REVIEW OF ACNE TREATMENT OPTIONS IN PREGNANCY

Patryk Rudzinski[1*], Inga Lopuszynska[1*], Joanna Kacperczyk-Bartnik[2], Pawel Bartnik[2], Agnieszka Dobrowolska-Redo[2#], Ewa Romejko-Wolniewicz[2]

*Equally contributing authors

1. Students' scientific group affiliated to 2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland
2. 2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland

#Corresponding author: Agnieszka Dobrowolska-Redo, 2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Karowa 2 St, 00-315 Warsaw, Poland, phone number: +48225966421, e-mail: agnieszka.dobrowolskaredo@gmail.com

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ABSTRACT

Acne is a chronic disease in which a dysfunction of the pilosebaceous apparatus of the skin is accompanied by excess sebum production. It may be clinically classified as mild, moderate and severe. Although many effective treatments against acne exist, their known and unknown effects on embryogenesis prevent doctors from prescription to pregnant women. Another factor hindering efficient treatment would be the uncertainty regarding acne course in a gravid. The following review summarizes topical and oral therapies, as well as procedure-based therapies, considering the severity of acne in patients. It also highlights the pathogenesis of acne, drugs' mode of action and the need for further research. Medical databases were used in order to retrieve articles regarding treatment of acne in pregnant women. This research shows that in all trimesters there is a safe acne treatment option. Concomitant therapies are thought to be more effective in combating acne, which may result in decreasing the number of medicines taken and/or applied to the skin and, hence, diminishing their side effects. In spite of an abundance of treatment options for adult women, lack of complete and trustworthy evidence-based data for pregnant women forces dermatologists and gynaecologists to rely on the current guidelines, which are written based on limited data. More research on targeting acne in pregnant women, including procedure-based therapies as well as delving into the psychological aspect of pregnant's wellbeing is needed.

BACKGROUND

Acne vulgaris is a common chronic disease of the pilosebaceous units, accompanied by seborrhoea. Causes are various and include increased sebaceous glands' activity, blockage of pilosebaceous apparatus due to excessive keratinisation, colonisation of ducts with Propionibacterium acnes, inflammation, hormonal imbalance (excess androgens), and hyperactivity of peroxisome proliferator-activated receptors (PPAR) (regulation of keratinocytic activity), as well as environmental factors (diet, smoking, occlusive cosmetics, occupational exposures). Proinflammatory cyto- and chemokines and bacterial antigens exacerbate the inflammatory response in acne [1, 2, 3, 4]. Elicitation of acne in pregnancy prevails in women with a history of acne. Management of acne in pregnant patients can be challenging because not only are effective treatments usually not recommended in pregnancy, but physiological changes in pregnancy also play a role in the unpredictability of the course of acne. Patients prone to acne are more likely to relapse during pregnancy or have more severe symptoms. Psychological effects of both acne and its treatment are also worth considering, including the risk of depression and suicidal thoughts [1, 5]. This paper aims to review possible treatment options of acne in pregnant women.

MATERIAL AND METHODS

For this review, PubMed, ProQuest and ScienceDirect were searched. Following keywords were used: acne, acne vulgaris, pregnancy, treatment, isotretinoin, pregnant, dermatologic therapy, teratogenicity. The websites of American Academy of Dermatology and Polish Dermatological Society were searched for the guidelines on acne treatment. There were no date restrictions used. Papers were restricted to those published in Polish, English and German. To evaluate the level of recommendation for each medicine, FDA pregnancy categories were used, which are as follows [6]:

- A - clinical data show no evidence of risk to the foetus;
- B - clinical data are limited or not available, but animal studies show no evidence of risk to the foetus, or clinical data show no evidence of risk to the foetus, but animal studies show adverse effect to the foetus;
- C - clinical data are not available and animal studies are not available, or clinical data are not available, but animal studies show adverse effects to the foetus;
- D - positive evidence of risk to the foetus from clinical data;
- X - contraindicated based on animal studies or clinical data;
- N - not yet classified.

TOPICAL THERAPIES

Topical therapies are the least invasive treatment options, given low systemic availability and used for mild to moderate acne. Frequently, they are used in combination, providing a synergistic effect or preventing bacterial resistance. The most common combinations include benzoyl peroxide (BPO) with azelaic acid, topical erythromycin or topical clindamycin.

Azelaic acid

This pregnancy category B medicine, naturally present in wheat, rye and barley, is considered safe to use in mild to moderate inflammatory acne vulgaris. It targets all factors contributing to the pathogenesis of acne, i.e. reduces inflammation and seborrhoea, acts as an antimicrobial and comedolytic agent, and inhibits melanogenesis, thus, diminishing dyspigmentation. It can be used as monotherapy because no data show bacterial resistance development [3,4 5,7].

Benzoyl peroxide

Benzoyl peroxide (BPO) is classified as category C in pregnancy. Its spectrum of action encompasses anti-inflammatory, comedolytic and keratinolytic properties. Its production of reactive oxygen species is effective against P. acnes and Staphylococcus sp. No antibacterial resistance is known. It can be used as monotherapy in mild to moderate acne and as combined therapy in severe cases. It is contraindicated in the last month of pregnancy by the Rote Liste Service (German equivalent of the FDA pregnancy category) [1, 3, 4, 5, 7].

Salicylic acid

Salicylic acid is classified as category C in pregnancy. It acts as a comedolytic and keratinolytic agent and is less effective than azelaic acid and benzoyl peroxide. When used in abundance and high concentration, it may result in systemic salicylic toxicity. Experiments on rat embryos have shown deformities upon systemic salicylic acid administration [3, 7]. Hence, salicylic acid peelings should be avoided during pregnancy [1]. On the other hand, different studies indicate that when used according to recommendations, it is deemed safe [5].

Erythromycin, Clindamycin

Both are classified as a category B antibiotics. They should be used in combination with BPO in order to reduce the risk of bacterial resistance. Erythromycin, in comparison with clindamycin, has been proven less effective due to Staphylococci and P. acnes resistance. Clindamycin should be restricted in patients with a history of gastrointestinal issues, as studies show an increased risk of C. difficile diarrhoea after topical treatment [1, 5, 7, 8].

Tazarotene, Tretinoin, Adapalene

Tazarotene is classified as category X retinoid and is contraindicated in pregnancy, as it was associated with skeletal, cardiac and neural abnormalities in gestating rats. Tretinoin and adapalene are classified as category C and should be avoided in pregnancy. Retinoids are vitamin A derivatives, altering nuclear transcription by binding to retinoid acid receptors and retinoid X receptors and, thus, advancing corneocyte exfoliation. Tretinoin and BPO should be administered at different times as BPO can oxidise and inactivate tretinoin. Regardless of low systemic resorption, rare cases of otic, ophthalmic and central nervous system malformations were reported. Studies show that the teratogenicity of

tretinoin and adapalene are only to be expected in the first trimester, and no complications have been accounted for in the second and third trimester. Despite the risk of deformities, there is no indication for termination of pregnancy upon conception during retinoid therapy [1, 4, 5, 7, 8, 9, 10, 11, 12].

Dapsone

Dapsone is a category C synthetic sulfon. Clinical trials showed modest to moderate efficacy, especially in respect to inflammatory lesions reduction. The data on its mechanism of action and antibiotic properties with regards to P. acnes are lacking. It is thought to act as an anti-inflammatory agent. Studies report a theoretical hyperbilirubinemia and haemolytic anaemia hazard in neonates when dapsone is administered close to labour time. Although there is no information on the risks of teratogenicity, even in high doses, it is not recommended, unless benefits exceed the risks [5, 7, 8, 10, 13].

Corticosteroids

Prednisone is an anti-inflammatory drug classified as category C in pregnancy. No foetal deformities or preterm childbirths were reported upon topical corticosteroid therapy. Potent corticosteroid use during the third trimester has been associated with a reduced intrauterine growth. An increase in stretch mark formation may be observed on corticosteroid therapy [6, 14].

ORAL THERAPIES

They are prescribed for moderate to severe acne. In order to achieve higher effectiveness, they are prescribed in a combination with topical treatments. Regarding antibiotics, the recommended order of preference is penicillins, cephalosporins and erythromycin/macrolide agents [11].

Erythromycin, Azithromycin

These category B macrolides inhibit bacterial ribosomes, neutrophil chemotaxis, decrease prostaglandin and cytokine production, and restrict lipase production by P. acnes, reducing free fatty acids, hence decreasing inflammation of the pilosebaceous unit. Cautious use of those antibiotics is desirable as bacteria may become resistant. Erythromycin barely crosses the placental barrier, whereas azithromycin has a higher ability to enter the amniotic sac, but both have a satisfactory safety profile. Nevertheless, the available data provide an account of foetal cardiac malformations and maternal hepatotoxicity, as well as gastrointestinal problems. Erythromycin estolate should not be used based on its potential hepatotoxic risk [1, 3, 4, 5, 8, 11, 15].

Cephalexin

This category B cephalosporin is not associated with anomalies in animal foetuses, but human studies are deficient. Even though it infiltrates comedones less effectively than other antibiotics, it is proven to be effective against P. acnes [5, 11].

Amoxicillin

This pregnancy category B antibiotic, a ß-lactam, is commonly used as a first-choice agent in pregnancy for inflammatory acne treatment. In treatment-resistant acne, it is used alone or in combination. Indeed, studies report a risk of cleft lip and palate, which can be encountered in early pregnancy or third trimester, and maternal gastrointestinal problems [3, 7, 8, 16].

Trimethoprim/Sulfamethoxazole

Trimethoprim/sulfamethoxazole (TMP/SMX) is category C antifolate/antibiotic. In the first months of pregnancy, it is associated with increased risk of the neural tube defect, oral cleft, limb, cardiovascular and urinary tract anomalies, as well as miscarriage, preterm birth and low birth weight. Trimethoprim causes decreased folate levels which may persist for up to 50 days subsequent to its withdrawal. The use of TMP/SMX is discouraged during the third trimester due to possible maternal hyperbilirubinemia [4, 6, 17, 18].

Tetracycline, Minocycline, Doxycycline

They are classified as pregnancy category D. They may be used in the first weeks of pregnancy but are contraindicated after 15 weeks of gestation due to the possible risk of deciduous teeth discolouration, maternal hepatitis, limb hypoplasia, decline in foetal size (reversible), inguinal hernia and hypospadias, as they enter foetal circulation and bind strongly to calcium ions. Cases of a third-trimester maternal hepatotoxicity caused by tetracyclines were also reported [1, 4, 5, 6, 8, 11, 19, 20].

Isotretinoin

Isotretinoin is a category X oral retinoid. Even though no other treatment of acne is as effective, the retinoid is teratogenic and multiple regulations exist, preventing the risk of simultaneous isotretinoin therapy and conception (iPLEDGE in the USA and PPP - Pregnancy Prevention Programme in the EU). Nevertheless, the number of pregnancies exposed to isotretinoin ranges from 2 to 6 per 1000 women. Deformations include malformations of the head and central nervous system (hydrocephalus, microtia, external ear canal stenosis, cleft palate), heart (malformations of the great vessels) and thymic hypoplasia. It is thought to interfere with the development and migration of the cephalic neural crest cells [5, 6, 13, 21, 22, 23, 24, 25].

Prednisone

Prednisone is classified as category C (D if used in the first trimester) corticosteroid. It is a first-choice corticosteroid due to low passage to the embryo as a result of placental enzymes activity. When treated with prednisone, the risk of cleft palate increases 4 weeks prior to and 12 weeks after conception. Miscarriage risk, premature delivery, intrauterine growth retardation, gestational diabetes, pre-eclampsia and eclampsia may occur [1, 5, 6].

Spironolactone

Spironolactone is a category C antiandrogen inhibiting 5α-reductase, misadvised for acne treatment by the FDA. It may lead to male foetus feminization and hypospadias [6, 7, 26].

Zinc

Pregnancy category C drug, which has anti-inflammatory, antibacterial and anti-sebaceous features. It is effective against mild to moderate acne, as monotherapy or

combined with another medicine. When used longer than 3 months, a copper deficiency was observed [1, 5].

PROCEDURE-BASED THERAPIES

Chemical peels

Classified as category N, glycolic acid exfoliates the epidermis, leading to sebaceous glands' cleansing, and has anti-inflammatory properties. It also increases the absorption of topical agents [5].

Phototherapy

Narrowband UV-B phototherapy is an effective anti-inflammatory treatment, has a satisfactory safety profile and no known teratogenicity risk, however, melasma may worsen and serum folate level may decline, especially in the first months of pregnancy. It may also be effective against P. acnes [6, 8, 11].

Laser therapy is deemed generally safe in population but its effect on foetus remains unknown [8].

Photodynamic therapy is assumed to reduce the number of bacteria and sebaceous gland size. Photosensitizing agents include topical aminolevulinic acid which has not been studied sufficiently and is not recommended [11, 27].

Blue light therapy can be used for treating mild to moderate inflammatory acne, as it interacts with P. acnes porphyrins. Red light has been shown to possess great anti-inflammatory properties by controlling cytokines release and keratinisation. However, no guidelines for such a therapy in pregnant women exist [1, 11, 28].

DISCUSSION

The effects of the medicines used in acne treatments, as well as their pharmacokinetics, are difficult to investigate in pregnant patients as physiological changes occur. Moreover, ethical concerns prevent pregnant women from becoming study subjects, as a risk to the wellbeing of the foetus cannot be excluded. Lack of sufficient evidence-based data causes doctors to rely on information collected in animal studies which may not fully represent the effect on human subjects. There are equivocalities and missing studies on the safety and efficiency of certain treatments, which should be further investigated and systematized. Acne, when left untreated, may lead to another underrepresented aspect - a socio-psychological situation of the patient, which is hard to assess and evaluate. The treatment must always be suited to the individual needs of the patient.

CONCLUSIONS

The aim of this review was to present the reader with the current state of knowledge on the methods of acne treatment in pregnancy, not to create guidelines. The goal was to summarize existing knowledge on the subject. Considering the aforementioned therapies available, the treatment of mild to moderate acne should encompass topical agents because of their best safety profile and slightest level of systemic absorption, and therefore present the lowest risk of foetal exposure. In case of moderate to severe acne, oral treatment is recommended, while still considering risk-benefit ratio. Both treatment options may be used with adjuvants, and therefore increasing its spectrum and efficacy. Depending on the stage of foetal development and considering the fact of differing safety profiles throughout pregnancy, multiple treatment options are available and should be carefully considered. Thus, both the patient and the doctor should agree upon a decision on how to best treat the condition, considering maternal psychological and physical wellbeing, as well as lowest possible foetal exposure.

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ABBREVIATIONS

BPO – Benzoyl peroxide
PPAR – peroxisome proliferator-activated receptors
TMP/SMX – Trimethoprim/sulfamethoxazole

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