Treatment of rosacea during pregnancy

Tamar Gomolin[1] MD, Abigail Cline[1] PhD MD, Frederick Pereira[1] MD

Affiliations: [1]Department of Dermatology, New York Medical College, New York, New York, USA

Corresponding Author: Abigail Cline PhD MD, Department of Dermatology, New York Medical College, 1901 1st Avenue, New York, NY 10029, Tel: 212-423-6511, Email: aecline25@gmail.com

Abstract

Background: Exacerbation of rosacea may occur during pregnancy and there are multiple associated cases of rosacea fulminans (RF). Treatment during pregnancy poses a significant challenge as many rosacea treatments are contraindicated or have limited evidence regarding potential adverse fetal effects.

Objective: Review the pregnancy categories of various treatments and develop algorithms for treating pregnant patients with rosacea and RF.

Methods: Rosacea treatments showing efficacy in randomized controlled trials were searched through DailyMed to review pregnancy labelling. Searching the PubMed/MEDLINE database for English articles using keywords "rosacea fulminans AND pregnancy" without publishing-time restrictions yielded 8 articles. We summarized treatments used in cases of RF during pregnancy.

Results: Topical ivermectin was more effective than metronidazole, but has a more concerning pregnancy category. Three pregnant women with RF were treated successfully with topical metronidazole in combination with other therapies. Azithromycin is the only oral rosacea therapy that is considered safe for pregnant patients and it has been used to treat RF.

Conclusions: This review highlights the challenging aspects of treating pregnant patients with rosacea, as there is limited pregnancy-related treatment efficacy and safety data. The pregnancy categories of therapeutic options are summarized. Further studies are needed to learn which therapies are effective and safe for use during pregnancy.

Keywords: pregnancy, rosacea, therapeutics

Introduction

Rosacea is a common inflammatory skin disease that is difficult to manage because of its unknown etiology and variable manifestations [1]. Proposed contributing factors include abnormalities in innate immunity, inflammatory reactions, ultraviolet damage, vascular dysfunction, and hormone shifts [2]. Hormonal changes may increase cutaneous vascularity, seborrhea, and dermal edema, thus exacerbating rosacea [1]. These hormonal changes resemble those of pregnancy and may be related to eruption or exacerbation of rosacea during pregnancy [1]. Additionally, rosacea fulminans (RF), a rare and severe subtype of rosacea associated with poor obstetric outcomes, may develop during pregnancy [3]. There have been multiple reports of RF during pregnancy and in women taking oral contraceptives [4]. Accordingly, hormonal factors may be a trigger for RF in these cases [1].

Although many rosacea treatments are available, including topical, systemic, and laser and light-based therapies, treatment of rosacea during pregnancy poses a significant challenge. Randomized controlled trials (RCT) for treating rosacea in pregnant patients do not exist [5]. Some treatments are contraindicated during pregnancy or have limited evidence regarding fetal effects. Furthermore, the severity of RF makes it difficult to treat with conventional rosacea therapies. Systemic corticosteroids and isotretinoin are regarded as the mainstays of therapy for treating RF, but isotretinoin is absolutely contraindicated in pregnancy. Systemic use of corticosteroids is only justified if the benefits outweigh the risks of side effects such as intrauterine growth retardation, maternal diabetes mellitus, and

hypertension [4]. In situations where oral corticosteroids and isotretinoin are contraindicated, oral antibiotics could be considered along with topical therapy, with the caveat that antibiotics alone may not be sufficient [6].

This article reviews the literature regarding rosacea during pregnancy, particularly the safety of available treatment options. It also proposes treatment algorithms for treating pregnant patients with rosacea and rosacea fulminans.

Methods

All rosacea treatments showing efficacy in RCTs from the 2015 Cochrane review on rosacea interventions [7], regardless of level of evidence, were searched through DailyMed. DailyMed is a service provided by the National Library of Medicine and is the official provider of FDA label information. This source provides a standard, comprehensive, up-to-date, look-up and download resource of medication content and labeling found in medication package inserts [8]. Through DailyMed, the pregnancy categories of the treatments were reviewed.

Searching through the PubMed/MEDLINE database without publishing-time restrictions, we identified 11 articles using the keyword "rosacea fulminans AND pregnancy." Only articles in English were considered. There were no clinical trials of rosacea treatment during pregnancy but multiple case reports exist. We summarized treatments used in these cases.

Results

Topical therapies

Based on RCTs, the topical therapies effective for rosacea include azelaic acid, brimonidine, ivermectin, and metronidazole (Table 1). Of the topical therapies, brimonidine had the highest risk ratio based on participant and physician assessments of efficacy in treating erythema [9]. Furthermore, ivermectin was found to be slightly more effective than metronidazole in one RCT [10]. However, in pregnant women, it may be preferable to try other topical therapies first because of ivermectin's higher pregnancy risk category. All other topical therapies are category B, whereas ivermectin is a category C drug. This classification is based on systemic embryofetal studies done in mice, rats, and rabbits during the original New Drug Application in the 1990s by Merck; oral doses of ivermectin administered to pregnant animals during time of organogenesis led to various adverse maternal and fetal outcomes [11]. Maternal deaths, cleft palate, incomplete ossification, fetal weight decreases, abortions, and stillbirths occurred at higher doses in these animals [11].

Oral Therapies

Oral therapies that have shown efficacy in RCTs, include azithromycin, doxycycline, isotretinoin, and minocycline (Table 2). Doxycycline and minocycline, like other tetracycline-class antibiotics, can cause fetal harm when administered to pregnant women. The use of drugs of the tetracycline-class during pregnancy may cause permanent discoloration of the teeth and tooth enamel hypoplasia [12]. Results of animal studies indicate that tetracyclines cross the placenta, make their way into fetal tissues, and exert toxic effects on the developing fetus. One such manifestation of tetracycline embryotoxicity is retardation of skeletal development [12]. Isotretinoin is a known teratogen and absolutely contraindicated during pregnancy. Therefore, of these oral therapies, the only safe option for pregnant patients is azithromycin. Based on one study, azithromycin may be as effective as doxycycline [13]. Better quality studies are needed to confirm the efficacy of azithromycin in the treatment of rosacea as it appears to be safe for use during pregnancy.

Light-based therapies

Lasers and light-based therapies are used in the treatment of rosacea. In one RCT, pulsed dye laser (PDL) was more effective than neodymium yttrium-aluminium-garnet (Nd:YAG) laser and appeared to be as effective as intense pulsed light therapy [7].

In a review examining the safety of laser therapy during pregnancy, there was a case of severe acne in a woman at 6 weeks' gestation, who was treated with 10 weekly sessions of low-fluence 1,064-nm Nd:YAG laser using 400 to 800 pulses per session and standardized settings [14]. In this case, there was

complete clearance of active inflammatory lesions and no reported pregnancy-related complications [14].

Treatments used in cases of rosacea fulminans during pregnancy

We identified 11 articles using the keyword "rosacea fulminans AND pregnancy." We excluded three articles because they were not written in English. There were no clinical trials on rosacea treatment during pregnancy, but multiple case reports exist (**Table 3**).

The average age of the patients affected by RF during pregnancy was 30. The average week of pregnancy at diagnosis was 16 weeks in the seven patients in whom week of gestation was specified. One-third of patients were affected by RF during their first pregnancy, four of nine in their second, and two in their third or fourth pregnancy. Six of the nine pregnancies resulted in the births of healthy children, one pregnancy outcome was not described, one was terminated, and one resulted in intrauterine death. The most commonly used treatment was oral corticosteroids. Six of nine patients were treated with systemic corticosteroids, five with oral erythromycin, three with topical metronidazole, and three with fusidic acid cream.

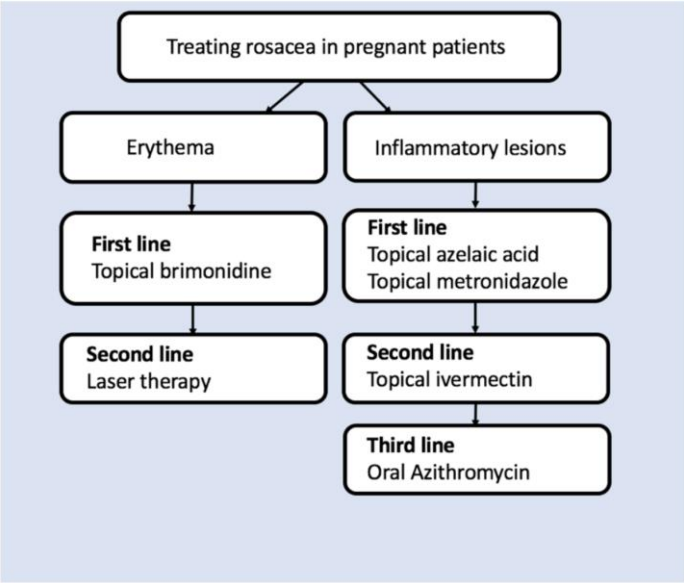

Figure 1. *Pregnancy treatment algorithm for rosacea. This algorithm provides an approach for the treatment of erythema and inflammatory lesions of rosacea in pregnancy, taking into consideration the efficacy and pregnancy categories of treatment options.*

Discussion

Pregnancy poses a significant challenge to the treatment of rosacea, as many of the therapies used to manage rosacea are contraindicated during pregnancy or have limited evidence regarding potential fetal effects. Furthermore, data suggests eruption or exacerbation of rosacea can occur during pregnancy. This article reviews the pregnancy categories of efficacious rosacea treatments, as well as treatments used in cases of RF occurring during pregnancy. It also proposes treatment algorithms for treating pregnant patients with rosacea (**Figure 1**) and rosacea fulminans (**Figure 2**).

The algorithm proposed for treating erythema of rosacea in pregnant patients begins with topical brimonidine because of its efficacy and relative safety as a category B drug. Laser therapy is probably a safe alternative, but further studies are warranted to evaluate its safety during pregnancy. To treat inflammatory lesions of rosacea during pregnancy, proposed first line agents include the category B topical therapies: azelaic acid and metronidazole, owing to their demonstrated efficacy in RCTs. A possible second line option is topical ivermectin, which has excellent efficacy, but higher pregnancy category. If systemic therapy is warranted, oral azithromycin, a category B drug, may be the best

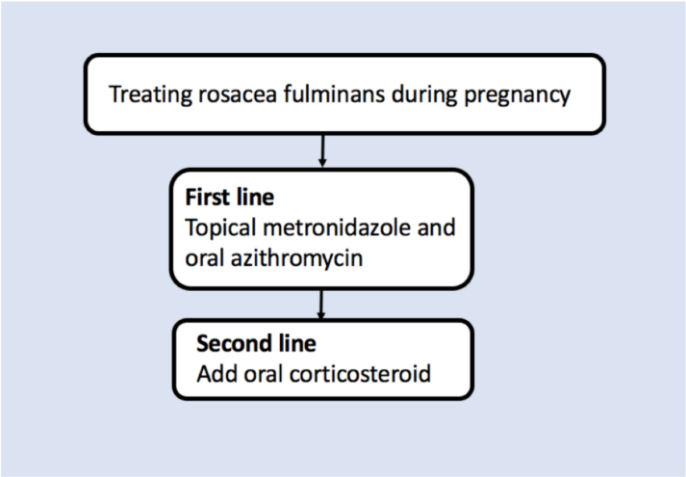

Figure 2. *Pregnancy treatment algorithm for rosacea fulminans. This algorithm proposes an approach for the treatment of rosacea fulminans in pregnancy, taking into consideration the efficacies of known rosacea treatments, pregnancy categories, and data from reported cases (randomized controlled trials on rosacea treatment during pregnancy do not exist).*

choice. However, better quality studies are needed to confirm its efficacy in the treatment of rosacea.

The algorithm proposed for treating RF in pregnant patients begins with the combination of a topical therapy and oral antibiotic. We chose topical metronidazole and oral azithromycin because of efficacy and category B classifications. In addition, both were used to treat RF during pregnancy and resulted in births of healthy children. When further therapy is needed, we propose adding an oral corticosteroid to the above regimen. It may be best to begin with the lowest category corticosteroid first, such as methylprednisolone, which is category C, over prednisone or prednisolone, which are both category D drugs.

Regarding oral therapies, only one study addressed treatment with azithromycin and better-quality studies are needed to confirm its comparative efficacy to doxycycline [7]. Furthermore, the evidence of efficacy for minocycline was based on low-quality evidence [7]. Although there is moderate-quality evidence that tetracycline is effective, this is based on two old studies of short duration [7].

Regarding non-pharmacologic therapies, more studies are needed to evaluate the safety of laser therapy during pregnancy. In the reviewed cases of RF, no light-based therapies were used. However, in a systematic review of the maternal and fetal effects of laser therapy during pregnancy, there is evidence that laser treatment during pregnancy with commonly used cutaneous lasers is safe for both mother and fetus [14].

With respect to surgical management of rosacea during pregnancy, one of the patients with RF underwent a corneal transplant [15] and another patient had lesions surgically drained [16]. When considering the timing of surgery in pregnant patients, most experts recommend performing non-emergent surgery in the second trimester or in the postpartum period to avoid the risk of preterm labor in the third trimester and spontaneous abortion in the first trimester [17]. Local destruction of lesions, commonly performed by dermatologists using laser ablation, cryotherapy, or the application of trichloroacetic acid, is safe to perform during pregnancy [17]. When local anesthetics are needed, category B drugs such as lidocaine and prilocaine are preferred during pregnancy as multiple studies have shown no adverse effects in the fetus [17]. The pregnancy categories of the antibiotics and pain control medications used during surgery should be reviewed as well.

Many of the therapies used in cases of RF during pregnancy have not been investigated as rosacea treatments in RCTs. In addition, some require further studies owing to biased study design. Topical clindamycin, topical erythromycin, and 5% permethrin lotion (all category B drugs) are some examples. Fusidic acid, a category C treatment was used in many of the cases. Furthermore, some of the oral antibiotics used in pregnant women with RF, such as amoxicillin-clavulanic acid and metronidazole, have no RCTs studying their efficacy in rosacea. Lastly, despite their pregnancy categories, corticosteroids have been used in pregnant patients with RF. When corticosteroid use is needed, it would be reasonable to begin with methylprednisolone, a category C drug, rather than with the category D drugs, prednisone or prednisolone.

A limitation of this paper is that the FDA has changed its prescription labelling and no longer uses the pregnancy letter categories—A, B, C, D and X, preferring descriptive narrative [18]. However, owing to simplicity and familiarity with these categories, we have included them in this paper. Additionally, the RCTs were mostly conducted on participants with certain subtypes of rosacea, whereas dermatologists are transitioning from a subtype-based approach to a phenotype-based approach [19]. Therefore, many rosacea patients were likely excluded from these studies. Many studies also excluded patients requiring antibiotics or corticosteroids. In addition, RCT studies did not include pregnant women or the rare variant of RF, thus highlighting the challenging aspect of treating pregnant patients. Lastly, this paper reviewed treatments used in cases of RF during pregnancy. In these women, many treatments were used simultaneously, therefore it is difficult to know which were effective. Further

studies on rosacea treatments are needed to determine which therapies are most effective, with special attention to treatments that can be used during pregnancy.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *Topical rosacea therapies.*

Treatment	Rosacea Indication	Dosing	Contraindications	Pregnancy Category	Efficacy*
Azelaic acid	Inflammatory papules and pustules of mild-to-moderate rosacea	Azelaic acid cream, 20% [20] Azelaic acid foam, 15% [21] Azelaic acid gel, 15% [22]	None	B	More effective than placebo (Risk ratio (RR) 1.46, 95% Confidence Interval (CI) 1.30 to 1.63) in data on participants' assessments from four trials [20, 21, 22].
Brimonidine	Persistent erythema of rosacea	Brimonidine tartrate gel, 0.5% [23]	History of hypersensitivity reaction to any component	B	More effective than vehicle in reducing erythema at all time points over 12 hours. At three hours the participants' assessments had a RR of 2.21 (95% CI 1.52 to 3.22) in favor of brimonidine, with data confirmed by physicians' assessments [23, 24]. More effective than vehicle in reducing erythema at all time points over 12 hours. At three hours the participants' assessments had a RR of 2.00 (95% CI 1.33 to 3.01) in favor of brimonidine, with data confirmed by physicians' assessments [23, 24].
Ivermectin	Inflammatory lesions of rosacea	Ivermectin cream, 1% [25]	None	C	Participant's assessments had a RR of 1.78 (95% CI 1.50 to 2.11), which were supported by physicians' assessments [25]. Participant's assessments had a RR of 1.92 (95% CI 1.59 to 2.32), which were supported by physicians' assessments [25].
Metronidazole	Inflammatory papules and pustules of rosacea	Metronidazole cream, 1% [26, 27, 28]	History of hypersensitivity to metronidazole, or other ingredients of the formulation	B	Pooled data from physician assessments in three trials demonstrated that metronidazole was more effective compared to placebo (RR of 1.98, 95% (CI) 1.29 to 3.02), [26,27,28].

Information on indications, contraindications and pregnancy categories taken from FDA label information from DailyMed [8].
*No RCTs conducted in pregnant patients.

Table 2. *Oral rosacea therapies.*

Treatment	Rosacea Indication	Dosing	Contraindication	Pregnancy Category	Efficacy*
Azithromycin	Non-FDA-approved treatment	500mg thrice weekly in the first, 250mg thrice weekly in the second, and 250mg twice weekly in the third month	Known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drug. History of cholestatic jaundice/hepatic dysfunction with prior use of azithromycin	B	Azithromycin may be as effective as 100mg doxycycline based on participant-assessed changes in rosacea severity: Although there was no measurable difference in change in severity between the two treatment groups, 29 out of 37 participants in the azithromycin group considered themselves improved versus 24 of 30 in the doxycycline group (RR 0.98, 95% CI 0.77 to 1.25), [13], but only one study addressed this treatment and better quality studies are needed to confirm [7]
Doxycycline	Inflammatory lesions (papules and pustules) of rosacea in adult patients	40mg once daily [29]	History of hypersensitivity to doxycycline or any of the other tetracyclines	D	Physician-based assessments in two trials indicated that 40mg doxycycline appeared to be significantly more effective than placebo (RR 1.59, 95% CI 1.02 to 2.47 and RR 2.37, 95% CI 1.12 to 4.99), [29] There was no statistically significant difference in effectiveness between 100mg and 40mg doxycycline, but there was evidence of fewer adverse effects with the lower dose (RR 0.25, 95% CI 0.11 to 0.54), [30]
Isotretinoin	Non-FDA-approved treatment	0.3mg/kg (significant superiority versus placebo and significant non-inferiority versus doxycycline [31])	Female patients who are or may become pregnant Hypersensitivity to this medication or to any of its components	X	Participants (RR 1.23, 95% CI 1.05 to 1.43) and physicians (RR 1.18, 95% CI 1.03 to 1.36) considered low dose isotretinoin to be slightly more effective than doxycycline 50-100mg based on high quality evidence [31]
Minocycline	Non-FDA-approved treatment	Minocycline	History of hypersensitivity to any of the tetracyclines	D	45mg minocycline was effective for papulopustular rosacea at reducing the number of pimples and pustules [32] based on low quality evidence [7]
(oxy)tetracycline	Non-FDA-approved treatment	250mg TID for 1 week, then BID in weeks 2-6 [33]	History of hypersensitivity to any of the tetracyclines	D	Moderate quality evidence that tetracycline was effective based on physician-assessed improvement in rosacea severity (RR 4.04, 95% CI 1.66 to 9.83; P=0.002), [33]

		250mg BID [34]			Moderate quality evidence that tetracycline was effective based on physician-assessed improvement in rosacea severity (RR 1.72, 95% CI 1.18 to 2.50; P=0.005), [34]

Information on indications, contraindications and pregnancy categories taken from FDA label information from DailyMed [8].
*No RCTs conducted in pregnant patients.

Table 3. *Treatments and pregnancy outcomes of rosacea fulminans during pregnancy.*

Reference	Year Published	Age of Patient	Time at Diagnosis	Treatment during pregnancy	Outcome
Garayar Cantero M et al. [35]	2020	28	13 weeks, second pregnancy	Mupirocin ointment, topical zinc oxide, topical erythromycin, oral erythromycin, metronidazole gel, oral metronidazole, and oral amoxicillin/clavulanic acid; oral metronidazole and reducing doses of prednisone, 5% permethrin cream	Normal spontaneous vaginal delivery at full term
Demir O et al. [1]	2018	22	10 weeks, first pregnancy	Amoxicillin-clavulanic acid 1 gr/day, wet compresses, and a fusidic acid cream	Pregnancy outcome not specified; Lesions disappeared with only mild erythema/flushing remaining and no telangiectasia
Markou AG et al. [36]	2017	37	37 weeks, fourth pregnancy	Artificial tears, cleansing of the eyelashes, oral prednisone, and azithromycin and paracetamol	Planned cesarean delivery at 38 weeks and three days. Birth of healthy girl weighing < 10th percentile; Improvement was seen in the immediate postpartum period and isotretinoin was started one month after delivery
Fuentelsaz V et al. [4]	2011	33	11 weeks, first pregnancy	Oral azithromycin with topical metronidazole; topical metronidazole and topical clindamycin, topical combination of fusidic acid and 0.1% betamethasone on one specific nodule	Normal spontaneous vaginal delivery at full term; By the sixth month of pregnancy, the patient had no skin lesions on her face
De Morais e Silva FA et al. [15]	2011	26	Week 21, second pregnancy	Oral prednisone and erythromycin; corneal transplant	Healthy child born via Cesarean delivery at 40 weeks; Steroid tapering following delivery
Jarrett R et al. [37]	2010	35	Discovered pregnancy at time of RF diagnosis, Second pregnancy	Oral prednisolone and erythromycin	Termination at 12 weeks gestation
		31	8 weeks gestation, third pregnancy	oral erythromycin	Pregnancy progressed uneventfully; Post-partum treatment with isotretinoin and prednisolone
Ferahbas A et al. [16]	2006	31	First trimester, second pregnancy	Oral methylprednisolone, wet compresses, fusidic acid cream; surgical drainage of some lesions; tapering corticosteroid dose; 0.75% metronidazole topical cream	Normal spontaneous vaginal delivery at full term; Lesions disappeared with only mild erythema/flushing remaining and no telangiectasia. After 1 year of follow-up, no relapse seen.
Lewis VJ et al. [38]	2004	28	12 weeks gestation, first pregnancy	Oral erythromycin and systemic prednisolone; tapering of steroid dose; maintenance steroids	Intrauterine death

Adapted from Jarrett et al. 2010 table on previous reported cases of rosacea fulminans associated with pregnancy [37].