Safety of Common Medications for Treating Dermatology Disorders in Pregnant Women

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Abstract Treating the pregnant woman poses challenges to the physician that requires balancing between eliminating or alleviating a condition or disease and ensuring no untoward effects on the mother and fetus. Despite the importance of the task, human studies are limited for obvious reasons, and animal studies do not fully resemble human physiology. Nevertheless, thanks to epidemiology studies and large-scale reviews of case reports on pregnant patients with comorbidities or refractory diseases that necessitate treatment with drugs of uncertain safety, data are accumulating on the safety of medications during pregnancy. This review summarizes the current literature on the safety during pregnancy of medications frequently used for common dermatologic diseases. The goal is to provide physicians with a handy database for when to, and when not to, prescribe those medications.

Keywords Pregnancy · Safety · Teratology · Contraindication · Evidence-based · Dermatology · Medication · Drug · Systemic · Biologic therapy · Immune-modifiers · Phototherapy

Introduction

One of the challenges physicians and dermatologists face is treating women with dermatologic conditions or diseases who are pregnant, planning to become pregnant, or sexually active and not using contraceptives. Teratogenic medications must be avoided in all of them. This review summarizes the current literature on the safety during (and before) pregnancy of

medications frequently prescribed for common dermatologic diseases. The goal is to provide dermatologists and physicians with a handy database to consult when confronted with such a patient. The data are based on a literature survey of animal studies and human cases. This article does not contain any studies with human or animal subjects performed by any of the authors.

Safety Categories of Medications During Pregnancy

The U.S. Food and Drug Administration (FDA) pregnancy and lactation categories are commonly referred to for the safety of medications during pregnancy (Tables 1 and 2). These categories do not cover breastfeeding risk. Because experimental medications cannot be tested on pregnant women, the categories are based on animal studies and epidemiologic data. According to the FDA chart: categories A and B are safe during pregnancy, C should be given only if the potential benefit justifies the potential risk to the fetus, and D should be given only in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective. Drugs from category X should be avoided in pregnant women, because the risks outweigh any possible benefit [1].

Corticosteroids

Topical corticosteroids are used as first-line treatment for a wide range of dermatoses, including psoriasis, atopic dermatitis, allergies, and polymorphic eruption of pregnancy (PEP) [2•]. Although listed in category C, the literature indicates that they are first-line therapy in inflammatory diseases during pregnancy [3]. Several studies of infants whose mothers were treated with topical corticosteroids during pregnancy found no increased risk of low birth weight, congenital anomalies, or preterm delivery

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Table 1 Food and Drug Administration (FDA) pregnancy and lactation categories

Category	Description
X	Contraindicated in pregnancy; there is no reason to risk use of drug in pregnancy
D	Positive evidence of risk to human fetus, but benefits may outweigh risks of drug
C	Risk cannot be ruled out; human studies have not been performed; animal studies may or may not show risk; potential benefits may justify potential risk
B	No risk to human fetus despite possible animal risk; or no risk in animal studies and human studies not done
A	Controlled studies show no fetal risk

[4]. However, there are case reports of low birth weight after large amounts of topical corticosteroid therapy [3]. Some studies reported a higher prevalence of cleft lip and palate when topical corticosteroids were used during pregnancy, whereas other studies found no such association [5, 6].

Systemic corticosteroids are not commonly used during pregnancy, except for bullous diseases, severe allergies, and specific dermatoses of pregnancy, such as pemphigoid gestationis [2•]. High-dose oral corticosteroid therapy during pregnancy was associated with intrauterine growth retardation, low birth weight infants, and inhibition of endogenous corticosteroid production, and several studies have documented a higher prevalence of orofacial clefts, although other studies found no such association [5, 6].

Anti-Fungal Agents

There is a higher prevalence of certain fungal infections during pregnancy, such as candida vaginitis, and a higher risk of a more virulent course for infections, such as coccidioidomycosis [7].

Azoles

Ketoconazole is indicated as topical treatment for superficial fungal infections, such as tinea pedis, due to dermatophytes. The drug was associated with teratogenic risk in animal studies when administered orally, and it is category C. Systemic ketoconazole was associated with androgen synthesis inhibition, increased risk of sexual ambiguity of male fetus, progesterone secretion impairment, and interference with early pregnancy and implantation; it should not be used during pregnancy. However, because the topical absorption is minimal, ketoconazole is generally considered safe as topical treatment [7].

Clotrimazole and Mycostatin are used topically against local fungal infections due to candida, such as oral thrush or vaginal candidiasis. Both are category B and safe during pregnancy [7]. Itraconazole and fluconazole were associated

with congenital malformations. Both are category C and should not be given during pregnancy [7].

Other Antifungal Agents

Terbinafine is commonly indicated as a systemic treatment for onychomycosis. It is category B, considered safe during pregnancy, and the treatment of choice for dermatophyte infection during pregnancy. However, the manufacturer recommends delaying the treatment of onychomycosis with oral terbinafine until after delivery [7].

Griseofulvin was associated with skeletal and central nerve system anomalies and fetal loss in animal studies. It is category C and should not be used during pregnancy [7].

Selenium sulfide is indicated for tinea versicolor. In animal studies, oral selenium sulfide was associated with carcinogenic risk, but when administered topically, there was no such association. It is category C [8].

Antibiotics

Miscellaneous Topical Antibiotics

Mupirocin is indicated as a topical treatment of localized bacterial infection, such as impetigo, folliculitis, and nose or perianal staphylococcal carriage. It is category B and is recommended for use during pregnancy [9].

Other topical treatments for impetigo and folliculitis are fusidic acid, gentamicin, and bacitracin. Data on their effect on pregnancy is meager, and they are classified as category C. There are, however, several reports on the use of topical fusidic acid and systemic gentamicin during pregnancy, with no untoward effects [10, 11].

Beta Lactamases

Penicillin is the treatment of choice for erysipelas and syphilis [12•, 13]. It is category B and is considered safe during pregnancy. When treating syphilis, it is important to keep in mind the Jarisch-Herxheimer reaction, which may appear 4–6 hours after initiation of the treatment. It is caused by release of treponemic antigens to the blood and is characterized by fever, headache, chills, and muscle pain. In pregnant patients, it may cause fetal death [12•]. Other beta lactamase antibiotics, such as cephalexin, cefazolin, cloxacillin, and amoxicillin/clavulanic acid, which are used to treat cellulitis, are all category B and safe during pregnancy [1].

Cephalosporins

Ceftriaxone is the first-line treatment for gonococcal urethritis. It is category B and safe during pregnancy [12•].

Table 2 FDA pregnancy safety category of common topical/systemic medications used in dermatology

FDA	T/S	Common indications	Generic name	Medication class
Corticosteroids				
C	T	Eczema, allergic reactions	Topical corticosteroids	
C	S	Bullous diseases, allergic reactions	Prednisone	
C	S	Allergic reactions	Hydrocortisone	
Antifungal agents				
B	S		Terbinafine	Allylamine
B	T		Clotrimazole	Imidazole
C	T		Miconazole	Imidazole
C	S		Griseofulvin	(Penicillium mold)
B	T		Mycostatin	Polyene
C	S		Ketoconazole	Triazole
C	T		Ketoconazole	Triazole
C	S		Itraconazole	Triazole
C	S		Fluconazole	Triazole
C	T		Selenium sulfide	
Antibiotics				
C	T	Impetigo, folliculitis	Gentamicin	Aminoglycoside
B	S	Cellulitis	Amoxicillin/clavulanic acid	β Lactam
B	S	Cellulitis	Cloxacillin	β Lactam
B	S	Erysipelas, syphilis	Penicillin	β Lactam
B	S	Cellulitis	Cefazolin	Cephalosporin
B	S	Gonococcal urethritis	Cefixime	Cephalosporin
B	S	Gonococcal urethritis	Ceftriaxone	Cephalosporin
B	S	Cellulitis	Cephalexin	Cephalosporin
C	S	Cellulitis	Ciprofloxacin	Fluoroquinolone
C	S	Nongonococcal urethritis	Ofloxacin	Fluoroquinolone
C	T	Impetigo, folliculitis	Fucidin	Fucidic Acid
B	S	Non gonococcal urethritis	Azithromycin	Macrolide
C	S	Atypical mycobacteria	Clarithromycin	Macrolide
B	T/S		Erythromycin	Macrolide
B	S		Roxithromycin	Macrolide
B	T	Impetigo, folliculitis	Mupirocin	Monoxycarboxylic acid
B	T/S	Acne, cellulitis	Clindamycin	Lincosamide
D	S	Nongonococcal urethritis	Doxycycline	Tetracycline
D	S	Acne	Minocycline	Tetracycline
C	T	Local infections	Bacitracin	
Antiviral agents and substances				
B	T/S	Herpes simplex / zoster	Acyclovir	Guanosine analogue
X	T	Viral warts	Fluorouracil	
C	T	Viral warts	Imiquimod	
Antiparasitic agents				
B	S	Leishmaniasis	Amphotericin B	Polyene
C	S	Norwegian scabies	Ivermectin	
-	T	Leishmaniasis	Paromomycin	
B	T	Scabies	Permethrin	
-	S	Leishmania	Sodium stibogluconate	
Immunosuppressants				
X	S	Psoriasis	Methotrexate	Antifolate
B	S	Psoriasis	Ustekinumab	(Bio.) Anti-IL12 and

Table 2 (continued)

FDA	T/S	Common indications	Generic name	Medication class
IL-23				
B	S	Psoriasis	Adalimumab	(Bio.) TNF inhibitor
B	S	Psoriasis	Etanercept	(Bio.) TNF inhibitor
B	S	Psoriasis	Infliximab	(Bio.) TNF inhibitor
C	T	Atopic dermatitis	Pimecrolimus, tacrolimus	Calcineurin inhibitors
C	S	Psoriasis	Cyclosporine	Calcineurin inhibitors
D	S	Pemphigus vulgaris	Cyclophosphamide	Oxazophorine
D	S	Pemphigus vulgaris	Azathioprine	Purine analogue
Antihistamines				
B	S	Allergic reactions, pruritus	Chlorpheniramine	First-generation
B	S	Allergic reactions, pruritus	Dimethindene	First-generation
C	S	Allergic reactions, pruritus	Promethazine	First-generation
C	S	Allergic reactions, pruritus	Desloratadine	Second-generation
C	S	Allergic reactions, pruritus	Fexofenadine	Second-generation
B	S	Allergic reactions, pruritus	Lorastine, loratadine	Second-generation
Retinoids				
C	T	Acne, rosacea	Adapalene	
X	S	Psoriasis, keratoderma	Acitretin	
D	S	Chronic hand eczema	Alitretinoin	
X	S	Acne	Isotretinoin	
C	T	Acne	Tretinoin	
Phototherapy associated medications and substances				
C	T	Psoriasis	Anthralin, dithranol	
C	T	Psoriasis	Coal tar	
D	S	Psoriasis	Methoxsalen, trioxsalen	Psoralens
Miscellaneous medications and substances				
C	S	Discoid lupus erythematosus	Hydroxychloroquine	Aminoquinoline
C	T	Keratolytic agent	Salicylic acid	NSAID
C	T	Psoriasis	Calcipotriol	Synthetic vitamin D
B	T	Acne, rosacea	Azelaic acid	Tyrosinase inhibitor
-	T	Local inflammation	Ammonium bituminosulfonate (Ichthyol)	
C	T	Acne, folliculitis	Benzoyl peroxide	
C	S	Bullous diseases	Dapsone	
C	T	Androgenic alopecia	Minoxidil	

Lincosamides

Clindamycin is a safe, category B, topical treatment for acne during pregnancy and an alternative safe systemic treatment for pregnant patients with cellulitis who are allergic to penicillin [12•].

Fluoroquinolones

Ciprofloxacin is suggested as a part of empiric antibiotic regimen therapy for moderate to severe infected diabetic foot [14]. It is category C, but a number of reviews and studies found no increased risk of preterm delivery, spontaneous

abortion, or major malformations with the drug, and the authors considered it safe during pregnancy [15–17]. An optional treatment for nongonococcal urethritis is ofloxacin [12•], but because it is category C, it is better to use macrolides (discussed below) for this condition during pregnancy.

Macrolides

Erythromycin, category B, is an alternative treatment for nongonococcal urethritis in pregnant women and for treating syphilis in pregnant women sensitive to penicillin [12•]. It may cure the mother of syphilis but not the infant. If the mother is an HIV carrier, the physician should be aware of

therapy failure [12•]. Erythromycin can be used safely as a topical treatment for acne [18].

Because it is a category B drug, erythromycin is considered safe during pregnancy, although some studies found an association between use of erythromycin early in pregnancy and cardiovascular malformations, and between prolonged use of erythromycin ethylsuccinate formulation and hepatotoxicity [12•]. Other studies found no such associations [19]. An alternative macrolide for later pregnancy is azithromycin, which also is category B and considered safe during pregnancy [12•, 20].

Clarithromycin, a category C drug, is indicated as a systemic treatment for skin infections due to atypical mycobacteria [21]. Recent animal studies and reviews of pregnant human patients who were treated with clarithromycin did not turn up a higher risk of congenital anomalies and malformations [16, 19]. Other studies, however, have documented a higher risk of miscarriage in patients treated with clarithromycin during early pregnancy [21].

Tetracyclines

Doxycycline, which is indicated for treatment of nongonococcal urethritis and Q fever, and minocycline, which is indicated for treatment of acne and rosacea, are category D and should not be used during pregnancy. Tetracyclines are associated with enamel hypoplasia and yellowish staining of the teeth in the second and third trimesters, and acute fatty liver of pregnancy in the third trimester. They were not associated with congenital anomalies when given in the first trimester [20].

Anti-Viral Agents

Acyclovir is indicated as a topical treatment for herpes simplex or as a systemic treatment for herpes zoster, genital herpes, or varicella. Acyclovir is extremely important as a treatment for seronegative pregnant patients who are infected with varicella, in order to lower the risk of congenital varicella syndrome [22]. It is category B and safe during pregnancy [12•, 23, 24].

Topical fluorouracil and imiquimod are indicated for treatment of viral warts. They are classified as category X and C, respectively, and should not be used during pregnancy. It is recommended to use physical methods to treat verruca, such as cryotherapy, during pregnancy [12•].

Antiparasitic Agents

The treatment of choice indicated for pregnant patients suffering from scabies is topical permethrin, which is category B and safe during pregnancy [22, 25]. Ivermectin is an off-label treatment for Norwegian scabies. Several studies included

pregnant patients treated with ivermectin, but data are insufficient to determine its safety [26]. Ivermectin is currently a category C drug and should not be used during pregnancy.

A formulation of paromomycin and methylbenzethonium chloride is a topical treatment indicated for cutaneous leishmaniasis. Data on its safety during pregnancy are inadequate, and it is not categorized [27].

Sodium stibogluconate is indicated as a treatment for leishmaniasis. Studies have included pregnant patients treated with the drug, but data are insufficient to determine its safety [28].

Liposomal amphotericin B is a broad spectrum antifungal, which is used in dermatology as a safe (category B) treatment for visceral leishmaniasis during pregnancy [7, 29, 30]. Although it crosses the placenta, animal studies did not demonstrate a teratogenic risk, and there are no reports of congenital anomalies in infants whose mothers were exposed to amphotericin B during pregnancy. The disadvantages of the drug are its side effects, which include nephrotoxicity and hypokalemia [7].

Immunosuppressants

Methotrexate, which is indicated for treatment of psoriasis, is category X and should not be used in pregnant women. Methotrexate is associated with an increased risk of miscarriage, micrognathia, developmental delays, craniosynostosis, small low-set ears, limb abnormalities, prenatal growth retardation, and mental retardation [3].

Pimecrolimus and tacrolimus, which are used topically to treat atopic dermatitis, are category C. There were reports of congenital anomalies, neonatal hyperkalemia, low birth weight, and premature delivery when pimecrolimus was given orally, but the complex medical background of the patients made the association unclear. There are no reports on women treated with topical pimecrolimus during pregnancy, but because the absorption of the medication is low, the risk of teratogenic effect when used topically and sparingly is probably low [3, 31•].

Cyclosporine is used in patients with severe psoriasis, especially the pustular and erythrodermic types [2•]. There are more than 800 reports of pregnant women treated with cyclosporine after kidney transplant, most of which were not associated with a higher rate of congenital anomalies than the general population. Some studies reported an increased incidence of prematurity and intrauterine growth retardation, but because the patients were mainly women with serious medical problems, undergoing kidney transplantation and being treated with several medications, the role of cyclosporine could not be determined. Cyclosporine is category C and is given to pregnant women when the benefits outweigh the potential risks [6, 31•]. The toxicities of cyclosporine, hypertension and nephrotoxicity, could complicate pregnancy [3].

Cyclophosphamide, a nitrogen mustard alkylating agent, is used as an adjuvant therapy for dermatoses, such as pemphigus

vulgaris, that are refractory to other treatments. It inhibits cell division and is teratogenic in animals and humans. It is category D and should be considered only if the benefits outweigh the risks. Some reviews consider it safe after the second trimester of pregnancy [6, 31•, 32].

Azathioprine, a purine analogue, is another adjuvant therapy. Some studies found an association between azathioprine and a higher risk of preterm deliveries, without a higher risk of congenital malformations [6]. It is classified as category D and should be considered only if the benefits outweigh the risks described [6, 31•, 33].

Biologic Immune Modifiers

These are indicated for treatment of moderate-to-severe plaque type psoriasis that is refractory to phototherapy and systemic treatments, or when other treatments are contraindicated; 40–60% of the patients with chronic psoriasis improve during pregnancy, but 10–20% experience worsening of the disease during pregnancy [34]. Most of the studies covered in our literature search were based on women with rheumatologic or gastrointestinal diseases, who were treated with immune modifiers during pregnancy.

The following immune modifiers are category B, but data on their effects during pregnancy are limited and conflicting [3]. Most of the cited studies examined antitumor necrosis factor alpha (TNF α). Although there were reports of congenital malformations and higher abortion rate [35] for infants born to patients treated with anti TNF α during pregnancy, it is important to emphasize that no specific pattern of congenital malformations was found in these studies. In addition, most of these patients had rheumatoid arthritis, which is associated with a higher risk of congenital anomalies or prematurity compared with the general population; some of the patients were treated with several teratogenic medications, such as methotrexate.

In general, pregnant patients with widespread psoriatic plaques should be treated with UVB (discussed below) or cyclosporine. When there are contraindications, side effects, or refractory disease, the physician should consider immune modifiers [34]. Current data suggest that the risk of congenital anomalies is relatively low, and the benefits may outweigh the risks for patients with severe disease refractory to other treatments [36•].

Etanercept is an anti-TNF α . A safety interval ranging from 3 weeks to 2 months is recommended between the last etanercept given and conception [37]. There are several reports of congenital malformations in infants born to pregnant women who had been treated with etanercept during their pregnancy. Several authors conclude that current data are insufficient to determine etanercept's safety, and it should be avoided during pregnancy [36•, 38].

Infliximab is a chimeric anti-TNF α . A safety interval of 2 to 6 months is recommended between the last infliximab

given and conception [37]. Some reviews report several congenital malformations and other complications in infants born to mothers treated with infliximab during pregnancy [36•], whereas other studies found no such association [6]. One study reported a higher rate of lower birth weight and prematurity, but it was not higher than the infants of pregnant patients with rheumatoid arthritis or Crohn's disease who were not treated with infliximab during pregnancy [3].

Transplacental transport of IgG antibodies increases during the second and third trimesters. According to a few studies, when infliximab was given during the third trimester, it was detected in the infant's blood [37, 39]. However, it did not predispose the infants to a higher risk of infections, with the exception of one report of disseminated mycobacterial infection in an infant whose mother was given infliximab during pregnancy and the infant received BCG vaccine at 3 months of age. If infliximab is administered to a pregnant patient, it should be given during the first 30 weeks of pregnancy and resumed after delivery. Vaccinations with live viruses should be postponed in these infants until they are at least 6 months old [34, 39].

Adalimumab is an anti-TNF α . A safety interval ranging from 2 to 5 months is recommended between the last adalimumab given and conception [37]. One review reported congenital malformations and other complications after adalimumab treatment during pregnancy [36•], whereas other studies reported no such association [6].

Ustekinumab is a human monoclonal anti-interleukin (IL)-12 and IL-23 antibody. There was a single report of an abortion in a pregnant woman receiving the drug [40]. Despite the comorbidities in this patient that included heavy smoking and psoriasis, which are associated with a higher risk of abortions [41], it is currently recommended to avoid ustekinumab during pregnancy and to avoid pregnancy for at least 15 weeks after treatment.

Antihistamines

Antihistamines are indicated for treatment of allergies and to alleviate pruritus, one of the major dermatologic symptoms during pregnancy. It may be caused by specific dermatoses of pregnancy, atopic dermatitis of pregnancy, and allergies. Approximately 20–30% of pregnant patients experience allergic reactions during pregnancy [42].

Chlorpheniramine, a first-generation antihistamine, category B, did not demonstrate any teratogenic risk in women or animal studies. It is regarded as first-line antihistamine treatment for pregnant patients who do not get relief with topical medications [42]. It is recommended as a treatment for dermatoses of pregnancy, such as mild pemphigoid gestationis, during the first trimester [2•]. The major side effects include sedation and anticholinergic effects, such as dry mouth,

blurred vision, constipation, and urinary retention, so patients are advised to drink more water during the treatment [42].

There are insufficient data on two other first generation antihistamines, promethazine and dimethindene. Promethazine is category C, whereas dimethindene is not categorized at all.

Previous studies have suggested that loratadine, a second-generation antihistamine, was associated with an increased risk of hypospadias, but more recent studies have found no such association and it is categorized as B. Loratadine is recommended as a treatment for dermatoses of pregnancy, such as mild pemphigoid gestationis, after the first trimester or for polymorphic eruption of pregnancy, if symptoms are not alleviated by topical treatment [2•]. Like all second-generation antihistamines, loratadine does not enter the central nerve system and is not sedating but might cause photosensitivity, tachycardia, and prolonged QT interval [42]. Fexofenadine and desloratadine, two other second generation antihistamines, are classified as category C.

Retinoids

The topical retinoids, tretinoin and adapalene, are indicated mainly for the treatment of inflammatory acne and rosacea. Several studies have suggested that these retinoids are teratogenic during the first trimester. Both are category C and should not be used during pregnancy [18].

Acitretin is systemic retinoid used to treat psoriasis. It is category X. The risk of fetal anomalies is 25 times higher than for the general population. It may cause microtia/anotia, micrognathia, cleft palate, conotruncal heart defects and aortic-arch abnormalities, thymic defects, retinal or optic-nerve abnormalities, and central nervous system malformations. Normally, total elimination of acitretin and its metabolites from the body takes up to 2 months. However, with alcohol consumption during treatment, acitretin is metabolized to etretinate, which has a half life of up to 168 days, and the teratogenic effect may hold up to 3 years. So, female patients should be advised not to drink alcohol during and at least 2 months after discontinuation of acitretin therapy and to use at least two kinds of contraception for 3 years after discontinuation of the drug [3].

Alitretinoin, category D, is a systemic retinoid indicated for chronic hand eczema. It is teratogenic and may cause fetal malformations [43]. Female patients in their child-bearing years are required to use at least two forms of contraception for at least 1 month before starting treatment, during treatment, and for at least 1 month after finishing treatment, and also are required to take monthly pregnancy tests [44].

Isotretinoin is a systemic retinoid prescribed for treating acne. It is category X and should not be used during pregnancy. During the first trimester, it may cause fetal loss, and later use may cause malformations, such as microtia, stenosis of the external ear canal, cleft palate, hydrocephalus, and cardiac

outflow tract defects. Female patients of child-bearing age who are sexually active should use two methods of birth control during and for 1 month after treatment [18].

Phototherapy-Associated Medications

Anthralin is a topical therapy for psoriasis used in the Ingram method, which combines topical anthralin with ultraviolet wave length B (UVB) phototherapy. There are no data on the effects of anthralin on human or animal pregnancies, and no evidence of anthralin's systemic absorption [3]. It is not categorized by the FDA.

Coal tar is combined with ultra UVB phototherapy in the Goeckerman method for treatment of psoriasis. Animal studies demonstrated teratogenic effects of the substance [3]. The only report in humans is a case of lethal anomaly in an infant whose mother was treated with coal tar during her pregnancy. Thus, the effects on pregnancy are not clear. It is listed as category C, although risk of anomalies during pregnancy is considered to be small if used for a short period of time [3].

Narrow band UVB is used alone or with coal tar or anthralin to treat miscellaneous dermatopathies. It is the first-line treatment for patients with extensive moderate psoriasis. UVB does not penetrate the skin and therefore is safe during pregnancy [45•, 46].

Psoralen increases skin reactivity to ultraviolet wavelength A (UVA) and can be administered orally (systemic PUVA), or topically (local PUVA), with UVA phototherapy. In turn, UVA enhances psoralen's ability to bond with DNA, which inhibits DNA synthesis and cell division and leads to cell injury and mutagenic effects in vitro.

Several studies on systemic PUVA during human pregnancy found no increased risk of congenital anomalies or malformations. There was, however, a higher rate of low birth weight, and animal studies reported an increased rate of fetal death, growth retardation, and congenital anomalies, making it a category D drug and not to be used during pregnancy [45•].

When psoralen is administered topically on small body surface areas, there is no evidence of systemic levels. In a study on local PUVA for the treatment of palmoplantar psoriasis, after the patients washed the psoralen off their hands and feet the drug was not detected in the blood [3].

Miscellaneous Medications

Hydroxychloroquine is an aminoquinoline, antimalaria medication used for dermatopathies, such as discoid lupus erythematosus. Although it is category C, several reviews and studies found no association between hydroxychloroquine and increased risk of congenital defects, spontaneous abortions, fetal death, prematurity, or decreased numbers of live births in

patients with autoimmune diseases and consider it a safe medication during pregnancy [20, 47].

Salicylic acid is a nonsteroidal anti-inflammatory drug (NSAID), used as a keratolytic medication, especially for psoriatic plaques. In addition, it improves the penetration of other topical medications. There are no studies on the effects of salicylic acid on human pregnancy, but other salicylates have been associated with human birth anomalies. For example, aspirin was associated with an increased risk of gastroschisis, hemostasis, and low birth weight; diclofenac, another NSAID, was associated with constriction of the ductus arteriosus. Therefore, salicylic acid is considered category C. If prescribed during pregnancy, the patient should be advised to use it for only a short period of time on small areas, with no occlusive dressings [3].

Calcipotriol is a synthetic vitamin D3 for treatment of local psoriasis. It can be used with betamethasone to lower its local irritation and increase its effectiveness. Animal studies demonstrated a higher risk of coronary anomalies and miscarriages when administered during pregnancy. Although it is suggested that local topical treatment would not increase teratogenic risk, there are no reports on humans, so it is classified as category C [3].

Azelaic acid is indicated for treatment of acne. It is category B and considered safe during pregnancy [48].

Ammonium bituminosulfonate (ichthammol) is produced from oil shell, an organic rich sedimentary rock. In the United States, it is approved only for veterinary use. Outside the United States, it is used as a “drawing salve” for a variety of inflammatory dermatoses, including psoriasis, leg ulcers, eczematous, and seborrheic dermatitis, with no evidence of a teratogenic risk [49, 50].

Benzoyl peroxide is a topical substance for treatment of acne. It reduces anaerobic bacteria by oxidation processes. Because it is category C, it is less recommended for pregnant patients with rosacea and acne, compared with topical azelaic acid or erythromycin, which are recommended for these patients [18].

Dapsone is indicated as an adjuvant therapy for treatment of severe pemphigoid gestationis. Dapsone is category C and should be considered only in severe refractory cases of pemphigoid gestationis during pregnancy. It is important to remember that patients with G6PD deficiency have a higher risk of developing severe dapsone hypersensitivity reaction [51].

Minoxidil is a topical treatment for androgenetic alopecia. Small studies report its safety during pregnancy, so it is listed as category C [52].

Conclusions

It is clear that more research is needed on the effects of dermatologic medications on the pregnant woman and her

fetus. While experimental studies on humans are out of the question, the data gleaned from the many case reports and reviews are helping to answer important life-and-death questions about drugs that physicians routinely prescribe for dermatology patients. Clinicians are urged to publish more articles on the safe use of drugs, as well as the harm unknowingly done by them. Only in this way can the medical community improve the safety of its practice and provide the best care to our patients without putting the pregnancy or the baby on board in jeopardy.

Compliance with Ethics Guidelines

Conflict of Interest Itay Malka declares no conflicts of interest. Michael Ziv declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Eric M, Sabo A. Teratogenicity of antibacterial agents. *Coll Antropol*. 2008;32(3):919–25.
2. • Roth M. Pregnancy dermatoses: diagnosis, management, and controversies. *Am J Clin Dermatol*. 2011;12(1):26–41. *This review analyzes the various pregnancy, while subsequently offering an algorithmic approach to their diagnosis and management.*
3. Lam J, Polifka JE, Dohil MA. Safety of dermatologic drugs used in pregnant patients with psoriasis and other inflammatory skin diseases. *J Am Acad Dermatol*. 2008;59(2):295–315.
4. Tauscher AE, Fleischer Jr AB, Phelps KC, Feldman SR. Psoriasis and pregnancy. *J Cutan Med Surg*. 2002;6(6):561–70.
5. Hviid A, Mølgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. *CMAJ*. 2011;183(7):796–804.
6. Østensen M, Forger F. How safe are anti-rheumatic drugs during pregnancy? *Curr Opin Pharmacol*. 2013;13(3):1–6.
7. Moudgal V, Sobel J. Antifungal drugs in pregnancy: a review. *Expert Opin Drug Saf*. 2003;2(5):475–83.
8. Selenium Sulfide. Report on Carcinogens, Twelfth Edition. 2011;376–77.
9. Tipton A, Cohen S, Chelmsow D. Wound infection in the obese pregnant woman. *Semin Perinatol*. 2011;35(6):345–9.
10. Wollenberg A, Degitz K. Herpetic eczema in pregnancy. *Dtsch Med Wochenschr*. 1995;120(41):1395–8.
11. Ward K, Theiler RN. Once-daily dosing of gentamicin in obstetrics and gynecology. *Clin Obstet Gynecol*. 2008;51(3):498–506.
12. • Carvalho M, Demarch EB, Azulay DR, et al. Sexually transmitted diseases during pregnancy: a synthesis of particularities. *An Bras Dermatol*. 2010;85(6):767–82. *This review explores features of the natural course and treatment during pregnancy of the major STDs: soft chancre, donovanosis, gonorrhea, chlamydia, viral hepatitis, genital herpes, human papillomavirus (HPV) infection, lymphogranuloma venereum, syphilis, and vulvovaginitis.*
13. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis*. 2005;41(10):1373–406.

14. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America Clinical Practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54(12):132–73.
15. Mottet C, Vader JP, Felley C, et al. Appropriate management of special situations in Crohn's disease (upper gastro-intestinal; extra-intestinal manifestations; drug safety during pregnancy and breastfeeding): Results of a multidisciplinary international expert panel—EPACT II. *J Crohns Colitis*. 2009;3(4):257–63.
16. Cassina M, Fabris L, Okolicsanyi L, et al. Therapy of inflammatory bowel diseases in pregnancy and lactation. *Expert Opin Drug Saf*. 2009;8(6):695–707.
17. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation; what is and is not known about teratogenic and toxic risks. *Am Coll Obstet Gynecol*. 2006;107(5):1120–38.
18. Kraft J, Freiman A. Management of acne. *CMAJ*. 2011;183(7):430–5.
19. Lin KJ, Mitchell AA, Yau WP, et al. Safety of macrolides during pregnancy. *Am J Obstet Gynecol*. 2013;208(3):221.e1–8.
20. Nosten F, McGready R, D'Alessandro U, et al. Antimalarial drugs in pregnancy: a review. *Curr Drug Safe*. 2006;1(1):1–15.
21. Andersen JT, Petersen M, Jimenez-Solem E, et al. Clarithromycin in early pregnancy and the risk of miscarriage and malformation: a register based nationwide cohort study. *Plos One*. 2013;8(1):1–6.
22. Müllegger RR, Glatz M. Skin infections in pregnancy. *Hautarzt*. 2010;61(12):1034–9.
23. Trizna Z. Viral Diseases of the skin: diagnosis and antiviral treatment. *Pediatr Drugs*. 2002;4(1):9–19.
24. Pasternak B, Hviid A. Use of acyclovir, valacyclovir, and famciclovir in the first trimester of pregnancy and the risk of birth defects. *JAMA*. 2010;304(8):859–66.
25. Mytton O, McGready R, Lee S, et al. Safety of benzyl benzoate lotion and permethrin in pregnancy: a retrospective matched cohort study. *BJOG*. 2007;114(5):582–7.
26. Ndyomugenyi R, Kabatereine N, Olsen A, Magnussen P. Efficacy of ivermectin and albendazole alone and in combination for treatment of soil-transmitted helminths in pregnancy and adverse events: a randomized open label controlled intervention trial in Masindi District, Western Uganda. *Am J Trop Med Hyg*. 2008;79(6):856–63.
27. Valesky EM, Thaçi D, Meissner M, et al. Cutaneous leishmaniasis: clinical report of two cases and review of the recent literature. *JDDG*. 2007;5(9):770–2.
28. Adam GK, Abdulla MA, Ahmed AA, Adam I. Maternal and perinatal outcomes of visceral leishmaniasis (kala-azar) treated with sodium stibogluconate in eastern Sudan. *Int J Gynecol Obstet*. 2009;107(3):208–10.
29. Mueller M, Balasegaram M, Koummuki Y, et al. A comparison of liposomal amphotericin B with sodium stibogluconate for the treatment of visceral leishmaniasis in pregnancy in Sudan. *J Antimicrob Chemother*. 2006;58(4):811–5.
30. Pagliano P, Carannante N, Rossi M, et al. Visceral leishmaniasis in pregnancy: a case series and a systematic review of the literature. *J Antimicrob Chemother*. 2005;55(2):229–33.
31. • Psenak O, Studnicka-Benke A, Greil R. Safety of immunosuppressants. *Z Rheumatol*. 2012;71(5):420–9. *Azathioprine, chloroquine, cyclosporin A, prednisolone, sulfasalazine, tacrolimus and cyclophosphamide (only after the second trimester) may be administered during pregnancy.*
32. Monteiro DL, Trajano AJ, Menezes DC, et al. Breast cancer during pregnancy and chemotherapy: a systematic review. *Rev Assoc Med Bras*. 2013;59(2):174–80.
33. Natekar A, Pupco A, Bozzo P, Koren G. Safety of azathioprine use during pregnancy. *Can Fam Physician*. 2011;57(12):1401–2.
34. Puig L, Barco D, Alomar A. Treatment of psoriasis with Anti-TNF drugs during pregnancy: case report and review of the literature. *Dermatology*. 2010;220(1):71–6.
35. Verstappen SM, King Y, Watson KD, et al. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. *Ann Rheum Dis*. 2011;70(5):823–6.
36. • Bogas M, Leandro MJ. Biologic therapy and pregnancy: a systemic review. *Acta Rheumatol Port*. 2011;36(3):219–32. *Although the numbers are small and with few controlled studies the reviewed data suggest that the overall risk of TNF antagonists is relatively low and benefits may outweigh the risks of drug exposure to the fetus. Information on other biologic agents is still very limited. Large controlled studies with longer follow-up periods will be necessary before firm conclusions about the safety of biologics during conception and pregnancy can be drawn.*
37. Rustin MHA. Long-term safety of biologics in the treatment of moderate-to-severe plaque psoriasis: review of current data. *BJD*. 2012;167(3):3–11.
38. Romero-Mate A, Garcia-Donoso C, Cordoba-Guijarro S. Efficacy and safety of etanercept in psoriasis/psoriatic arthritis: an updated review. *Am J Clin Dermatol*. 2007;8(3):143–55.
39. Djokanovic N, Klieger-Grossmann C, Pupco A, Koren G. Safety of infliximab use during pregnancy. *Reprod Toxicol*. 2011;32(1):93–7.
40. Fotiadou C, Lazaridou E, Sotiriou E, Ioannides D. Spontaneous abortion during ustekinumab therapy. *J Dermatol Case Rep*. 2012;6(4):105–7.
41. Cohen-Barak E, Nachum Z, Rozenman D, Ziv M. Pregnancy outcomes in women with moderate-to-severe psoriasis. *J Eur Acad Dermatol Venereol*. 2011;25(9):1041–7.
42. Kar S, Krishnan A, Preetha K, Mohankar A. A review of antihistamines used during pregnancy. *J Pharmacol Pharmacother*. 2012;3(2):105–8.
43. Bissonnette R, Worm M, Gerlach B, et al. Successful retreatment with alitretinoin in patients with relapsed chronic hand eczema. *BJD*. 2010;162(2):420–6.
44. Ruzicka T, Lynde CW, Jemec GBE, et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *BJD*. 2008;158(4):808–17.
45. • Matz H. Phototherapy for psoriasis: what to choose and how to use: facts and controversies. *Clin Dermatol*. 2010;28(1):73–80. *Unlike PUVA, UVB can be used during pregnancy.*
46. Beani JC, Jeanmougin M. Narrow-band UVB therapy in psoriasis vulgaris: good practice guideline and recommendations of the French Society of Photodermatology. *Ann Dermatol Venereol*. 2010;137(1):21–31.
47. Abarientos C, Sperber K, Shapiro DL, et al. Hydroxychloroquine in systemic lupus erythematosus and rheumatoid arthritis and its safety in pregnancy. *Expert Opin Drug Saf*. 2011;10(5):705–14.
48. Fluhr JW, Degitz K. Antibiotics, azelaic acid and benzoyl peroxide in topical acne therapy. *J Dtsch Dermatol Ges*. 2010;8(1):24–30.
49. Cholcha W, Leuschner J, Leuschner F. The tolerability of pale sulfonated shale oil following local and systemic administration. *Arzneimittelforschung*. 1994;44(2):170–7.
50. Boyd AS. Ichthammol revisited. *Int J Dermatol*. 2010;49:757–60.
51. Intong LR, Murrell DF. Pemphigoid gestationis: current management. *Dermatol Clin*. 2011;29(4):621–8.
52. Shapiro J. Safety of Topical minoxidil solution: a one-year, prospective, observational study. *J Cutan Med Surg*. 2003;7(4):322–9.