



Case Report

Management of severe acne during pregnancy: A case report and review of the literature^{☆,☆☆}

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ABSTRACT

The treatment of acne during pregnancy is often limited by the potential toxicities that are posed to the fetus by the most common and effective acne therapies. As with all dermatoses during pregnancy, the treatment of acne vulgaris in this population requires a thorough understanding of the risks and benefits that are inherent to each treatment. We report on a case of a 30-year-old pregnant patient with severe acne conglobata who showed significant improvement with a combination treatment of topical modalities, oral metronidazole, and low dose prednisone during pregnancy. We also review the literature and present an approach for the care of these patients.

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Introduction

Acne vulgaris has long been one of the most common reasons for a visit to the dermatologist. Acne affects more than 80% of young adults worldwide and can be found in individuals of all ethnicities and nationalities (Bhate and Williams, 2013; Lynn et al., 2016). Although the general public often considers acne a condition that affects teenagers, studies have shown that a substantial number of pregnant and non-pregnant women in their late 20s and early 30s suffer from acne vulgaris (Collier et al., 2008; Dréno et al., 2014). Acne shows a predominance for female persons through all decades of adult life (Collier et al., 2008) and a recent French survey found that more than 40% of patients of a dermatologist's office who are pregnant presented with acne. The majority of these patients had experienced some degree of acne prior to their pregnancy (Dréno et al., 2014). The mechanisms by which pregnancy alters the course of acne are not well understood. Although some patients experience improvements or no change in their acne status during pregnancy, a substantial number suffer acne flare ups during this time. Women who experience acne exacerbations during

pregnancy may be at a higher risk for similar flare ups during future pregnancies (Dréno et al., 2014).

Although sometimes dismissed as a wholly cosmetic complaint, studies show that acne significantly impacts the quality of life and social functioning of patients and may increase the risk of depression and suicidal ideation (Halvorsen et al., 2011; Pagliarello et al., 2015; Ramrakha et al., 2016; Ritvo et al., 2011; Vilar et al., 2015; Wen et al., 2014; Yang et al., 2014). The treatment of acne vulgaris can be separated into topical, oral, and physical-based treatments and a wide variety of tools are available to combat acne. However, this repertoire shrinks when a dermatologist faces acne during pregnancy. The potential risks to the developing fetus may significantly limit the available treatment options. The dermatologist must carefully weigh the severity and psychosocial impact of an individual's acne against short- and long-term adverse effects. In this paper, we present a rare case of severe acne conglobata that was successfully controlled during pregnancy and review the multiple modalities that are available to treat patients with acne during pregnancy.

Case report

A 30-year-old primigravid patient at 14 weeks of gestation presented to the dermatology clinic with a chief complaint of severe painful acne. She had previously developed acne vulgaris as a young adult and previously experienced moderate success when treated with minocycline, adapalene, and various oral contraceptive

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Fig. 1. At 14 weeks of gestation: Initial presentation revealed inflammatory nodules and cysts that coalesced into edematous plaques

medications. The patient discontinued all treatment shortly before conception and experienced a significant acne flare up over the past 6 to 7 weeks prior to her initial presentation. Prior to her first visit

with our clinic, an outside dermatologist attempted treatment with sequential courses of oral amoxicillin, cephalexin, and erythromycin with no improvement. The patient was taking oral erythromycin at the time of her presentation to our clinic. A physical examination revealed large inflammatory papules that coalesced into edematous plaques and tender draining nodules that were symmetrically distributed primarily over her central and lower areas of the face (Fig. 1) with lesser involvement on her posterior shoulders.

To formulate our initial diagnosis and treatment plan, both acne conglobata and pyoderma faciale were considered. Although clinically the patient showed several features of pyoderma faciale (i.e., her particular facial distribution, lack of comedones, and demographics), her overall picture was more consistent with acne conglobata. Patients with pyoderma faciale typically have no preceding history of acne vulgaris (Mantovani et al., 2016; Plewig, 1992) and lack truncal involvement. In Plewig et al.'s seminal paper (1992), the authors described trigger-induced flushing that is reminiscent of rosacea as a clear clinical sign of rosacea fulminans and noted that the condition occurs "in previously healthy women with unblemished skin." Our patient's long history of acne vulgaris, lack of trigger-induced flushing, and mild truncal involvement led us to favor a diagnosis of acne conglobata. However, we did feel that her prominent facial nodules and cysts on a background of erythema can certainly be found in patients with pyoderma faciale and acknowledge that our patient displayed features of both conditions.

Due to the patient's severe discomfort at the time of initial presentation and the refractory nature of her cystic acne, the patient was prescribed 40 mg prednisone daily after receiving clearance from her obstetrician. Treatment with erythromycin was continued at

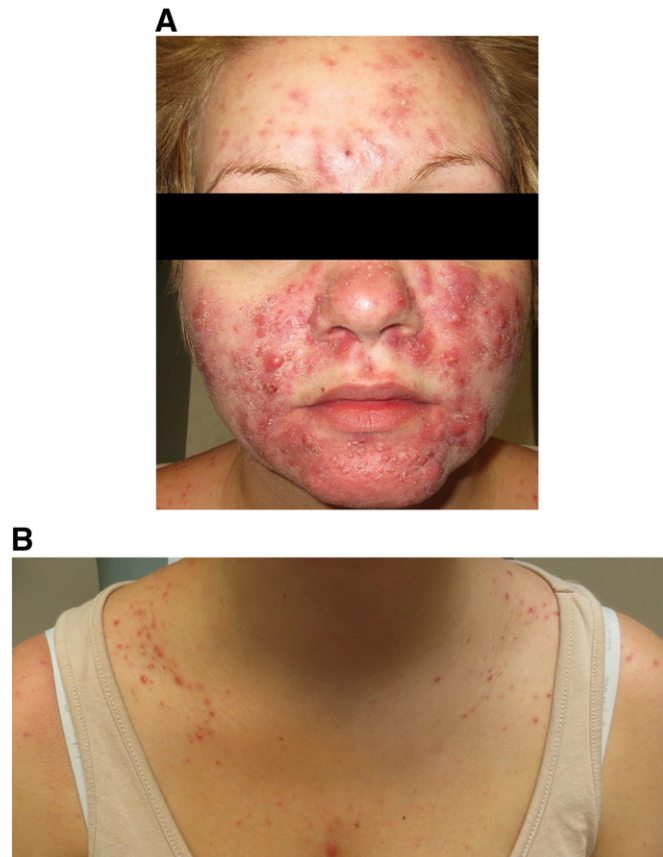


Fig. 2. A. At 20 weeks of gestation: Examination revealed modest improvement of inflammatory chin lesions but a wider distribution of nodulocystic acne on the cheeks and forehead B. Flaring of the patient's truncal acne, present at baseline but worsening likely secondary to treatment with prednisone



Fig. 3. At 34 weeks of gestation: After several weeks of oral metronidazole therapy in combination with low-dose prednisone and topical sulfacetamide and sulfur lotion, the patient exhibited a significant decrease in the number of inflammatory papules and plaques

250 mg twice daily. Within 2 weeks, the patient experienced significant relief and noted improvement of her acneiform lesions. However, at the time of her 6-week follow-up, the patient complained of worsening lesions on her nose, cheeks, scalp, and shoulders (Fig. 2A). Her flaring truncal component (Fig. 2B) was determined to be due in part to steroid-induced acne; thus, the erythromycin dose was doubled and prednisone decreased to 20 mg daily.

At 28 weeks of gestation, the patient showed no worsening but also no further improvement in her condition. Treatment with erythromycin was discontinued and replaced with oral metronidazole at 250 mg twice daily. A topical lotion of sodium sulfacetamide (10%) and sulfur (5%) was added as adjunct therapy. By the time of 34 weeks of gestation, the patient showed significant decreases in the number and sizes of her inflammatory lesions (Fig. 3). As her condition showed a striking improvement, a slow taper of the prednisone dose was initiated. The patient's acne control while treated with oral metronidazole remained satisfactory for the remainder of her pregnancy. She went on to have a successful delivery with no complications and remained content with her treatment regimen for several more months. Once she finished breastfeeding 3 months postdelivery, the patient returned to the clinic and initiated a course of isotretinoin with excellent results (Fig. 4).

Discussion

In late 2014, the U.S. Food and Drug Administration (FDA) first approved the Pregnancy and Lactation Labeling Rule (PLLR) as a replacement for the lettered pregnancy categories that had been used historically. Beginning in June 2015, the historical lettered categories assigned to each drug were eschewed in favor of more complete analyses of the risks and benefits of each newly approved medication. Under the new system, each recommendation contains a synopsis of the existing data during pregnancy and lactation. This summary may explain whether adverse effects were observed during animal studies or human cases, whether the drug in question crosses the



Fig. 4. Postdelivery: After 1 month of postdelivery isotretinoin therapy, examination revealed virtual clearance of all nodulocystic lesions

placenta or is secreted into breast milk, or whether a pregnancy registry exists for a particular drug. For the purposes of this overview and to facilitate the ease of communication, references to the old categories may be made. When faced with an individual, patient-based decision, we agree with the FDA's recommendation to move to a more nuanced discussion of the benefits and risks of a particular drug.

Treatment of mild-to-moderate acne typically begins with topical antibiotic medications. Topical clindamycin and erythromycin have been classified as a Category B treatment and have long been two of the most common first-line agents to treat patients with acne. Benzoyl peroxide has strong keratolytic, comedolytic, and antibacterial properties and although it is classified as Category C, the risk of congenital malformations is theoretically small and most experts agree on its safety during pregnancy (Chien et al., 2016; Pugashetti and Shinkai, 2013). Studies have shown that a combination of benzoyl peroxide and clindamycin is superior to each case individually and may decrease the risk of antibiotic resistance (Lookingbill et al., 1997). It should be noted that rare reports of *Clostridium difficile* have been seen with patients who were treated with topical clindamycin (Milstone, 1981; Parry, 1986) although it is unclear if this holds true clinical significance (Siegle et al., 1986).

Bacteriostatic azelaic acid exerts broad antimicrobial effects via an unknown mechanism and has a well-documented safety profile during pregnancy (Graupe et al., 1996). Azelaic acid shows benefits in the treatment of patients with acne vulgaris, rosacea, and perioral dermatitis, and thus is an excellent option for patients with a clinical overlap or imprecise presentation.

Because systemic retinoid medications are absolutely contraindicated during pregnancy, some researchers have extrapolated this caution to topical retinoid medications as well. Animal studies have shown an equivocal teratogenicity with supratherapeutic doses of topical tretinoin (Vahlquist, 2007) but no such potential risk with adapalene (FDA, 2016). Despite this, studies show that the systemic absorption of most topical retinoid medications is low (Wolverton, 2012). Although there are case reports of ear, eye, and central nervous system malformations that occur after topical retinoid use (Autret et al., 1997; Camera and Pregliasco, 1992; Lipson, 1993; Selcen et al., 2000), several later studies have shown no increased

risk to exposed fetuses (Jick et al., 1993; Loureiro et al., 2005; Panchaud et al., 2012). Given these discrepant results, the routine use of topical retinoid medications during pregnancy cannot be recommended at this time. It must also be mentioned that unlike tretinoin and adapalene, tazarotene historically has been classified as a Category X. Despite its low systemic absorption of 6% (Panchaud et al., 2012), experts agree on the complete avoidance during pregnancy at this time (Leachman and Reed, 2006; Wolverton, 2012).

Sodium sulfacetamide inhibits bacterial dihydropteroate synthetase and subsequently decreases folic acid formation. Despite this, no reports of congenital anomalies have been linked to sulfacetamide and the combination treatment of sulfacetamide and sulfur is not contraindicated during pregnancy (Leachman and Reed, 2006). Historically, sulfacetamide was classified as a Category C drug (Wolverton, 2012). Salicylic acid is a strong keratolytic agent with mild comedolytic effects. Although salicylic acid has rarely shown systemic toxicity when applied to broad swaths of erythrodermic or injured skin, it is deemed safe when used within a limited scope for short periods of time (Murase et al., 2014). Topical dapsone is relatively new and does not possess decades of safety data in support compared with other topical agents. No clear link to congenital malformations exists but its use is recommended only when the benefits clearly outweigh the risks (Chien et al., 2016).

Careful discussions between dermatologists and patient musts outline the impact of acne on the patient's psychosocial functioning. In general, mild-to-moderate acne is best treated with topical agents during pregnancy. However, given the impact severe acne may have on an individual's psychosocial status (Halvorsen et al., 2011; Tasoula et al., 2012), it would be inappropriate to dismiss oral treatments without careful consideration. Of the oral antibiotic medications, the beta-lactams are generally considered to be first-line agents. Penicillins and cephalosporins are compatible with pregnancy and show efficacy in the treatment of acne (Czeizel et al., 2001b; Fenner et al., 2008). Amoxicillin is an aminopenicillin and has shown good efficacy in the treatment of patients with acne (Turowski and James, 2007). Although certain reports do indicate an increased risk for cleft lip and palate after third-trimester exposure (Lin et al., 2012), amoxicillin has often been used during pregnancy for a variety of conditions and most studies support its safety (Czeizel et al., 2001a; Jepsen et al., 2003). Amoxicillin was historically classified as a pregnancy Category B drug.

Should beta-lactams fail, macrolides are generally recommended as the next indicated class of antibiotic medications (Czeizel et al., 1999; Lin et al., 2013). Erythromycin base or ethylsuccinate is recommended over erythromycin estolate due to the non-negligible risk of maternal hepatotoxicity (Czeizel et al., 1999). Studies indicate that azithromycin is effectively compatible with pregnancy as well (Fernandez-Obregon, 2000; Sarkar et al., 2006).

Tetracyclines, which are commonly used in the general population, are contraindicated after 15 weeks of gestation due to deposition in fetal teeth and bones with subsequent malformations (Murase et al., 2014). Trimethoprim use in the first trimester has been associated with an increased risk of spontaneous abortion (Andersen et al., 2012). Although the treatment is effective for acne (Turowski and James, 2007), it is generally recommended to avoid treatment with trimethoprim-sulfamethoxazole and tetracyclines during pregnancy unless the benefits clearly outweigh the risks. Fluoroquinolones have been associated with tendinopathy in animal and in vitro studies as well as through adverse event self-reporting databases (Bidell and Lodise, 2016). Although no clear fetal risk has been established, amounts of fluoroquinolones cross the placenta (Polachek et al., 2005). Given the chondrotoxicity in animal studies (von Keutz et al., 2004), avoidance during pregnancy is recommended by most experts due to the theoretical risk of fetal cartilage damage and the relative benignity of acne.

Oral metronidazole is rarely used to treat uncomplicated acne vulgaris but is used as a common treatment for perioral dermatitis. Metronidazole has an excellent record of safety during pregnancy and is frequently used as the treatment of choice for several common nondermatologic infections during pregnancy (Koss et al., 2012; Sheehy et al., 2015). When confronted with a patient who is resistant to standard oral antibiotic medications, our case shows that the selection of oral metronidazole may be a safe and reasonable next step.

Oral retinoid medications have a clear causal link to congenital malformations and are absolutely contraindicated during pregnancy (Ceviz et al., 2000; Rappaport and Knapp, 1989). Spironolactone is commonly used to treat adult acne due to its anti-androgenic effects. The treatment is contraindicated during pregnancy due to the risk of feminization of the male fetus (Rathnayake and Sinclair, 2010).

Oral prednisone may be linked to cases of cleft palate (Park-Wyllie et al., 2000) and high doses should generally be coordinated with an obstetrician. Our patient presented with a rare case of severe acne conglobata with severe impact on her daily life. In acne that is refractory to multiple modalities, prednisone may be used in low-to-moderate doses in controlled courses. However, safer alternatives exist and we do not advocate the routine use of corticosteroid medications during pregnancy unless the benefits clearly outweigh the risks.

In refractory cases, alternative methods of treatment may be considered. Narrowband ultraviolet B (NB-UVB) phototherapy has anti-inflammatory properties that have been shown to be effective in the treatment of acne during pregnancy (Zeichner, 2011). Although generally thought to have an excellent safety record during pregnancy, studies have shown a decrease in serum folate levels with as few as 18 sessions of NB-UVB (El-Saie et al., 2011). Short-term treatment during pregnancy is likely safe and the highest risk with folate deficiency occurs in the early stages of pregnancy. Still, experts recommend caution in patients with a prior history of UVB treatments and it may be wise to measure serum folate levels for patients who are trying to conceive or during the early stages of a pregnancy (Pugashetti and Shinkai, 2013). Pulsed dye (Seaton et al., 2003), potassium titanyl phosphate (Baugh and Kucaba, 2006), and neodymium-doped yttrium aluminum garnet (Jung et al., 2012) lasers have all shown efficacy for the treatment of acne in the general population. The shallow depth of penetration conceptually poses little risk to the fetus but the effects of a painful stimulus in the late stages of pregnancy are unclear. Although these lasers have an excellent overall safety profile in the general population, actual reports of use during pregnancy are limited and make it difficult to establish clear safety guidelines (Powell et al., 1994).

Conclusion

Acne vulgaris is one of the most common complaints for which dermatologists are consulted and may be exacerbated during pregnancy in a subset of patients. Topical antibiotic medications remain first-line agents for the treatment of patients with mild-to-moderate acne. For more severe cases, penicillins or cephalosporins are the most reasonable next step with macrolides as a second-line oral treatment option. Severe cases of nodulocystic acne or acne conglobata with severe psychosocial impact may require controlled courses of corticosteroid medications to ameliorate symptoms. Oral metronidazole represents a potential, alternative, third-line oral therapy that may be used, as our case illustrates, in combination with topical treatments and low doses of prednisone. Our case also shows a practical approach to the most refractory form of acne during pregnancy. When conventional treatments fail, the physician's goal may shift from treatment to controlling the disease severity until after delivery. As with all dermatoses during pregnancy, the clinician must carefully weigh the negative impact of a disease against the risks of a therapy before tailoring a treatment regimen for each individual patient.

Epilogue

Medicine is one of our oldest apprenticeships. It is a field passed from generation to generation through parchment and tomes, via touchscreen and slideshows, and – perhaps most significantly of all – from teacher to learner. Over time, methodologies have changed, theories transformed, but the field of medicine has retained one constant: the passing of knowledge from mentor to student. While many have practiced medicine, only a small subset has devoted itself to the education of trainee physicians. Fewer still have accomplished on the same rarefied level as Jane Grant-Kels.

While much can be written about Dr. Grant-Kels's awards and articles and advocacy for the field of dermatology, I, as a resident physician, choose to honor her contributions as educator. As both our department's founding chair and program director, Dr. Grant-Kels worked tirelessly to create something from nothing; she endeavored to select and nurture residents who in turn have gone on to mentor trainees of their own. She has created a department that is skilled and congenial and that shares her commitment to mentorship and education. To realize such a far-reaching vision requires immense sacrifice and a resolve that is rarely seen, but sorely needed in the field of medicine.

This apprentice, for one, is grateful.

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