Safety of Topical Dermatologic Medications in Pregnancy

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ABSTRACT

Dermatologic drugs should be employed with caution in women of childbearing age who are pregnant or considering pregnancy. Topical drugs have little systemic absorption. Therefore, they are deemed safer than oral or parenteral agents and less likely to harm the fetus. However, their safety profile must be assessed cautiously, as there is limited available data. In this article, we aggregate human and animal studies and provide recommendations on using topical dermatologic medications in pregnancy.

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INTRODUCTION

Pregnant women and those of childbearing age should be treated with caution as medications can adversely affect a fetus. Topical medications are preferred, as they have little systemic absorption and therefore are less likely to harm a fetus. Many skin disorders are treated topically before starting systemic therapy. Dermatologists must be aware of medications that are safe in pregnancy. In this article, we present FDA pregnancy category ratings (see Table 1 for interpretation), animal and human studies, and recommendations on safe use of topical dermatologic medications in pregnancy. Table 2 provides summary of recommendations on using topical dermatologic medications in pregnancy.

In December 2014, the FDA published the Pregnancy and Lactation Labeling Rule (PLLR), which eliminated the pregnancy letter categories and created descriptive subsections for drug use in pregnancy, lactation, and effects on human reproductive potential. The old label was viewed as confusing, overly simplistic, and as poorly communicating the risks of drug use during pregnancy and lactation. This rule is effective as of June 30, 2015. All new submissions for prescription drugs will use the new labeling formation, while drugs approved on or after June 30, 2001 will switch gradually to the new format. Since the medications discussed in this article may not have switched to the new labeling format, we still present the FDA pregnancy category rating along with a description of available studies and recommendations on their use in pregnancy.

Anti-inflammatory, Immunosuppressants, Anti-neoplastics

Corticosteroids, Category C

A 2015 Cochrane review of 5 cohort and 9 case-controlled studies concluded that topical corticosteroids (regardless of potency) do not lead to increased risks of fetal malformations or anomalies, and perinatal outcomes such as mode of delivery, preterm birth, stillbirths, low APGAR scores, or fetal death.[1] However, there does appear to be an association between use of very potent topical corticosteroids and low birth weights, especially when cumulative dose is very high throughout pregnancy.[1] Topical corticosteroid absorption is low on the forearm (1%) while eyelids, face, neck, axilla, and groin absorb increased amounts.[2] The current recommendation is to use mild or moderate potency corticosteroids, and utilize potent topical corticosteroids for as short a time as possible with appropriate obstetrics care given possible risk of fetal growth restriction.[3,4]

Diclofenac, Category C (<30 weeks gestation); Category D (≥30 weeks gestation)

Animal studies of oral diclofenac were associated with dystocia, prolonged gestation, low fetal weights, impaired fetal growth, and decreased fetal survival with some of these outcomes attributed to prostaglandin synthesis inhibition.[5] Both animal and human studies indicate that topical diclofenac crosses the placenta.[6,7] A prospective observational cohort study of 145 pregnant women exposed to diclofenac (median dose 109 mg/day; median treatment duration 3.8 weeks) between 5th and 14th gestation weeks did not report increased occurrence of abortions, premature births, or birth defects.[8] A patient had reversible constriction of fetal ductus arteriosus due to topical diclofenac and methyl salicylate.[9] As with other NSAIDs, use of diclofenac beyond 30 weeks should be avoided due to risk of premature closure of ductus arteriosus in the fetus. There are no studies of topical diclofenac use in pregnancy; however, given that oral diclofenac use in early pregnancy has not demonstrated increased risk of congenital malformations, it is recommended that topical diclofenac be used only in <30 weeks gestation and when benefits outweigh risks.[8, 10]

Tacrolimus, Category C

Topical tacrolimus has not been studied in pregnancy, so much of the data is extrapolated from systemic tacrolimus use and physical properties of tacrolimus. Increasing evidence is supporting successful pregnancies with systemic tacrolimus, although maternal and fetal complications are increased. Maternal

TABLE 1.

FDA Pregnancy Category Interpretation	
FDA Pregnancy Category	**Interpretation**
A	Controlled studies show no risk: Adequate, well-controlled studies in pregnant women have not shown increased risk of fetal abnormalities.
B	No evidence of risk in humans: No adequate human studies are performed, animal studies are negative.
C	Risk cannot be ruled out: Human studies are lacking and animal studies are either positive for fetal risks or lacking as well. However, potential benefits may outweigh risks of use.
D	Evidence of adverse effects: Positive evidence of human risks exists based on adverse reaction data; however, potential benefits may outweigh risks of use – use only if no safer alternatives available.
X	Contraindicated in pregnancy: Positive evidence of human risk exists based on human or animal studies and/or adverse reaction data. Risk of using medication clearly outweighs benefits.
N	Drug has not been classified.

complications include preeclampsia, hypertension, infections, and miscarriages.[11,12] Fetal and neonatal complications include preterm birth, low birth weights, stillbirths, hyperkalemia, and diabetes mellitus, although tacrolimus has not been linked to congenital malformations.[11-13] When used topically, it is poorly absorbed systemically due to its large molecular size. Therefore, topical use on small surfaces is permissible, especially when no alternatives exist.[14]

Pimecrolimus, Category C

In animal studies, topical pimecrolimus has not shown maternal or fetal toxicity.[15] Unlike tacrolimus however, there is no data on pimecrolimus safety in pregnant women so it should be avoided. However, if no alternatives exist, it can be used if benefits outweigh risks.[14,16]

Fluorouracil, Category X

5-fluorouracil is an antimetabolite that interferes with DNA synthesis, and is topically used for actinic keratosis and basal cell carcinoma. When used topically for actinic keratosis, about 6% of fluorouracil is absorbed systemically.[17] Several cases of fetal malformations have been described in women who employed topical fluorouracil during pregnancy. One case of cleft lip and palate was reported in a pregnant female who used fluorouracil on skin and another case of ventricular septal defect was reported in a woman who used fluorouracil on mucous membranes.[17] Miscarriages have been observed in women who used fluorouracil on mucous membranes.[17] Due to the risk of fetal harm, use of topical fluorouracil in pregnancy is contraindicated.

Anti-Psoriatic

Calcipotriene, Category C

Topical calcipotriene is an important treatment option for psoriasis in pregnancy.[16,18] Following contact with psoriatic plaque, about 6% of calcipotriene is absorbed systemically while 5% is absorbed if applied on normal skin.[19] Animal studies have shown increased incidence of skeletal abnormalities such as enlarged fontanelles, extra ribs, incomplete ossification of pubic bones, and forelimb phalanges of fetus, but no human studies have been conducted and data is thus limited.[20,21] Some articles recommend[22,23] while another did not favor[24] topical calcipotriene therapy for psoriasis in pregnancy, instead opting for narrowband UVB therapy. Most consider topical calcipotriene safe in pregnancy.[25-27]

Anthralin, Category C

There are no published studies regarding anthralin safety in pregnancy in either animals or humans.[24,28] One manufacturer of this drug states that anthralin metabolites are not detected in urine, while another manufacturer cites a limited study that concluded systemic absorption is negligible.[14,29] Theoretical risk of using an anti-mitotic agent in pregnancy always exists and when combined with lack of data on safety, it is best avoided in pregnancy. But if it must be used as third or fourth line therapy, avoid using large amounts on inflamed skin as systemic absorption can be increased.[14,24]

Coal tar, Category C

Animal studies using high dose coal tar have shown increased risk of cleft palate, small lungs and thymus, and reduced fetal growth rates.[30,31] However, several studies in humans have not shown any adverse effects. A large cohort study and a small retrospective study did not reveal significant increase in spontaneous abortions or fetal abnormalities.[32,33] Due to concerns raised by animal studies, many authorities recommend avoiding coal tar products in pregnancy, although accidental use does not require any action.[14,16,25,34]

Retinoids

Tazarotene, Category X

About 6% of tazarotene is absorbed systemically after topical applications and its metabolites are water soluble so they are not stored in adipose tissues.[14,35] Water soluble metabolites are highly bound to plasma proteins (>99%) so placental transfer is unlikely

TABLE 2.

Summary of Recommendations on Safety of Topical Dermatologic Medications

Topical Medications	Pregnancy Category	Comments
Corticosteroids	C	Use mild or moderate potency corticosteroids. Avoid high potency due to low birth weight.
Diclofenac	C (< 30 weeks gestation)	Limited human data; likely safe <30 weeks, avoid use >30 weeks due to risk of premature closure of ductus arteriosus.
	D (≥ 30 weeks gestation)	
Tacrolimus	C	Limited human data; likely safe when applied topically to small areas.
Pimecrolimus	C	Limited human data; avoid use due to lack of experience with use in pregnancy.
Fluorouracil	X	Absolutely contraindicated in pregnancy.
Calcipotriene	C	Limited human data; adverse effects in animal studies but no studies/case reports of abnormalities in humans. Likely safe to use.
Anthralin	C	No human or animal studies; avoid use based on theoretic risk of using anti-mitotic agent in pregnancy.
Coal tar	C	Animal studies show fetal anomalies; few human studies show no evidence of risk. Avoid use.
Tazarotene	X	Absolutely contraindicated in pregnancy.
Tretinoin	C	Limited human data, animal data indicates fetotoxic or teratogenic risk. Avoid use.
Isotretinoin	X	Absolutely contraindicated in pregnancy.
Adapalene	C	Limited human data, animal data suggest bone problems. Avoid use in first trimester.
Benzoyl peroxide	C	Limited human and animal data. Limited use permitted.
Sodium sulfacetamide	C	Limited human and animal data. Use if benefits outweigh risks.
Salicylic acid	C	Do not apply in large amounts, especially in 3rd trimester due to closure of ductus arteriosus.
Azelaic acid	B	Limited human data. Avoid in first trimester, apply on small skin areas.
Minoxidil	C	Limited human data, avoid in pregnancy due to reports of fetal malformations.
Camphor	C	Limited human data, safe to use topically.
Echinacea	N	Limited human data; avoid use.

to occur.[35] In rats and rabbit studies, topical tazarotene caused reduced fetal body weights, reduced skeletal ossification, and retinoid malformations including spina bifida, hydrocephaly, and cardiovascular anomalies. Of 9 reported human pregnancies that were inadvertently exposed to topical tazarotene, 1 patient decided to terminate her pregnancy for non-medical reasons unrelated to tazarotene, while the other 8 pregnancies delivered apparently healthy babies.[36] Because tazarotene is a retinoid and some animal studies reported adverse effects, it is classified as pregnancy category X and should be avoided during pregnancy. And before prescribing to young women of child bearing age, a pregnancy test should be ordered 2 weeks before starting medication.

Tretinoin, Category C

There is limited human data on topical tretinoin safety in pregnancy. Five early case reports indicated ear, cardiovascular, and neurological malformations. However, two subsequent larger trials involving a total of 300 pregnancies indicated no teratogenic potential.[37-40] Another prospective study of 106 women treated topically with tretinoin in first-trimester did not report higher malformation or spontaneous abortion rate.[41] Topical tretinoin studies in animals have revealed bone anomalies (short, bent, or incompletely ossified bones), skull anomalies, hydrocephalus, and increased intrauterine death.[42] Although some studies cited above recommend its use in pregnancy, especially after first-trimester, most experts avoid its use during pregnancy.[25]

Isotretinoin, Category X

Topical isotretinoin is absolutely contraindicated in pregnancy due to ample data showing increased pregnancy loss in first-trimester and numerous birth defects, some of which are hydrocephalus, cleft palate, ear canal stenosis, thymic defects, spina bifida, and cardiac conotruncal malformations.[7,43] In the United States, isotretinoin users must register with iPLEDGE, which is a national registry that is designed to prevent fetal exposure to isotretinoin. Periodic pregnancy tests are required before drug refills are issued by pharmacy. However, some studies are skeptical if such programs actually decrease fetal exposure to isotretinoin, which makes it imperative for physicians to counsel their patients on the dangers of becoming pregnant while using isotretinoin.[44,45]

Adapalene, Category C

In animal studies, topical adapalene has not been shown to be fetotoxic, with only minimal increase in occurrence of

supranumerary ribs and delayed ossification. Of 6 woman that became pregnant while using adapalene, one patient terminated her pregnancy, two patients delivered healthy babies, two patients delivered premature babies that reached a healthy state after intensive care, and one patient was lost to follow up.[46] One report was published of a woman using topical adapalene from 1 month prior to conception to 13 weeks of gestation, who terminated her pregnancy after ultrasound revealed a small for gestational age fetus with anophthalmia. Post-abortion examination revealed anophthalmia and agenesis of optic chiasm. It was concluded that such defects were not typical of retinoids (heart, CNS, craniofacial, thymus, and limb defects).[47] It is possible that the drug is safe in pregnancy, but due to nearly absent human data, it is best to avoid this drug especially in first-trimester.[7,18]

Other Acne Medications

Benzoyl peroxide, Category C

A commonly used drug to treat acne, it has not been well studied in animals or humans to accurately assess safety profile in pregnancy. About 5% of topical dose is absorbed systemically.[20] It is also broadly used in plastics and the food industry and despite its widespread use, there are no indications of teratogenic effects. Therefore, it may be used in pregnant women on limited areas.[14]

Sodium sulfacetamide, Category C

This bacteriostatic agent has not been studied in human or animals to assess safety profile in pregnancy. When applied topically, about 4% is absorbed.[48] Oral sulfonamide use during pregnancy has been reported to cause neonatal jaundice, although no problems with topical sulfacetamide have been reported.[49] Use only if there are clear indications and benefits outweigh risks.[50]

Salicylic acid, Category C

This anti-inflammatory agent that is absorbed between 9-25% when used topically.[51,52] In third trimester, its use can potentially cause early closure of ductus arteriosus and oligohydramnios, so it should not be applied over large surface areas for prolonged time periods, or under occlusive dressings which may enhance systemic absorption.[28]

Azelaic acid, Category B

About 4% of topical azelaic acid is absorbed systemically after one application.[53] Animal studies show no teratogenic potential even when used in high doses.[48] Human studies are lacking. It should only be used on small skin surfaces and preferably not in first trimester.[54,55]

Miscellaneous

Minoxidil, Category C

Minoxidil is antihypertensive and a vasodilator that is topically used for androgenic and other types of alopecia. In a prospective study of 17 women treated with topical minoxidil, 1 fetus had heart malformations.[56] One case report of a women who applied topical minoxidil on scalp at least twice daily had numerous fetal malformations such as heart with distal stenosis of aorta, longer sigmoideum, ventricular broadening of brain, cerebral hemorrhages, and ischemic areas of placenta.[57] In another case, a woman used topical 2% minoxidil over many years who had a fetus that had suffered significant caudal regression syndrome with aplasia of the lower spine, lower extremity and urinary tract malformations, renal agenesis, and esophageal atresia.[58] As there is insufficient and inconclusive data on topical use of minoxidil, its use in pregnancy should be avoided.[14,25]

Camphor, Category C

When used topically, camphor has a cooling and local anesthetic effect, which makes it useful for pruritic skin conditions. In animal studies, maternally toxic doses of camphor failed to produce evidence of embryotoxicity or teratogenicity.[59,60] When it is ingested, it has the potential to cause fetal demise and neonatal respiratory failure, as camphor can cross the placenta.[61] The collaborative perinatal project followed 168 women with first trimester exposure to topical camphor and found no evidence of congenital malformations.[62] Furthermore, 763 patients used camphor at any time in their pregnancies, but no congenital defects were found.[62] Therefore, topical camphor is safe to use during pregnancy.[7,14,16,63]

Echinacea, Category N

Echinacea is a commonly used herbal product that has not been well studied. In a small study, 206 women reported use of Echinacea (112 women in first trimester). This cohort was matched to women exposed to nonteratogenic substances. There was no statistically significant difference in abortions, mode of birth, birth weight, gestational age at delivery, fetal distress, and fetal malformations.[64] Despite these results, this small study lacked sufficient statistical power. In animal studies, extracts of plant *E. purpurae* interfered with embryonic angiogenesis and caused decreased levels of growth factors compared to control group.[65,66] Many authors are skeptical about Echinacea use in pregnancy since it has not been studied in detail, and thus, do not support its use in pregnancy.[67] Furthermore, herbal supplements may be mixtures of numerous plants and may have contaminates, raising questions about their safety.

DISCLOSURES

The authors have no conflicts of interests to declare.

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