species variation and the role of all-trans-retinoic acid. J Am Acad Dermatol. 2001;45:S183-187.

116. Oztürk S, Oztürk T, Ucak H, et al. Evaluation of ovarian reserve and function in female patients treated with oral isotretinoin for severe acne: an exploratory study. Cutan Ocul Toxicol. 2015;34(1):21–24.

117. Cinar SL, Kartal D, Aksoy H, et al. Long-term effect of systemic isotretinoin on female fertility. Cutan Ocular Toxicol. 2017;36 (2):132–134.

118. Etminan M, Bird ST, Delaney JA, et al. Isotretinoin and risk for inflammatory bowel disease: a nested 1250 case-control study and meta-analysis of published and unpublished data. JAMA Dermatol. 2013;149:216-220.

119. Lee SY, Jamal MM, Nguyen ET, et al. Does exposure to isotretinoin increase the risk for the development of inflammatory bowel disease? A meta-analysis. Eur J Gastroenterol Hepatol. 2016;28:210-216.

120. Margolis DJ, Fanelli M, Hoffstad O, Lewis JD. Potential association between the oral tetracycline class of antimicrobials used to treat acne and inflammatory bowel disease. Am J Gastroenterol. 2010;105(12):2610-2616.

121. Wright S, Strunk A, Garg A. Risk of new-onset inflammatory bowel disease among patients with acne vulgaris exposed to isotretinoin. J Am Acad Dermatol. 2021;84(1):41-45.

122. Singer S, Tkachenko E, Sharma P, et al. Psychiatric adverse events in patients taking isotretinoin as reported in a Food and Drug Administration database from 1997 to 2017. JAMA Dermatol. 2019;155(10):1162–1166.

123. Huang YC, Cheng YC. Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis. J Am Acad Dermatol. 2017;76:1068-1076.

124. Borghi A, Mantovani L, Minghetti S et al. Low-cumulative dose isotretinoin treatment in mild-to-moderate acne: efficacy in achieving stable remission. J Eur

Acad Dermatol Venereol. 2011;25(9):1094-1098.

125. Rademaker M, Wishart JM, Birchall NM. Isotretinoin 5mg daily for low-grade adult acne vulgaris - a placebo-controlled, randomized double-blind study. J Eur Acad Dermatol Venereol. 2014;28:747-754.

****This was a very well-designed study, including 60 patients with mild acne vulgaris; the ITT population was 58 and PP population, 45. The very low daily dose of oral isotretinoin was compared in two phases: a double blind, compared to placebo for 16 weeks and an open-label of 16 weeks with the drug. Finally, they compared oral isotretinoin versus placebo during 16 weeks and the drug during 16 versus 32 weeks. Considering total lesion count, self-assessment and scores of DLQI, authors observed highly significant differences between oral isotretinoin and placebo; reduction of acne lesions after 4 weeks and similar efficacy between 16 and 32 weeks of drug use. This may be an interesting regimen of oral isotretinoin, with much less adverse effects, for AFA associated with spironolactone and / or oral contraceptives. Attention is need for the risk of pregnancy, as teratogenicity is dose-independent.**

126. Bagatin E, Costa CS, Rocha MADD, et al. Consensus on the use of oral isotretinoin in dermatology - Brazilian Society of Dermatology. Brazilian Ann Dermatol. 2020;95 Suppl 1(Suppl 1):19-38.

127. Spring LK, Krakowski AC, Alam M, et al. Isotretinoin and timing of procedural interventions: a systematic review with consensus recommendations. JAMA Dermatol. 2017;153(8):802-809.

128. Waldman A, Bolotin D, Arndt KA, et al. ASDS guidelines task force: consensus recommendations regarding the safety of lasers, dermabrasion, chemical peels, energy devices, and skin surgery during and after isotretinoin use. Dermatol Surg. 2017;43(10):1249–1262.

129. McDonald KA, Shelley AJ, Pierscianowski T, et al. A 2017 update: challenging the cosmetic procedural delay following oral isotreti- noin therapy. J Cosmet Laser Ther. 2019;21:58–60.

130. Chandrashekar BS, Varsha DV, Vasanth V. Safety of performing invasive acne scar treatment and laser hair removal in patients on oral isotretinoin: a retrospective study of 110 patients. Int J Dermatol. 2014;53(10):1281–1285.

131. Khatri KA, Iqbal N, Bhawan J. Laser skin resurfacing during isotretinoin therapy. Dermatol Surg. 2015;41(6):758–759.

132. Guadanhim LR, Gonçalves RG, Bagatin E. Observational retrospective study evaluating the effects of oral isotretinoin in keloids and hypertrophic scars. Int J Dermatol. 2016;55:1255–1258

133. Picosse FR, Yarak S, Cabral NC, Bagatin E. Early chemabrasion for acne scars after treatment with oral isotretinoin. Dermatol Surg. 2012; 38(9):1521-1526.

134. Saluja SS, Walker ML, Summers EM, et al. Safety of non-ablative fractional laser for acne scars within 1 month after treatment with oral isotretinoin: A randomized split-face controlled trial. Lasers Surg Med. 2017;49(10):886–890.

135. Xia J, Hu G, Hu D, et al. Concomitant use of 1,550-nm nonablative fractional laser with low-dose isotretinoin for the treatment of acne vulgaris in Asian patients: a randomized split-face controlled study. Dermatol Surg. 2018;44(9):1201–1208.

136. Yoon JH, Park EJ, Kwon IH, et al. Concomitant use of an infrared fractional laser with low-dose Isotretinoin for the treatment of acne and acne scars. J Dermatolog Treat. 2014;25:142–146.

137. Labrie F, Martel C, Bélanger A, Pelletier G. Androgens in women are essentially made from DHEA in each peripheral tissue according to intracrinology. J Steroid Biochem Mol Biol. 2017;168:9-18.

**** This review summarizes the role of DHEA, mainly of adrenal origin, as the exclusive source of androgens in women of all ages by the action of intracrine enzymes in peripheral tissues. These intracellular androgens are inactivated in the same cells, with no significant release in the circulation. However, DHEA secretion decreases by an average of 60% at menopause and continues to decrease thereafter.**

138. Zouboulis CC. Acne and sebaceous gland function. Clin Dermatol. 2004;22(5):360-366.

139. Van Vloten WA, Van Haselen CW, Van Zuuren EJ, et al. The effect of 2 combined oral contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea. Cutis. 2002;69(4):2–15.

140. Redmond GP, Olson WH, Lippman JS, et al. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: a randomized, placebo-controlled trial. Obstet Gynecol.1997;89(4):615-622.

141. Maloney JM, Dietze P Jr, Watson D, et al. Treatment of acne using a 3-milligram drospirenone/20-microgram ethinyl estradiol oral contraceptive

administered in a 24/4 regimen: a randomized controlled trial. Obstet Gynecol. 2008;112(4):773–781.

142. Zouboulis CC. Sebaceous gland receptors. Dermatoendocrinol. 2009;1(2):77–80.

143. Golobof A, Kiley J. The current status of oral contraceptives: progress and recent innovations. Semin Reprod Med. 2016;34(3):145-151.

*** This review emphasizes the use of oral contraceptives containing estrogen and progestin for reversible birth control method by millions of women in the whole world. Older formulations contained up to 500 µg of mestranol or 150 µg of ethinyl estradiol (EE), responsible for the majority of pills side effects. The first-generation of progestins included: norethindrone, norethynodrel, norethindrone acetate, and ethynodiol diacetate. The second-generation, norgestrel and levonorgestrel, which are potent progestins, but with more androgenic activity and side effects. The third-generation includes desogestrel and gestodene and the fourth-generation — drospirenone, chlormadinone, nomegestrol acetate, and dienogest— also having anti-mineralocorticoid and antiandrogenic properties. The later generation progestins are very useful in the treatment of moderate and severe acne in women after menarche, associated with topical products. Therefore, the new contraceptives with lower doses of ethinyl estradiol (20 or 35 mcg), the most used estrogen, and novel progestins were developed, increasing the pills safety.**

144. Lemay A, Dewailly SD, Grenier R, Huard J. Attenuation of mild hyperandrogenic activity in postpubertal acne by a triphasic oral contraceptive containing low doses of ethynyl estradiol and d,l-norgestrel. J Clin Endocrinol Metab. 1990;71(1):8-14.

145. Barbieri JS, Mitra N, Margolis DJ, et al. Influence of contraception class on incidence and severity of acne vulgaris. Obstet Gynecol. 2020;135(6):1306-1312.

146. Bosanac SS, Trivedi M, Clark AK, et al. Progestins and acne vulgaris: a review. Dermatol Online J. 2018;24(5):13030/qt6wm945xf.

147. Koo EB, Petersen TD, Kimball AB. Meta-analysis comparing efficacy of antibiotics versus oral contraceptives in acne vulgaris. J Am Acad Dermatol. 2014;71(3):450-459.

148. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. Cochrane Database Syst Rev. 2012;7:CD004425.

**** This is a systematic review, including 17 comparative studies between two different COCs. Few consistent differences were found in their effectiveness for treating acne. Authors highlighted the use of variable and non-standardized methods for assessing acne severity. In relation to the progestins, COCs with chlormadinone acetate or cyproterone acetate improved acne better than levonorgestrel; cyproterone acetate was more effective than desogestrel; levonorgestrel showed a slight improvement over desogestrel, and drospirenone was more effective than norgestimate or nomegestrol acetate but less effective than cyproterone acetate. No differences in side effects were detected.**

149. Raymond EG, Burke AE, Espey E. Combined hormonal contraceptives and venous thromboembolism: putting the risks into perspective. Obstet Gynecol. 2012;119(5):1039–1044.

150. Dréno B, Bettoli V, Ochsendorf F, et al. European Expert Group on Oral Antibiotics in Acne. European recommendations on the use of oral antibiotics for acne. Eur J Dermatol. 2004;14(6):391-399.

151. Akamatsu H, Zouboulis CC, Orfanos CE. Spironolactone directly inhibits proliferation of cultured human facial sebocytes and acts antagonistically to testosterone and 5α-dihydrotestosterone in vitro. J Invest Dermatol. 1993;100(5):660–662.

152. Layton AM, Eady EA, Whitehouse H, et al. Oral spironolactone for acne vulgaris in adult females: a hybrid systematic review. Am J Clin Dermatol. 2017;18(2):169-191.

**** This systematic review comprised 10 randomized and controlled trials and 21 case series. The risk of bias was high and the quality of evidence was low or very low. Therefore, authors concluded that there is low evidence for the usual dose of spironolactone (≤100 mg/day) used in clinical practice.**

153. Helfer EL, Miller JL, Rose LI. Side-effects of spironolactone therapy in the hirsute woman. J Clin Endocrinol Metab.1988;66(1):208–211.

154. Wolverton SE, Wu JJ. Comprehensive dermatologic drug therapy. 4th Edition, Elsevier, 2021. Amsterdam, Netherlands. 858p.

155. Lainscak M, Pelliccia F, Rosano G, et al. Safety profile of mineralocorticoid receptor antagonists: spironolactone and eplerenone. Int J Cardiol. 2015;200:25–29.

156. Charny JW, Choi JK, James WD. Spironolactone for the treatment of acne in women, a retrospective study of 110 patients. Int J Womens Dermatol. 2017;3(2):111-115.

157. American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into human milk. Pediatrics. 1994;93:137-150.

158. Shaw JC. Low-dose adjunctive spironolactone in the treatment of acne in women: a retrospective analysis of 85 consecutively treated patients. J Am Acad Dermatol. 2000;43(3):498-502.

159. Barbieri JS, Choi JK, James WD, Margolis DJ. Real-world drug usage survival of spironolactone versus oral antibiotics for the management of female patients with acne. J Am Acad Dermatol. 2019;81(3):848-851.

*** This research letter presents a discussion about the assumption that spironolactone might have similar effectiveness as oral antibiotics for acne and can decrease the duration of their use. In a retrospective and observational study, by using a database, authors searched for the diagnosis of acne among women, from 12 to 40 years old, treated with spironolactone or tetracycline-class antibiotics. The mean duration was 697.8 days among 4321 female patients treated with spironolactone and 604.4 days among 7517 treated with antibiotics. They concluded, despite the study limitations, that the prolonged use of spironolactone suggested that in clinical practice, this drug might have good long-term effectiveness and tolerability. It should be considered a good alternative to oral antibiotics, which may be used at maximum for three months, considering the relevant risk of bacterial resistance.**

160. Roberts EE, Nowsheen S, Davis MDP, et al. Treatment of acne with spironolactone: a retrospective review of 395 adult patients at Mayo Clinic, 2007-2017. J Eur Acad Dermatol Venereol. 2020; 34(9):2106-2110.

****A cohort of 395 women, median age of 32 years, treated at Mayo Clinic in Rochester, Minnesota, with 100 mg daily of spironolactone was reported. It was demonstrated that 85.1% of patients had complete response or partial response (> 50%). The initial and maximum response occurred in 3 and 5 months, respectively. The efficacy, independently of acne severity, and few adverse effects pointed out the benefit of this drug for AFA.**

161. Gainder S, Sharma B. Update on management of polycystic ovarian syndrome for dermatologists. Indian Dermatol Online J. 2019;10(2):97–105.

162. Cyproterone Article-31 referral - Restrictions in use of cyproterone due to meningioma risk. Last updated: 20/05/2020 EMA/147755/2020.

163. Kim GK, Del Rosso JQ. Oral Spironolactone in post-teenage female patients with acne vulgaris: practical considerations for the clinician based on current data and clinical experience. J Clin Aesthet Dermatol. 2012;5(3):37-50.

164. de Melo AS, Dos Reis RM, Ferriani RA, Vieira CS. Hormonal contraception in women with polycystic ovary syndrome: choices, challenges, and noncontraceptive benefits. Open Access J Contracept. 2017;8:13-23.

165. Dréno B, Araviiskaia E, Kerob D, et. al. Nonprescription acne vulgaris treatments: Their role in our treatment armamentarium - an international panel discussion. J Cosmet Dermatol. 2020;19(9):2201-2211.

166. Thiboutot D, Del Rosso JQ. Acne vulgaris and the epidermal barrier: Is acne vulgaris associated with inherent epidermal abnormalities that cause impairment of barrier functions? Do any topical acne therapies alter the structural and/or functional integrity of the epidermal barrier? J Clin Aesthet Dermatol. 2013;6(2):18-24.

167. Decker A, Graber EM. Over-the-counter acne treatments: a review. J Clin Aesth Dermatol. 2012;5:32-40.

168. Del Rosso JQ. The role of skin care as an integral component in the management of acne vulgaris: Part 1: the importance of cleanser and moisturizer ingredients, design, and product selection. J Clin Aesthet Dermatol. 2013;6(12):19–27.

169. Araviiskaia E, Dréno B. The role of dermocosmetics in acne vulgaris. J Eur Acad Dermatol Venereol. 2016; 30:926-935.

170. Bagatin E, Holzmann R, Shakery K, et al. Adult female acne. Azelaic acid in the treatment of acne in adult female. Skin Pharmacol Physiol. 2014;27(Suppl 1):1-2.

171. Schorr ES, Sidou F, Kerrouche N. Adjunctive use of a facial moisturizer SPF 30 containing ceramide precursor improves the tolerability of topical tretinoin 0.05%: a randomized, investigator-blinded, split face study. J Drugs Dermatol. 2012;11(9):1104-1107.

172. Isoda K, Seki T, Inoue Y, et al. Efficacy of the combined use of a facial cleanser and moisturizers for the care of mild acne patients with sensitive skin. J Dermatol. 2015;42(2):181-188.

**** As hyperseborrhea is not always present in acne patients and the skin can be sensitive, especially in adult women, it is relevant to choose an adequate facial cleanser to be used just once a day, at night. Additionally, it should be**

recommended moisturizer cream or lotion or serum alternated or combined with topical treatment or oral isotretinoin to improve tolerability and adherence.

173. Lynde CW, Andriessen A, Barankin B, et al. Moisturizers and ceramide-containing moisturizers may offer concomitant therapy with benefits. J Clin Aesthet Dermatol. 2014;7(3):18-26.

174. Rocha MA, Bagatin E. Skin barrier and microbiome in acne. Arch Dermatol Res. 2018;310(3):181-185.

**** This review article refers to the emergent discussion about the less diversity of microbiome, with presence of a specific phylotype of *Cutibacterium acnes* in acne-prone skin. In addition, they call attention to the well-known skin barrier impairment in acne, which can also be related to microbiome alterations, when prescribing a therapeutic regimen.**

175. Barbaric J, Abbott R, Posadzki P, et al. Light therapies for acne. Cochrane Database of Systematic Reviews. 2016;9(9):CD007917.

176. Celasco G, Moro L, Bozzella R, et al. Biological profile of cortexolone 17alpha-propionate (CB-03-01), a new topical and peripherally selective androgen antagonist. Arzneimittelforschung. 2004;54(12):881–886.

177. Trifu V, Tiplica GS, Naumescu E, et al. Cortexolone 17alphapropionate 1% cream, a new potent antiandrogen for topical treatment of acne vulgaris. A pilot randomized, double-blind comparative study vs. placebo and tretinoin 0.05% cream. Br J Dermatol. 2011;165(1):177–183.

178. Han JJ, Falestsky A, Barbieri JS, Mostaghimi A. New acne therapies and updates on use of spironolactone and isotretinoin: a narrative. review. Dermatol Ther (Heidelb). 2021.https://doi.org/10.1007/s13555-020-00481-w

**** This recent review discussed the new options for acne treatment such as: clascoterone, trifarotene, novel lotion formulations of tretinoin and tazarotene and oral sarecycline. It also presented a useful update about spironolactone and isotretinoin. The first is used off-able to treat acne and have demonstrated similar efficacy compared to antibiotics. However, it still remains underutilized and antibiotics are prescribed 3–7 times more often for AFA, in courses of 6 months or more, increasing the risk of bacterial resistance. Cohort studies have highlighted that**

spironolactone is not associated with increased risk of breast cancer and hyperkalemia is not a common adverse event, indicating the low utility of checking potassium among healthy young women (< 45 years old). In respect to isotretinoin authors suggested a need to reconsider drug-monitoring guidelines and to simplify iPLEDGE requirements in USA. Highly effective contraception such as subdermal implants or IUDs may help to change the recommendation for using two forms of contraception and frequent pregnancy monitoring. Authors stated that removing unnecessary obstacles would benefit patients by early indication, increased accessibility, reduction of psychosocial sequelae, scarring, and mitigate the antibiotic over-prescription.

179. Eichenfield LF, Hebert A, Gold LS, et al. Open-label, long-term extension study to evaluate the safety of clascoterone (CB-03-01) cream, 1% twice daily, in patients with acne vulgaris. J Am Acad Dermatol. 2020;83(2):477–485.

180. Müderris II, Bayram F, Ozçelik B, Güven M. New alternative treatment in hirsutism: bicalutamide 25 mg/day. Gynecol Endocrinol. 2002;16(1):63-6.

181. Moretti C, Guccione L, Di Giacinto P, et al. Combined oral contraception and bicalutamide in polycystic ovary syndrome and severe hirsutism: a double-blind randomized controlled trial. J Clin Endocrinol Metab. 2018;103(3):824-838.

182. Fernandez-Nieto D, Saceda-Corralo D, Rodrigues-Barata R, et al. Oral bicalutamide for female pattern hair loss: A pilot study. Dermatol Ther. 2019;32(6):e13096.

183. Trivedi MK, Bosanac SS< Sivamani R, Larsen LN. Emerging therapies for acne vulgaris. Am J Clin Dermatol. 2018;19(4):505-516.

Table 1. Adult female acne (AFA) pathogenesis [33-35]
1. Genetic predisposition to have acne in adult life based in positive familial history
2. Non-regulation of some pathogenic factors after adolescence, leading to a chronic disease, such as: a) increased intracrine androgen production b) overexpression of toll-like 2 receptors → continuous activation of innate immunity
3. Presence in AFA of resistant strains of *Cutibacterium acnes* that cause chronic stimulation of the innate immune system, initiating and exacerbating inflammatory lesions
4. Endocrine dysfunction in some cases: e.g. polycystic ovary syndrome, congenital adrenal hyperplasia and adrenal tumours
5. Increased activation of Insulin/IGF-1/mTORC1 pathway
6. Obesity and insulin resistance.

Table 2: Peculiar aspects that distinguish adult female acne (AFA) from adolescent acne [33-35].

Regarding to:	ADULT FEMALE ACNE	ADOLESCENT ACNE
LOCATION IN FACE	Diffuse or lower third face	Forehead
	U-zone	**T-zone:** * Chin * Nose
SEBORRHEA	Present in 70%	Present in all patients
SKIN SENSIBILITY	+++	+
COMEDONES	Few or absent	Always present
INFLAMMATORY LESIONS	Papules, pustules, small nodules, rare cysts	Papules, pustules, nodules, cysts, abscesses
INTENSITY	Mild or moderate	Mild, moderate or severe
DURATION	Very long	Limited until 18 to 25 years
RESPONSE	Begins after 3 months of therapy	Respond quickly
TOPICAL TREATMENT	Less irritating options are better, such as: * Adapalene 0,1%, azelaic acid 15% and benzoyl peroxide 2,5%	All anti-acne options may be prescribed
ORAL TREATMENT		
* ANTIBIOTICS	Less recommended	Recommended to treat moderate to severe cases
* HORMONAL TREATMENT (FEMALE PATIENTS)	Very recommended	May be recommended