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A Practical Guide to Dermatological Drug Use in Pregnancy

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ABSTRACT

Although the developing fetus was once considered protected from the outside world, we now know that it can potentially be affected by any medication given to the mother. Despite this knowledge, use of medications during pregnancy is common and pregnant women often present for treatment of dermatological disease. Therapeutic options available for these patients will be discussed.

Key Words: *pregnancy, congenital malformations*

Two drugs given in the middle of the 20th century to pregnant women changed the attitude of physicians about the use of medications during this period. Diethylstilbestrol and thalidomide use in early pregnancy led to disastrous consequences for the exposed offspring, consequences that were not causally linked for years. These events led to the development of the US FDA Pregnancy Categories (Table 1) that are now assigned before a drug is released.

Despite awareness that any medication taken during pregnancy can potentially affect the fetus, a recent multinational survey indicated that 86% of women took an average of 2.9 medications during pregnancy.[1] This article will review options for the treatment of a variety of common dermatological disorders during pregnancy (Table 2).

A	No fetal risk in controlled studies
B	No risk to human fetus despite possible animal risk or no risks in animal studies but human studies lacking
C	Human risk cannot be ruled out. Animal studies may or may not show risk
D	Evidence of risk to human fetus
X	Contraindicated in pregnancy

Table 1: FDA Pregnancy Categories for Drugs

Disease	Medication Name
Acne	Topical clindamycin, erythromycin, benzoyl peroxide
Rosacea	Metronidazole, azelaic acid
Psoriasis	Topical corticosteroids, calcipotriol, broad band UVB
Dermatitis	Topical corticosteroids, chlorpheniramine or diphenhydramine
Genital human papillomavirus infection	Liquid nitrogen, trichloroacetic acid
Herpes simplex virus infection	Acyclovir
Fungal infections	Topical antifungals
Bacterial infections	Penicillins, cephalosporins after first trimester, azithromycin

Table 2: Safe treatments for dermatological disorders during pregnancy

Acne and Rosacea

Topical therapy is preferred for the treatment of acne during pregnancy.[2] Topical erythromycin (category B), clindamycin (category B) and benzoyl peroxide (category C) are considered safe in pregnancy. Use of topical tretinoin (category C) is not advised due to case reports of congenital malformations in infants whose mothers used tretinoin during the first trimester of pregnancy.[3,4] Moreover, some of these malform ations are consistent with those observed in retinoic acid embryopathy. However, the fetal risk, if any, from inadvertent exposure in early pregnancy appears to be very low.[5] Use of adapalene (category C) and tazarotene (category X) is also not recommended.

Topical metronidazole (category B) is minimally absorbed and considered safe in pregnancy. Topical azelaic acid (category B) is also minimally absorbed and likely safe in pregnancy.

Tetracyclines (category D) are associated with deciduous tooth staining when taken after the first trimester, decreased bony growth, and maternal liver toxicity. However, inadvertent exposure in the first few weeks of pregnancy is extremely unlikely to be harmful.[6] Erythromycin (category B) has long been considered safe in pregnancy. However, two recent Swedish studies have reported an increased risk of cardiovascular malformations with the use of oral erythromycin in early pregnancy.[7,8]

Oral isotretinoin (category X) is a well-known teratogen. However, it is safe for women to conceive 1 month after this medication is stopped.

Psoriasis

Topical corticosteroids (category C) have been widely used during pregnancy, although intrauterine growth retardation was reported in an infant whose mother applied 40mg/day of topical triamcinolone beginning at 12 weeks of gestation.[9] Calcipotriene (category C) is approximately 6% absorbed when the ointment form is applied to psoriatic plaques and is likely safe in pregnancy for the treatment of localized psoriasis.[10]

Broadband ultraviolet B phototherapy is considered the safest therapy for extensive psoriasis during pregnancy, although overheating during treatment should be avoided. PUVA is a potential teratogen because it is known to be mutagenic and to induce sister chromatid exchanges. However, adverse outcomes have not been reported in studies of women exposed to PUVA during pregnancy.[11,12]

Methotrexate and acitretin are both in pregnancy category X. Methotrexate can be used in women with childbearing potential who are using effective contraception. Pregnancy should be avoided for at least one ovulatory cycle after this medication is discontinued. Acitretin should not be prescribed for women of childbearing potential.

There are limited data on the safety of biologics used for the treatment of psoriasis during pregnancy. Animal reproduction studies of alefacept [13] (category B), a mouse analogue of efalizumab,[14] and etanercept (category B)[15] have shown no evidence of teratogenicity. No congenital malformations have been reported in the offspring of the few women who inadvertently became pregnant while taking alefacept or efalizumab (category C) in clinical trials. More data are available on the outcome of pregnancies exposed to etanercept given its utilization for the treatment of rheumatoid arthritis. Preliminary data from the Organization of Teratology Information Services (OTIS) study of pregnancy outcomes of women with rheumatoid arthritis exposed to anti-TNF therapy included information on 29 women exposed to etanercept. Spontaneous abortion, termination, and malformation rates were similar to those in the diseased and non-diseased control groups.[16]

Dermatitis

In some studies first trimester exposure to systemic corticosteroids (category C) has been associated with intrauterine growth retardation and a small increase in the incidence of cleft lip with or without cleft palate.[17,18] However, when needed, the maternal benefits of short courses of oral corticosteroids appear to outweigh the fetal risks, especially when given beyond the first trimester.

The topical calcineurin inhibitors, tacrolimus and pimecrolimus, are in pregnancy category C. Use of oral tacrolimus in pregnant organ transplant recipients has not been associated with fetal loss or teratogenicity thus far.[5] Pimecrolimus has shown no evidence of teratogenicity in animal studies.[19] To date, there have been no reports of adverse effects on pregnancy with topical use of either tacrolimus or pimecrolimus.

Chlorpheniramine and diphenhydramine (both category B) have been considered the antihistamines of choice for oral and parenteral use, respectively, in pregnancy,[20] although one case-control study showed an association between the use of diphenhydramine in the first trimester and cleft palate.[21] Antihistamines in general have been linked to retrolental fibroplasia in premature infants when taken in the last 2 weeks of pregnancy.

Viral Infections

For the treatment of genital warts, trichloroacetic acid and physical modalities such as cryotherapy are felt to be safe in pregnancy. Imiquimod (category B) is minimally absorbed, and animal studies, as well as very limited data of use in pregnant women, have not shown adverse fetal effects.[22,23] Podophylline and podophyllotoxin (category C) are not recommended for use in pregnancy because of fetal abnormalities and deaths associated with maternal use.[24,25] Acyclovir, famciclovir and valacyclovir are all pregnancy category B, and pregnancy registries exist for each of these agents. No adverse effects on the fetus or newborn have been attributed to their use in pregnancy, but because we have more data on the use acyclovir in human pregnancy, some authors consider it to be the drug of choice when indicated in pregnancy.

Fungal Infections

The use of topical antifungals is considered safe in pregnancy because of negligible percutaneous absorption. Animal reproduction studies involving oral terbinafine (category B) have shown no abnormalities, but human pregnancy data are lacking.[5] Oral fluconazole (category C) taken during the first trimester at a continuous daily dose of 400mg/day or more appears to be teratogenic and associated with a pattern of abnormalities involving the head and face, bones, and heart.[26]

Smaller doses of fluconazole, as used for treatment of vaginal candidiasis, have been associated with minimal or no risk of fetal abnormalities. The available data pertaining to human use of itraconazole (category C) indicates no significant risk for major abnormalities. However, because of concern regarding the use of fluconazole, a structurally related triazole antifungal, avoidance of itraconazole is suggested in the first trimester.

Bacterial Infections

Penicillins, cephalosporins and azithromycin are all pregnancy category B and are generally considered safe in pregnancy. However, a large surveillance study of Michigan Medicaid recipients conducted between 1985 and 1992 observed a possible association between certain cephalosporins (cefaclor, cephalexin, ceftriaxone and cephadrine) and congenital malformations when taken in the first trimester.[5]

Conclusion

Medications that are considered safe in pregnancy are available for the treatment of common dermatological disorders. Knowledge of these medications is important when considering treatment options for both pregnant patients and women of childbearing potential.

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Drug Treatments for Skin Disease Introduced in 2005

Drug Class	Generic/Trade Company Names	Indication	Approving Regultory Agency
Antiaging Treatments	*Aluma™ Skin Renewal System with FACES™* Lumenis	Approved for the noninvasive treatment of fine lines and wrinkles.	US FDA
Antibacterial Agents	**Meropenem for Injection** *MERREM®* AstraZeneca	Approved for the noninvasive treatment of fine lines and wrinkles.	US FDA
	Moxifloxacin HCl *Avelox®* Bayer HealthCare Schering-Plough	Approved for the treatment of complicated skin and skin structure infections in adults and children.	US FDA
	Tygacycline *Tygacil®* Wyeth	Approved for the treatment of complicated skin and skin structure infections in adults that are caused by methicillin-susceptible *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae*, or *Enterobacter cloacae.*	US FDA EMEA
Antifungal Agents	**Ciclopirox Topical Suspension 0.77%** Taro Pharmaceuticals	Abbreviated NDA approved for the treatment of fungal infections of the skin. It is the bioequivalent of Medicis Pharmaceutical's Loprox® Topical Suspension 0.77%.	US FDA
	Griseofulvin Oral Suspension USP Glades Pharmaceuticals	Approved for the treatment of tinea barbae, tinea capitis, tinea corporis, tinea pedis, and tinea unguium (onychomycosis).	US FDA
	Terbinafine HCl *Lamisil® Tablets* Ranbaxy Laboratories	Approved for the treatment of onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium).	US FDA
Antihist-amines	**Desloratidine** *Clarinex® Reditabs®* Schering-Plough	Reformulated 2.5mg and 5mg tablets approved for the treatment of allergy symptoms caused by both perennial indoor and seasonal outdoor allergens and for chronic idiopathic urticaria, or hives of unknown cause, in adults and children >6 years of age.	US FDA
Antipruritic Agents	**Epinastine HCl 1%** *Alesion® Dry Syrup* Nippon Boehringer Ingelheim/ Sankyo	Approved for the treatment of allergic rhinitis, urticaria, and pruritus associated with skin diseases such as eczema and dermatitis in pediatric patients.	Japanese Ministry of Health, Labour and Welfare
Antipsoriatic Agents	**Clobetasol Propionate 0.05%** *Clobex® Spray* Galderma	For the treatment of moderate-to-severe plaque psoriasis. Clobex® is already available as a lotion and shampoo.	US FDA

Drug Class	Generic/Trade Company Names	Indication	Approving Regultory Agency
Antipsoriatic Agents	**Efalizumab** *Raptiva®* Serono	Approved for the treatment of moderate-to-severe chronic plaque psoriasis in adults >18 years of age who are candidates for systemic therapy or phototherapy.	TPD Canada
	Etanercept *Enbrel®* Amgen/ Wyeth Pharmaceuticals	Approved for the treatment of moderate-to-severe psoriasis in adults.	TPD Canada
	Fluocinonide 0.1% *Vanos® Cream* Medicis Pharmaceuticals	A new class I topical corticosteroid approved for the treatment of plaque-type psoriasis affecting up to 10% of the body surface area.	US FDA
	Infliximab *Remicade®* Centocor/ Schering-Plough	Approved for the treatment of moderate-to-severe plaque psoriasis in adults who failed to respond to, or have a contraindication to, or are intolerant of other systemic therapies including cyclosporine, methotrexate, or PUVA.	EMEA
Atopic Dermatitis Agents	**Fluticasone Propionate 0.05%** *Cutivate® Lotion* Pharmaderm/Altana	Approved in patients >1 year of age for the treatment of atopic dermatitis.	US FDA
	Hydrogel Dressing *MimyX® Cream* Stiefel Laboratories	A topical nonsteroidal cream approved for the treatment of atopic dermatitis.	US FDA
HIV/AIDS	**Emtricitabine** *Emtriva® Oral Solution* Gilead Sciences	Approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients >3 months of age.	US FDA
	Tipranavir Capsule *Aptivus®* Boehringer Ingelheim Pharmaceuticals	Accelerated approval for this nonpeptide protease inhibitor as a combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, and who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors. The approved dose is 500mg taken with 200mg ritonavir twice daily.	US FDA EMEA
Leishmaniasis	**Miltefosine** *Impavido®* AEterna Zantaris	Approved for the treatment of the cutaneous form of leishmaniasis as well as the visceral form of this condition.	Columbian Food and Drug Agency
Oncologic Agents	**Imiquimod 5%** *Aldara™ Cream* 3M	Approved for the treatment of superficial basal cell carcinoma.	TPD Canada

Drug Class	Generic/Trade Company Names	Indication	Approving Regultory Agency
Psoriatic Arthritis Agents	**Adalimumab** *Humira®* Abbott Laboratories	Approved for the treatment of psoriatic arthritis.	US FDA
	Etanercept *Enbrel®* Amgen/ Wyeth Pharmaceuticals	Approved for the improvement of physical function in patients with psoriatic arthritis.	US FDA
	Infliximab *Remicade®* Centocor/ Schering-Plough	Approved for the treatment of psoriatic arthritis.	US FDA
Rosacea	**Metronidazole Topical Gel 1%** *MetroGel®* Galderma Laboratories LP	Approved for the topical treatment of inflammatory lesions of rosacea.	US FDA
Vaccines	**Measles, Mumps, Rubella, and Varicella Virus Vaccine, Live** *ProQuad®* Merck	Approved for simultaneous vaccination against measles, mumps, rubella, and varicella in children 12 months to 12 years of age.	US FDA EMEA
Wound Manage-ment	**Antimicrobial Barrier Dressing** *ACTICOAT* Moisture Control* Smith & Nephew	Approved for wound care as a barrier to bacterial penetration, featuring the patented Silcryst™ nanocrystalline silver technology.	US FDA

Class	Name/Company	Approval Dates and Comments
Corticosteroids	**Fluocinonide** *VANOS™ 0.1% Cream* Medicis	The US FDA approved an additional indication in March 2006 for this class I corticosteroid as a primary therapy for all inflammatory and pruritic skin conditions, including eczema and poison ivy, in patients 12 years of age or older who are responsive to corticosteroids. It was originally indicated for the treatment of plaque-type psoriasis.
Antiarthritic Agent	**Infliximab** *Remicade®* Centocor	The Australian Health Regulators approved an additional indication for this biologic therapy in March 2006 for the treatment of psoriatic arthritis. The US FDA granted priority review of this biologic therapy in April 2006 for the treatment of moderate-to-severe active pediatric Chrohn's disease in patients who have had an inadequate response to conventional therapies.
Antibacterial Agent	**Tigecycline** *TYGACIL®* Wyeth Pharmaceuticals	The EMEA's Committee for Medicinal Products for Human Use recommended approval of this new class of antibiotics in March 2006 for the treatment of complicated skin and soft-tissue infections and complicated intra-abdominal infections.

Drug News

Drug Warning	Finalizing a safety review of tacrolimus (Protopic®, Astellas) and pimecrolimus (Elidel®, Novartis) that began in April 2005, the EMEA's Committee for Medicinal Products for Human Use concluded that the benefits associated with the use of these dermatological medicinal products outweigh the risks, but that they should be used with greater caution in order to reduce potential risks of skin cancer and lymphoma as far as possible. The Committee recommended changes to the current product information, aimed at raising awareness of the potential long-term risks. They requested that the companies gather more data on the long-term safety profile.
Industry News	Metronidazole (MetroGel® 0.75%, Galderma) has been a mainstay for the treatment of rosacea. In July 2005, MetroGel® 1% was approved by the US FDA. It incorporates a higher concentration of metronidazole, allowing for a once-daily dosing as opposed to the twice-daily dosing required by most other rosacea treatments. Galderma reports that a new 60gm size is now available, and that they are no longer marketing the 0.75% formulation.
Industry News	Penciclovir 1% cream (Denavir®), which is approved in Canada for the treatment of outbreaks of herpes labialis in adults, is now being distributed by Barrier Therapeutics. It is the only topical antiviral prescription product approved by Health Canada for treating this condition.
Systemic Lupus Erythematosus	A study recently published in the *New England Journal of Medicine** reported that women with either inactive or stable systemic lupus erythematosus were able to take oral contraceptives without increased risk of flares. Subjects who took triphasic 35µg ethinylestradiol/0.5-1mg norethindrone for twelve 28-day cycles had no statistically significant difference in the occurrence of flares than those taking placebo. Severe flares occurred in about 7% of the women, regardless of whether they received oral contraceptives or placebo. *Petri M, et al. *N Engl J Med* 353:2550-8 (2005).

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