

INVITED ARTICLE

# Treatment of acne vulgaris in pregnant patients

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**ABSTRACT:** The management of acne vulgaris in the setting of pregnancy raises important clinical considerations regarding the efficacy and safety of acne treatments in this special patient population. Particular challenges include the absence of safety data, discrepancy in safety data between different safety rating systems, and lack of evidence-based recommendations for the treatment of acne during pregnancy. Nonetheless, many therapeutic options exist, and the treatment of acne in pregnant women can be safely and often effectively accomplished. For mild or moderate disease, patients can be treated with topical antimicrobial agents, anti-inflammatory agents, as well as glycolic and salicylic acid. Several topical agents, notably benzoyl peroxide, previously viewed as potentially dangerous are cited by many sources as being considered safe. When necessary, systemic therapies that can be safely added include penicillins, amoxicillin, cephalosporins, erythromycin, clindamycin, and tetracyclines or sulfonamides, depending on the stage of fetal development. Adjunct therapy may include phototherapy or laser treatments. Physicians should work with this often highly motivated, safety-conscious patient population to tailor an individualized treatment regimen. This treatment regimen will likely shift throughout the different stages of fetal development, as distinct safety considerations are raised prior to conception as well as during each of the trimesters of pregnancy. Important considerations regarding acne management in breast-feeding mothers is also discussed.

**KEYWORDS:** acne vulgaris, lactation, pregnancy, safety, treatment

## Introduction

Acne vulgaris in pregnancy presents a particularly challenging scenario for the practicing dermatologist. The pathophysiology and prevalence of acne in pregnant women are not well-characterized, and the pattern of change in acne

severity during pregnancy is not necessarily consistent. While some women may develop new-onset acne or flares of preexisting acne during pregnancy, others may experience disease improvement.

There are many important considerations in the management of acne in this special patient population. Although acne is almost ubiquitous in both male and female teenagers, it may persist into adulthood and has an impact on quality of life similar to psoriasis (1–4). While both men and women can have persistent acne, even into the sixth decade of life, in one survey of adults over age 20 ( $n = 1013$ ), self-report of acne was disproportionately higher in female patients as compared

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with males (2). Adult women are more likely to present for dermatologic evaluation, and one study showed that adult women make up 2/3 of dermatology office visits for acne (3). Furthermore, female patients were twice as likely to have depression in association with acne as compared with their male counterparts irrespective of acne disease severity (4).

## Pathophysiology of acne in pregnancy

The pathophysiology of acne in general is complex and includes a variety of factors (5). Acne is primarily a disease of the pilosebaceous unit with clinical features ranging from open and closed comedones, to inflammatory papules or pustules as well as deeper nodules, cysts, and various degrees of scarring (6). Numerous exacerbating factors include: excess sebum production, androgenic stimulation, overgrowth of bacteria such as *Propionibacterium acnes*, inflammatory mechanisms, follicular hyperkeratinization, and possible dietary influence (5–7).

Although it is not known which pathophysiologic pathways predominate in acne during pregnancy, hormonal shifts associated with the gravid state are likely to be significant. The importance of androgens in the pathogenesis of acne in female patients is well established. Work done by Ann Lucky and colleagues demonstrated that development of acne in pre-pubertal girls is preceded by a rise in androgens and that higher levels of dehydroepiandrosterone and testosterone, predict severity of clinical acne (8). The efficacy of hormonal treatments such as combined oral contraceptive pills and the anti-androgenic medication spironolactone also confirm that androgens play an important role in acne. The common prevalence of acne in hyperandrogenic states, such as polycystic ovary syndrome, further strengthens this hypothesis.

However, the specific mechanism(s) by which acne is exacerbated in pregnancy remains unknown. Increased levels of progesterone may result in some alterations of sebum production during pregnancy. The common complaint that stopping or even switching oral contraceptive pills can lead to acne flares supports the notion that for some women, the primary cause of their acne may be hormonal. Immunologic changes associated with the gravid state may also be a contributing factor.

## Important considerations for the treatment of acne in pregnancy and lactation

There are many important considerations for the treatment of acne in pregnancy. First and foremost is the safety of acne therapies on the developing fetus. The Food and Drug Administration (FDA) has five established categories to indicate potential teratogenicity of a medication when used by patients during pregnancy. The Briggs system also evaluates risk of medication use during pregnancy, and the Hale system assesses risk of medication use with lactation. Notably, there is great discrepancy between these systems. Furthermore, although a rating system may specify that a medication is not safe during pregnancy, careful review may indicate that it may only be unsafe during a specific time during pregnancy. Thus, tailoring the regimen to each phase of pregnancy (pre-conception, first, second, third trimesters, perinatal, and lactating periods) based on consideration of all of these rating systems may be the safest approach.

Lactation is a special consideration for acne management in this population. Medications may affect the volume of breast milk, and in some cases, medication transfer into the milk raises concern that an infant may be exposed to potentially harmful effects. However, many drugs are safe to ingest while breast-feeding. We have included the Hale classification system throughout the discussion; L1 is considered safest, L2 is considered safe, and L3 is considered moderately safe.

Unfortunately, very little data are available supporting the clinical efficacy of any acne medication during pregnancy or lactation. Thus, it is imperative for both the clinician and patient to delineate clear treatment goals and expectations. Amelioration of symptoms, rather than total clearance, may be a reasonable treatment endpoint. A step-wise approach, starting with topical agents and escalating to systemic agents, may be a reasonable option to balance risks of teratogenicity with disease severity. Use of a complex topical-only regimen is an important option to consider in this highly motivated, safety-conscious patient population.

## Approach to the treatment of acne in pregnancy

Oral and topical medications for acne are numerous, including topical antibiotics, topical retinoids,

oral antibiotics, and oral retinoids. Each category is discussed later. One important issue is whether or not to stop therapy while attempting to conceive. Unfortunately, there is little evidence to guide clear recommendations to this common clinical question. Unless a medication is considered safe to be used during the first trimester of pregnancy, it may be prudent to guide patients to avoid any potentially unsafe medication for one month or longer prior to attempts to conceive, depending on the half-life of the medication.

## Systemic therapy of acne

### Systemic retinoids

Topical and oral retinoids are a common, effective treatment for acne, ranging from mild comedonal acne to severe nodulocystic acne. However, given the potent teratogenicity of systemic retinoids and unclear data regarding topical retinoid safety, all retinoids should be avoided in pregnancy.

Isotretinoin, a systemic retinoid commonly used for the treatment of acne, is FDA pregnancy category X. It is associated with increased risk of spontaneous abortion as well as retinoid embryopathy, which can result in specific facial and palatal defects, micrognathia, cardiovascular defects, and developmental problems of the central nervous system and thymus (9). Pregnancy prevention programs while using oral isotretinoin (such as iPLEDGE and the previous program SMART) have been widely implemented. However, an article published by Shin et al. showed that the incidence of pregnancy did not decrease with the iPLEDGE system within a large managed care organization; furthermore, first-year data for iPLEDGE showed no statistically significant change in the number of pregnancies after institution of this program (10,11).

It is generally recommended that women have a one-month washout period (one month between completely discontinuing isotretinoin and beginning attempts to conceive a pregnancy). The half-life of isotretinoin is between 10 and 20 hours and its metabolite (4-oxo-isotretinoin) between 17 and 50 hours; both isotretinoin and its metabolite are thought to be teratogenic. Even if a half-life is considered to be 1 week, five times this half-life would be enough to allow levels of the drug to return to negligible levels (12). There is one case of suspected isotretinoin-induced microtia (congenital deformity of the external ear) in an infant born to women who had taken isotretinoin 10 mg daily for

2 years who had discontinued the isotretinoin 5 weeks prior to conception (13). This is a rare case where microtia was reported although isotretinoin was discontinued more than 1 month prior to conception (13). Published guidelines advise women that their risk for teratogenicity is not higher than baseline if they conceive one menstrual cycle after completely stopping isotretinoin (14,15).

### Systemic antibiotics

There are numerous oral antibiotics used for the treatment of acne; some may be safely used for the treatment of acne in pregnant patients. Although the general recommendation is to avoid use of systemic antibiotics during the first trimester if possible, certain agents have excellent safety profiles. The recommended antibiotics for use in pregnancy include (in order of preference) penicillin agents, cephalosporins, then erythromycin/macrolide agents (summarized in Table 1).

Regarding the use of antibiotics in lactation, the Hale classification category is listed later for each specific medication. When prescribing all oral antibiotics, it is important to inform patients of the need to monitor for gastrointestinal symptoms in infants, which may result from alterations in gastrointestinal flora of their mothers.

Penicillin and penicillin-like agents are considered first-line agents for use in acne in pregnant patients. Reported side effects include gastrointestinal upset, dry mouth, increased candidal yeast infections, hypersensitivity, anemia, leukopenia, reversible hepatotoxicity, and arthritis. Amoxicillin has a similar safety and side effect profile to penicillin; see Table 1 for dosing. These agents are Hale classification system L1–L2.

Oral cephalosporins including cephalexin are hydrophilic molecules, which are less effective at penetrating comedones, but do have activity against *P. acnes*. In one study of 93 non-pregnant patients, 45% of patients had significant improvement and 78% had some improvement as determined by lesion counts after 4 weeks (5). Cephalosporins are Hale classification system L1–L2.

Several macrolide antibiotics can be used for treatment of acne in pregnancy. Oral azithromycin has efficacy against *P. acnes* and anti-inflammatory actions; because of a longer half-life of 68 hours, it can be administered as a single daily dose. Although antibiotic cross-resistance between erythromycin and clindamycin may exist, *P. acnes* is not thought to be widely resistant to

**Table 1.** Oral antibiotics for acne vulgaris in pregnancy and lactation<sup>a</sup>

Antibiotic	FDA category	Briggs classification	Hale system	Possible dosing regimen	Common potential side effects
Azithromycin	B	Compatible	L2	Weekly pulse 500 mg for 3 consecutive days with 1-week intervals 500 mg daily for 3–4 days q10 days for 4 months 500 mg daily for 4 days q10 days for 4 months 500 mg daily for 4 days qmonth for 3 months 500 mg daily for 3 days qweek for 4 weeks, decrease to 250 mg every other day for 2 months 500 mg 3×/week for 8–12 weeks 500 mg twice daily	Gastrointestinal upset
Cephalosporins i.e., cephalixin	B	Compatible	L1–L2		Dizziness, gastrointestinal upset, headache Gastrointestinal upset, nausea
Erythromycin base	B	Compatible (excluding erythromycin estolate)	L3	250 mg twice daily 250 mg four times daily 500 mg twice daily 500 mg four times daily	
Clindamycin	B	Compatible	L2	75 mg twice daily 150 mg twice daily 150 mg three times daily 250 mg twice daily 500 mg twice daily 500 mg three times daily	Gastrointestinal upset, pseudomembranous colitis Nausea, vomiting
Amoxicillin	B	Compatible	L1–L2		

<sup>a</sup>Food and Drugs Administration (FDA) categories: A: adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters. B: animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. C: animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. D: there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. X: studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Briggs Pregnancy Recommendation Class: (Briggs G, et al. Drugs in pregnancy and lactation, 9th ed. 2011).

Compatible; no (limited) human data – probably compatible; compatible – maternal benefit >> embryo-fetal risk; human data suggest low risk; no (limited) human data – animal data suggest low risk; contraindication – first trimester; contraindication – second and third trimesters; contraindicated (at any time during pregnancy); no (limited) human data, no relevant animal data; human data suggest risk in first and third trimesters; human data suggest risk in second and third trimesters; human data suggest risk in third trimester; human and animal data suggest risk.

Hale Lactation Guidelines (Hale TW. Medications and mother's milk, 15th ed. 2012).

L1 – Safest, L2 – Safer, L3 – Moderately safe; give only if potential benefit justifies the potential risk to the infant; new medications are automatically placed in this category regardless of how safe they may be, L4 – Possibly hazardous, L5 – Contraindicated.

azithromycin. Azithromycin is also less frequently associated with gastrointestinal side effects. Numerous studies have showed azithromycin being at least as effective as doxycycline and tetracycline in non-pregnant patients (16,17). Azithromycin is Hale classification system L2.

Erythromycin base is another macrolide antibiotic considered safe for use in pregnancy. Erythromycin base is Hale classification system L3. Note that erythromycin estolate is not recommended in pregnancy because of potential risk of reversible hepatotoxicity in 10% of patients. Erythromycin is commonly formulated as an ester pro-drug known as erythromycin ethylsuccinate. This formulation has been associated with atrial and ventricular septal defects, and pyloric stenosis, when used during the first trimester, which is why it is considered second-line therapy. Notably, in one study there was a strong positive correlation between the use of erythromycin in breast-feeding mothers and development of infantile hypertrophic pyloric stenosis, and avoidance in mothers who are breast-feeding newborns is recommended (18). Side effects of erythromycin include gastrointestinal upset; it can also increase serum levels of medications metabolized by cytochrome p450 enzymes.

Oral clindamycin is also considered to be safe for use in pregnancy, and is third-line for oral antibiotic treatment after the macrolide antibiotics and penicillins/cephalosporins. While clindamycin is well tolerated, one serious potential side effect includes pseudomembranous colitis. Oral clindamycin is Hale classification system L2.

There are a number of oral antibiotics commonly used for the treatment in acne that are generally not recommended in pregnancy; however, careful review indicates that their use – in very special circumstances – may be possible. Tetracycline antibiotics (i.e., tetracycline, doxycycline, minocycline) are broad-spectrum antibiotics with bacteriostatic activity, which cross the placenta and bind strongly to calcium ions. After the 16th week of pregnancy, these can result in deciduous teeth discoloration and bone growth inhibition (19). No increased risk of congenital malformations was found in a study examining the inadvertent first-trimester use of tetracyclines (19). In two cohort studies examining tetracycline use in the first trimester, ( $n = 274$ ) there was no increased incidence of malformations (20). The recommendation is that tetracyclines are contraindicated beyond the 15th week of pregnancy, but can be considered for use during the first trimester.

Tetracyclines are generally considered safe in lactation. The tetracycline class of antibiotics are

excreted in extremely small levels into breast milk, and they bind to milk calcium, so short-term exposure of less than 3 weeks is safe. Tetracycline specifically binds calcium salts stronger than minocycline and doxycycline so it is absorbed by the infant the least and is therefore the drug of choice in this class. However, tetracycline should not be used long term in breast-feeding patients because the absorption of even small amounts over a prolonged period of time could result in dental staining. Oral tetracyclines are Hale classification L2–L4.

Sulfonamides are another class of antibiotics that inhibit bacterial metabolism and have bacteriostatic properties. They cross the placenta, but overall are not associated with increased incidence of congenital malformations (19). Trimethoprim has been associated with cleft palate in rat studies, but there is no strong evidence for teratogenicity in humans (19). However, there is ongoing concern about using this folic acid antagonist and potential increased risk of congenital malformations; there is a recommendation for folic acid supplementation when using trimethoprim in the first trimester (19). Because trimethoprim may interfere with folate metabolism, its long-term use for acne treatment should be avoided in breast-feeding mothers, or the infant should be supplemented with folic acid. Sulfonamides can increase risk of hyperbilirubinemia when used in the perinatal period so use during the late third trimester is not recommended (19). Regarding breast-feeding, sulfamethoxazole should be used with caution in mothers of weakened or premature infants, neonates with hyperbilirubinemia or infants with glucose-6-phosphate deficiency. Sulfonamides and trimethoprim are generally considered safe during pregnancy. Sulfonamides are Hale classification L3 and trimethoprim is classified as L2.

## Spirolactone

Spirolactone, an anti-androgen medication that inhibits 5-alpha reductase, can be particularly useful in the treatment of hormonal acne. However, this medication should not be used during pregnancy because it is FDA pregnancy category D and may increase the risk of hypospadias and feminization of a male fetus. It is Hale classification system L2. It is notable that the half-life of spiro lactone is 1–2 hours, but its anti-androgenic metabolites including canrenone, 7- $\alpha$ -methylthiospirolactone and 6- $\beta$ -hydroxy-7- $\alpha$ -methylthiospirolactone have half-lives up

to 20 hours. There is not a consensus regarding a washout period for spironolactone, but a reasonable recommendation is a one-month period.

### Topical treatments for acne

Topical agents offer an important therapeutic strategy for the management of acne in pregnant and breast-feeding women. When monotherapy is not sufficient, a more complex regimen incorporating several agents may be possible working in alliance with a highly motivated, safety-conscious patient. These agents are summarized in Table 2.

### Topical retinoids

Common topical retinoids are typically recommended as agents to avoid during pregnancy. Adapalene and tretinoin cream are FDA pregnancy category C and tazarotene is pregnancy category X. Topical tretinoin is Hale classification system L3. Tazarotene should be avoided because of teratogenic potential; while it is thought to have minimal systemic absorption into the circulation, when applied topically to rats during gestation, tazarotene was associated with reduced skeletal ossification, reduced fetal weights, spina bifida, hydrocephaly, and cardiac anomalies (19).

However, the safety data regarding adapalene and tretinoin are limited and less clear. Published case reports have described infants exposed in utero to topical tretinoin who have exhibited structural abnormalities that are consistent with retinoid embryopathy, specifically ear, cerebral, and cardiac malformations (21–25). Other studies have not shown a significantly increased risk associated with topical tretinoin (26,27). In one retrospective case control study of 234 patients, pregnant women exposed to topical retinoids in the first trimester (including adapalene, tretinoin, tazarotene, and retinol) were studied (28). No significant difference was found between the groups regarding the rate of spontaneous abortion, minor nor major birth defects; no children were born with retinoid embryopathy (28). However, study authors concluded that topical retinoids could not be safely recommended for use during pregnancy because of the inferred risk based on safety data associated with systemic retinoid medications. Expert opinion continues to recommend against using topical retinoids during pregnancy.

### Topical antibiotics

Numerous topical antimicrobial agents may be safely used for the treatment of acne in pregnancy. These include clindamycin, erythromycin, azelaic acid, sulfacetamide, metronidazole, and benzoyl peroxide; while there are minimal data regarding the use of these agents in pregnancy, there are no known fetal effects. In general, if a systemic antibiotic is considered safe in pregnancy, its topical formulation is also deemed safe (29). Whereas topical agents are often added to oral antibiotics because of synergistic effects (30), topical agents may comprise a reasonable and safe therapeutic strategy for pregnant patients with acne.

Topical erythromycin, clindamycin phosphate, and metronidazole are all considered safe for use in pregnancy and lactation. Clindamycin is effective against gram-positive cocci such as staphylococcus and streptococcus, anaerobic gram-negative bacteria and is thought to decrease levels of *P. acnes* in addition to possessing anti-inflammatory properties. While it is generally well-tolerated, topical clindamycin has rarely been reported to cause pseudomembranous colitis secondary to *Clostridium difficile* (31). Topical metronidazole gel is minimally absorbed and inhibits the release of neutrophil reactive oxygen species and can help reduce inflammatory lesions (32). Topical clindamycin is Hale classification system L2, metronidazole is classified as L3 and topical erythromycin is Hale classification L3.

### Other anti-microbial and anti-inflammatory agents

Benzoyl peroxide is a commonly used topical agent in the treatment of acne. With skin absorption of approximately 5%, use on limited areas for acne treatment in pregnant patients is now generally recognized as safe (29). Adverse effects include contact sensitization and skin irritation. Benzoyl peroxide is metabolized to benzoic acid within the skin and subsequently excreted in urine unchanged (29). When using oral antibiotics, the concurrent use of benzoyl peroxide can minimize the emergence of bacterial resistance (5). As a lipophilic molecule, it penetrates the pilosebaceous unit, leading to oxidation of proteins in bacterial cell membranes and bactericidal effects against *P. acnes* (33). All available efficacy data, however, stem from studies in non-pregnant patients. It is notably synergistic with erythromycin and clindamycin because when combined, benzoyl peroxide radicals are

**Table 2.** Topical agents for acne vulgaris in pregnancy and lactation

Topical agent	FDA category	Briggs classification	Hale system	Use in pregnancy	Dosing regimen
Erythromycin topical (solution, gel or pledgets formulations)	B	Compatible	L3	Considered safe	Twice daily
1% clindamycin phosphate (solution, gel or pledgets formulation)	B	Compatible	L2	Considered safe	Twice daily
0.75% or 0.1% metronidazole (gel or cream formulations)	B	No data	L3	Considered safe	Once to twice daily
Benzoyl peroxide 5% gel, benzoyl peroxide 5% wash	C	No data	L2	Skin absorption of 5%, can be used on limited areas	Twice daily
Combination benzoyl peroxide 5% gel with clindamycin 1%	B and C	No data for benzoyl peroxide	L2	Skin absorption of 5% for benzoyl peroxide gel, can be used on limited areas	Twice daily
Azeleic acid 20% cream	B	No data	L3	Skin absorption of 4–8%, considered safe for use	Twice daily
10% sulfacetamide compounded with 5% sulfur gel, cleanser, lotion, cream; 10% sulfacetamide available alone	C	No data	L2 (for sulfacetamide)	Minimal data, unclear data regarding safety in pregnancy	Once to twice daily
Topical glycolic acid and salicylic acid	No FDA classification	considered safe for use in pregnancy when used topically			Once to twice daily
Hydroquinone cream	C	Not recommended for use in pregnancy			N/A
Topical retinoid agents adapalene, tretinoin, tazarotene, retinol	C	Not recommended for use in pregnancy			N/A

FDA. Food and Drugs Administration.

increased (33). Combination treatment with clindamycin/benzoyl peroxide has been shown to be more effective than using either benzoyl peroxide or clindamycin topically alone, resulting in 61% reduction of inflammatory lesions after 3 months as compared with 39% and 35% (34). Topical benzoyl peroxide is Hale classification L2.

Azeleic acid is a topical agent with some activity against both inflammatory lesions and non-inflammatory comedones. It is a dicarboxylic acid that inhibits melanin synthesis and can effectively treat post-inflammatory hyperpigmentation associated with acne (35). It is both antioxidant and anti-inflammatory, and can help inhibit release of reactive oxygen species from neutrophils. Azeleic acid is thought to be absorbed by skin at a rate of about 4–8% (36). It is generally tolerated well; rare side effects include burning and pruritus. Azeleic acid is Hale classification system L3.

There are numerous formulations of topical sulfacetamide with sulfur compounds. It is not clear whether sulfacetamide can be used in pregnant women, as there are minimal data regarding safety during pregnancy. Sulfacetamide can inhibit bacterial growth via inhibition of dihydropteroate synthetase, with additional anti-inflammatory action from additional sulfur compounds (5). Elemental sulfur, typically compounded in cream or ointment form, is considered safe in pregnancy; it is Hale classification L2.

## Keratolytics and other topical agents

Hydroquinone cream, used in the treatment of post-inflammatory pigment change, is FDA pregnancy category C. Because there is 35–45% systemic absorption of topical hydroquinone and available safety data are limited, the general consensus is that it should be avoided during pregnancy (36). Hydroquinone is Hale classification system L3.

Other topical agents often used in the treatment of acne include keratolytic agents such as glycolic acid and salicylic acid. Topical salicylic acid is in many over-the-counter products. While studies have not shown increased risk of congenital malformations with women taking acetylsalicylic acid (aspirin) during pregnancy, no studies have assessed the safety of topical salicylic acid in pregnancy (37). It is generally advised that systemic absorption through the skin is so minimal that topical salicylic acid is unlikely to pose a risk in utero (37). Similarly, glycolic acid is an alpha-hydroxy acid that may be effective for acne treat-

ment. While animal studies have demonstrated adverse reproductive effects when using high-potency formulations, topical glycolic acid is thought to have minimal systemic absorption and is considered safe for use during pregnancy (although no FDA safety rating or Hale rating has been assigned) (37).

## Phototherapy and lasers

The use of narrowband-ultraviolet B phototherapy (NBUVB) has been reported as a treatment for acne in pregnancy, presumably through local immunosuppressive effects on skin. UV irradiation is postulated to stimulate Th2-derived cytokines which may down-regulate IL-1-alpha and lead to improvement of acneiform lesions; it may also have an antimicrobial effect against *P. acnes* (38). In one case report, a woman who was 5 months pregnant with new onset acne vulgaris was treated with escalating doses of NBUVB phototherapy three times weekly for 2 months, eventually leading to resolution of most of her inflammatory papules and pustules (38). It is not known how long she had disease remission upon treatment discontinuation. NBUVB is not known to have teratogenic effects and is considered safe in pregnancy.

Photodynamic therapy (PDT) is another treatment for acne, whereby a photosensitizer such as aminolevulinic acid (ALA) is used topically followed by intense pulsed light treatment. PDT is thought to lead to a reduction in size and function of sebaceous glands, as well as destruction of bacteria. In several studies, topical ALA with PDT was showed clinical improvement with fewer clinically inflammatory acne lesions (39,40). However, it is unclear whether PDT with photosensitizing agents can be safely used during pregnancy. ALA is FDA pregnancy category C, and thus is not considered safe in pregnancy. However, use of the blue or red light source alone (without a photosensitizing agent) may be an effective treatment for acne vulgaris is based on the observation that *P. acnes* naturally produces porphyrins such as coproporphyrin III and these have cytotoxic effects leading to further inflammation (41). Intense-pulsed light alone has been shown to reduce the number of inflammatory acne lesions although is less effective compared with when used with a photosensitizing agent (41,42).

Laser may also provide an important option for skin-directed therapy in acne in this patient population. Neodymium-doped yttrium aluminum garnet laser and pulse-dye laser treatment has also



**Table 3.** Alternative treatment options

Treatment option	Dosing regimen used	Comment
NUVB	Three times a week	Has been used in pregnancy (one case)
Nd : YAG laser, QS-Nd : YAG	Three sessions, 2-week intervals between treatments	Can work for both inflammatory and non-inflammatory lesions
Pulse-dye laser	One treatment with 12-week follow-up	Effective for inflammatory lesions as well as scars
Photodynamic therapy with aminolevulinic acid	One treatment or three sessions, 1-week interval between treatments	Minimal data regarding ALA use, unclear data regarding safety in pregnancy

ALA, aminolevulinic acid; NBUVB, narrowband ultraviolet B; Nd : YAG, neodymium-doped yttrium aluminum garnet laser.

been effectively used in the treatment of acne vulgaris (43) by reducing lesion counts, sebum production, inflammatory cytokines and thickness of the perifollicular stratum corneum (43,44). Side effects included transient erythema, purpura, xerosis, and desquamation (43,44). Laser treatment may thus be an option for patients who are pregnant given its excellent safety profile; however, it is important to note that no studies of laser have been published reporting safety or efficacy in pregnant cohorts.

Although all of these forms of light and laser treatments are not contraindicated during pregnancy, there should be mention regarding their effect on folic acid levels. There is now evidence that patients with high cumulative NBUVB doses (for instance patients who receive frequent treatments for psoriasis) have a decrease in serum folic acid levels (45). It is especially important to consider this for patients who are trying to conceive or are pregnant, who would need appropriate folic acid supplementation in order to prevent neural tube defects. In order to determine the amount of folic acid supplementation (usually 0.5 mg/day during pregnancy) dermatologists may need to check folate levels and consult with an obstetrician, in order to provide appropriate supplementation (29). These alternative treatment options are shown in Table 3.

## Conclusion

The treatment of acne in pregnancy is complex, as safety data are notably inconsistent and data regarding efficacy in pregnancy is entirely lacking. However, careful consideration of the available data highlights many potentially safe and effective treatment options. Consideration of the fetal stage of development, trimester-specific safety profiles of potential treatment options, and the severity of

disease are essential. Regarding mild and moderate disease, patients can be treated with topical agents including antimicrobial and anti-inflammatory agents, as well as topical glycolic acid and/or salicylic acid. For severe acne in the pregnant patient, a topical regimen in addition to an oral antibiotic such as a penicillin, cephalosporin, erythromycin/macrolide agent, or clindamycin can be recommended; if the patient fails systemic antibiotic therapy then there can be consideration of adjunct phototherapy or laser treatments. Thoughtful selection of a treatment plan, aligned with the patient's individual preferences, and frequent clinical follow-up will likely serve as the foundation of a satisfying therapeutic strategy for the management of acne during pregnancy.

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