Safety of dermatologic medications in pregnancy and lactation

Part I. Pregnancy

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After completing this learning activity, participants should be able to prescribe select dermatologic medications during pregnancy; to educate reproductive-age women, as well as expectant mothers, regarding the benefits and potential risks of taking select dermatologic medications during pregnancy; and to appropriately monitor for side effects in the expectant mother and newborn when administering select dermatologic medications during pregnancy.

Date of release: March 2014
Expiration date: March 2017

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http://dx.doi.org/10.1016/j.jaad.2013.09.010

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Dermatologists are frequently faced with questions about the safety of commonly prescribed topical and systemic medications during pregnancy and lactation from women of childbearing age who are pregnant, considering pregnancy, or breastfeeding. Safety data, particularly regarding medications that are unique to dermatology, can be difficult to locate and are not consolidated in a single reference guide for clinicians. Parts I and II of this continuing medical education article provide a capsule summary of key points for the most commonly prescribed dermatologic medications to facilitate patient medication risk counseling in pregnancy. A summary table details safety classification data for 3 primary international classification systems: the US Food and Drug Administration, the Swedish Catalogue of Approved Drugs, and the Australian Drug Evaluation Committee. In addition, this table includes an alternative pregnancy classification system developed by a consortium of active members of teratology societies in the US and Europe detailed in *Drugs during Pregnancy and Lactation: Treatment Options and Risk Assessment* and a safety classification system developed for breastfeeding mothers detailed in *Medications and Mother's Milk*. (J Am Acad Dermatol 2014;70:401.e1-14.)

Key words: acne; antibiotic; antifungal; antihistamines; antiviral; atopic dermatitis; biologics; breastfeeding; breast milk; corticosteroid; cosmetics; fetus; gestation; lactation; medication safety; nursing; phototherapy; pregnancy; psoriasis; surgery; trimester.

This month's Continuing Medical Education articles consolidate safety data for patients who are pregnant (Part I) and breastfeeding (Part II) while undergoing dermatologic therapy. Key safety data for commonly prescribed dermatologic medications in pregnancy are described below and summarized in Fig 1. Details regarding the safety classification data for 3 primary international classification systems are provided in Table I.

Abbreviations used:

ADEC:	Australian Drug Evaluation Committee
BBUVB:	broadband ultraviolet B light
FDA:	Food and Drug Administration
HCQ:	hydroxychloroquine
IVIG:	intravenous immunoglobulin
MMF:	mycophenolate mofetil
NBUVB:	narrowband ultraviolet B light
NTD:	neural tube defect
PUVA:	psoralen plus ultraviolet A light phototherapy
TNF:	tumor necrosis factor

TOPICAL ANTIINFLAMMATORY DRUGS IN PREGNANCY

Corticosteroids

Multiple large, population-based studies and a Cochrane review have not shown an increased risk of malformations, including oral cleft palate, or preterm delivery with topical corticosteroids.[1-7] Fetal growth restriction has been reported with use of potent topical corticosteroids during the third

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Funding sources: None.

Conflicts of interest: None declared.

A modified version of Fig 1 has been presented at the Women's Health Therapeutics Symposium, American Academy of Dermatology 71st Annual Meeting, Miami, Florida, March 4, 2013.

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0190-9622/$36.00

trimester, particularly when using >300 g.[2,4,8] Topical corticosteroids will also increase the risk of developing stretch marks. Evidence-based guidelines recommend mild to moderate cortisones over potent corticosteroids, which should be used in short durations.[9]

Calcineurin inhibitors

Oral tacrolimus is associated with prematurity and low birth weight, and has a safety profile similar to that of cyclosporine. When used topically, calcineurin inhibitors are poorly absorbed systemically because their molecular size prevents penetration. Because there are no studies on safety in human pregnancies, when no alternatives exist, topical use on small surfaces is permissible.[10]

Coal tar

While animal studies show that maternal exposure to high-dose coal products resulted in perinatal mortality, and increased risk of cleft palates, and small lungs in offspring, the literature on human exposure has failed to reveal any developmental effects.[11,12] Although there are no indications of teratogenic effects in humans, coal tar should ideally not be used in pregnancy, but incidental use does not require any action.[10]

Calcipotriene

In animal studies, calcipotriene, a vitamin D analog, resulted in an increased incidence of skeletal abnormalities, including incomplete ossification of pubic bones and forelimb phalanges.[13] Generally, D-hypervitaminosis should be avoided in pregnancy, but use in the recommended dosage range (≤ 100 g/wk of a 0.005% solution) does not lead to a disturbance in calcium homeostasis.[10] Because there are no studies on safety in human pregnancies, when no alternatives exist, topical use on small surfaces is permissible.

SYSTEMIC THERAPY FOR PSORIASIS

Methotrexate

Methotrexate has a well documented history as a teratogen and is absolutely contraindicated during pregnancy, although not all outcomes are poor in those with inadvertent exposure.[14] Methotrexate is associated with miscarriage and numerous congenital malformations, such as developmental delay and craniofacial, limb, cardiopulmonary, and gastrointestinal abnormalities.[15]

Cyclosporine

The majority of data on cyclosporine comes from transplant recipients, who are generally given higher doses (8-10 mg/kg/day) than dermatologic patients. Cyclosporine is not an animal or human teratogen in >1000 pregnancies, but risk of low birth weight and prematurity has been shown in cases of complicated health status.[16-20] Cohorts have been followed through early childhood, with no detectable long-term neurodevelopmental, nephrotoxic, or immunologic effects in the children.[21-23] Cyclosporine can cause maternal hypertension and should be reserved as a rescue therapy for severe disease.

Biologics

Limited data for tumor necrosis factor—alfa (TNFα) inhibitors, including infliximab, etanercept, and adalimumab, indicate numerous cases of safe use during pregnancy and no clear pattern of malformations. One group noted an association between the use of etanercept and the development of vertebral anomalies, anal atresia, cardiac anomalies, tracheoesophageal fistula, esophageal atresia, renal abnormalities, and limb anomalies (VATER syndrome), biologically plausible based on results seen in animal models.[24] A follow-up review submitted to the US Food and Drug Administration (FDA) revealed higher rates of VATER if combination etanercept and infliximab were used.[25] Responses to this study challenge the authors' definition of what constitutes VATER, ultimately declaring the data uninterpretable.[26] They remain pregnancy US FDA pregnancy class B.

There is an increased rate of spontaneous abortion if etanercept is used during the first trimester.[27] In the third trimester, immunoglobulin G readily crosses the placenta, and there are detectable levels in infant serum of infliximab from 2 to 7 months after birth.[28] Live vaccines need to be avoided in infants with in utero exposure at least the first 6 months of life because they may be unable to mount an immune response, as was the case in an infant who died of disseminated Bacillus-Calmette-Guérin after receiving his vaccination at 3 months of age.[29]

Data are extremely limited for adalimumab and the interleukin-12/-23 inhibitor ustekinumab. There were no maternal, fetal, or infantile toxicities in animal studies, but there have been reports of spontaneous abortions with both.[30-32] TNFα inhibitors can be used with caution for severe, recalcitrant disease, but it remains uncertain whether routine use during pregnancy is advisable.[33]

Acitretin

Retinoic acid is important in development of the brain, face, thymus, heart, and spinal cord during embryogenesis, and all systemic retinoids are

Continuing Medical Education

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Pregnancy: International Systems		
FDA	US Food & Drug Administration	Categories: A, B, C, D, X
FASS	Swedish Catalogue of Approved	Categories: A, B:1, B:2, B:3, C, D
ADEC	Australian Drug Evaluation Committee	Categories: A, B1, B2, B3,C, D, X

Pregnancy: Evidence Based Medicine

Schaefer C, Peters PWJ, Miller RK. Drugs during pregnancy and lactation: treatment options and risk assessment. 2nd ed. Amsterdam; Boston: Elsevier Academic Press; 2007.

1	Drug of 1st choice (In general, well-tolerated during pregnancy)
2	Drug of second choice (Use only if better-tested options fail; there is often insufficient experience during pregnancy)
S	Single dose and/or low dosages probably tolerable
T	Potentially teratogenic or toxic
X	Contraindicated (No rational indication for use during pregnancy)

Time Intervals: Embryonic period (until week 12), **Fetal period** (from week 13) & **Peripartum** (last month of gestation)

Level of Evidence	
IA	Meta-analysis of RCTs
IB	≥1 RCTs
IIA	non-randomized controlled studies
IIB	any quasiexperimental study
III	comparative, correlational, case-control
IV	expert reports/opinions or clinical reports

Lactation: Hale

Hale TW. Medications and Mothers' Milk, 14 ed

L1	Safest
L2	Safer
L3	Moderately Safe
L4	Possibly Hazardous
L5	Contraindicated

DERMATOLOGIC MEDICATIONS		PREGNANCY: International Systems			PREGNANCY: Evidence Based Medicine			PREGNANCY: Recommendations (Level of Evidence)	LACTATION: Hale	LACTATION: Recommendations (Level of Evidence)
		FDA	FASS	ADEC	Embryo	Fetal	Peri			
Topical anti-inflammatories	Topical Corticosteroids	C	C	A, B3, C	1	1	1	Prefer mild-mod potency(IB)[4]	L1-3	Ok apply nipple,except Class I(IV)
	Pimecrolimus	C	B:2	B3	Min data: avoid			Avoid (IV)[10]	L2 L4nipple	Contraindicated on nipple, since oral absorption may be high(IV)
	Tacrolimus	C	B:3	C	Min data: avoid			Avoid (IV)[10]	L2 L4nipple	Contraindicated on nipple, since oral absorption may be high(IV)
	Coal Tar	–	–	–	Min data: avoid			Avoid; mutagenic/carcinogenic(III)[12]	–	Avoid or use minimally(IV)
	Calcipotriene	C	C	B1	≤100g/wk of 0.05% solution has no effect on calcium homeostasis			Use small surfaces permissible(IV)[10]	L3	Compatible; limit to <20% surface area (IV)
Systemic therapy for psoriasis	Oxsoralen (PUVA)	C	–	B2	–	–	–	Avoid; mutagenic/carcinogenic(III)[39]	–	Pump & discard for ≥1 day(IV)
	Methotrexate	X	D	D	X	X	X	Contraindicated(III)[14]	L5	Pump & discard for ≥4 days(IV)
	Cyclosporine *(888)522-5581	C	C	C	Risk of fetal growth restriction/ prematurity/maternal HTN			Avoid;no long-term ill effects in child cohorts(III)[18]	L3	Avoid or monitor infant plasma levels(III)[136]
	Etanercept *(877)311-8972	B	B:2	B2	X	X	X	Uncertain if advisable(III)[24]	L3	No adverse effects reported(IV)
	Adalimumab *(877)311-8972	B	C	C	X	X	X	Uncertain if advisable(IV)[31]	L3	No adverse effects reported(IV)
	Infliximab *(800)526-7736	B	C	C	X	X	X	Uncertain if advisable(III)[24]	L2	No adverse effects reported(IV)
	Ustekinumab *(800)526-7736	B	B:1	–	X	X	X	Uncertain if advisable(IV)[33]	L3	No adverse effects reported(IV)
Other systemic anti-inflammatories	Corticosteroids	C	C	A	2	2	2	↑risk of oral clefts in 1st tri(IB)[15]	L2	Use <3wks;nurse after≥4hrs(IIa)[139]
	Hydroxycholoroquine	C	B:3	D	1	1	1	1st line active lupus(Ib)[45]	L2	Uncertain if advisable(IV)
	Dapsone	C	–	B2	Reserve for specific indications			Associated with hyperbilirubinemia/ hemolytic anemia(IV)[54,55]	L4	Case of hemolytic anemia, avoid in G6PD/hyperbilirubinemia(IV)
	Mycophenolate mofetil *(800)617-8191	D	D	D	X	X	X	Contraindicated; can interfere with hormonal contraception(III)[59]	L4	Avoid, likely enters milk(IV)
	Azathioprine	D	D	D	2	2	2	Reduce dose if preg woman is leukopenic in 3rd tri; can interfere with IUD efficacy (III)[61]	L3	Infant TPMT levels; monitor for decreased growth/ immunosuppression(IV)
	IVIG	C	_	_	Reserve for specific indications			Used for infertility tx, crosses the placenta >32 wks gestation(III)[64]	L2	Can be used safely(III)[136]
	Rituximab*(888)835-2555	C	–	–	Impacts fetal B-cell development			Avoid, neonatal hematologic abnormalities(III)[68]	L2	Min data: avoid(IV)
Systemic anti-pruritics	Chlorpheniramine **(1st gen)	B	–	A	Preferred over 2nd gen			Preferred above 2nd gen (III)[41]	L3	Observe for sedation(III)[135]
	Diphenhydramine **(1st gen)	B	B:2	A	1	1	T	↑uterine contractions, especially IV or overdose in 3rd tri(III)[71]	L2	Observe for sedation(III)[135]
	Hydroxyzine **(1st gen)	C	C	A	Monitor for infant withdrawal symptoms w/ regular maternal use			May be associated with an ↑risk of congenital malformations(III)[41]	L1	Observe for sedation, tachycardia, dry mouth(III)[135]
	Cetirizine **(2nd gen)	B	B:1	B2	2	2	2	2nd line after loratadine (III)[71]	L2	Observe for sedation(III)[135]
	Fexofenadine **(2nd gen)	C	B:2	B2	Min data			Use alternatives(IV)[71]	L2	Observe for sedation(III)[135]
	Loratadine **(2nd gen)	B	B:3	B1	1	1	1	1st line 2nd gen antihistamines(III)[71]	L1	Observe for sedation, tachycardia, dry mouth(III)[135]
	Doxepin	Btopical Coral	–	C	1	1	T	Hypotonia, emesis, and weak suck in newborns with 3rd tri exposure (III)[41]	L5	Sedation, respiratory depression, hypotonia, emesis(IV)
Acne, Cosmetics & Surgery	Lidocaine	B	–	A	1	1	1	Safe as local anesthetic(III)[80]	L2	Safe as local anesthetic(IV)
	Epinephrine	C	–	A	Local anesthetic use is acceptable in pregnancy			Safe as local anesthetic(III)[80]	L1	Safe as local anestheic(IV)
	Minoxidil (topical)	C	B:3	C	Oral: infant hypertrichosis, disappears over first 3 months			Avoid, cases of newborns with birth defects(IV)[82]	L2	Compatible; low systemic effect when used topically(IV)
	Botulinum toxin A	C	B:3	B3	Avoid cosmetic products			Fetal movement observed in mother paralyzed w/ systemic botulism(III)[86]	L3	Prob compatible; case of nursing mother w/ botulism and no fetal adverse effects(IV)
	Hydroquinone	C	–	–	–	–	–	Avoid; mutagen(IV)[10]	L3	Prob compatible(IV)
	Tretinoin (topical)	C	B:3	D	T	T	T	Large studies indicate safe, but most experts do not recommend(IIb)[98]	L3	Unlikely absorbed in significant quantities, likely safe(IV)
	Spironolactone	D	B:3	B3	2	2	2	Avoid, male feminization(III)[41]	L2	Possible suppresion of milk(IV)
	Tazarotene	X	–	–	X	X	X	Teratogen(IV)[100]	L3	Limit to <20% surface area(IV)

*Enroll if pregnancy occurs while on these medications or within 8 wks of treatment

**If 1st gen antihistamines are too sedating, 2nd gen antihistamines can then be considered. Antihistamines may be associated with ↑risk of retrolental fibroplasia in premature infants with use within 2 wks of delivery.

Fig 1. Pregnancy: evidence-based medicine.

Topical antibiotics	Benzoyl peroxide	C	A	–	May be used on limited areas			Metabolized to benzoic acid, food derivative(IV)[101]	–	Compatible(IV)
	Clindamycin	B	B:1-2	A	Min data: no known fetal effects			Case of pseudomembrane colitis w/ intravaginal use	L2	Compatible(IV)
	Erythromycin	B	–	A	Min data: no known fetal effects			Presumed safe	–	Compatible(IV)
	Azelaic acid	B	B:1	B1	Min data: no known fetal effects			Skin absorption is about 4-8%	L3	Normal constituent of milk; found in wheat, rye, and barley(IV)
	Sulfacetamide	C	–	–	Min data: no known fetal effects			Skin absorption is about 4%	–	Compatible(IV)
	Metronidazole	B	B:1	B2	Min data: no known fetal effects			Presumed safe	L3	Compatible(IV)
	Mupirocin	B	B:1	B1	Min data: no known fetal effects			Local use ok; limited sys absorption	L1	Topical antibiotic of choice(IV)
	Bacitracin	C	–	–	Min data: no known fetal effects			Local use ok; limited sys absorption	L2	Min data: compatible(IV)
	Polymyxin B	B	–	–	Min data: no known fetal effects			Local use ok; limited sys absorption	L2	Compatible; use in small amounts if applied to nipple(IV)
	Neomycin	C	–	D	Min data: no known fetal effects			Local use ok; limited sys absorption	L2	Min data: compatible(IV)
Systemic antibiotics	Penicillins	B	A	A, B1-3	1	1	1	Antibiotics of choice(IIb)[41]	L1	Compatible(III)[139]
	Cephalosporins	B	A	A, B1-2	1	1	1	Safe, older cephalosporins preferred(IIb)[41]	L1-2	Compatible(III)[139]
	Erythromycin (not erythromycin estolate!)	B	D	A	2	1	1	↑risk of heart defects/pyloric stenosis; estolates cause maternal hepatotoxicity in 2nd tri(IIa)[108]	L2, L3early	Compatible; may cause pyloric stenosis with early postpartum use(III)[138]
	Azithromycin	B	B:1	B1	Min data: 2nd choice macrolide			2nd line after erythro(III)[108]	L2	Min data: prob compatible(III)[138]
	Clarithromycin	C	B:3	B3	2	2	2	2nd line after erythro(III)[108]	L2	Min data: prob compatible(III)[138]
	Clindamycin	B	B:1-2	A	Only if penicillins, macrolides and cephalosporins are ineffective			2nd line b/c of pseudomembranous colitis(IV)[109]	L2	Compatible; case of child w/ transient bloody stool episode(IV)
	Rifampin	C	C	C	1	1	1	Tx of choice for tuberculosis; give vit K prophylaxis peripartum(IV)[110]	L2	Compatible(IV)
	Sulfonamides	B, C	C	C	2	2	X	↑ risk of heart defects,preterm birth, hyperbilirubinemia peripartum(III)[112]	L3	Avoid in G6PD/hyperbilirubinemia(IV)
	Trimethoprim	C	B:3, C	C	2	2	2	May cause folate depletion(III)[112,114]	L2	Supplement with folic acid(IV)
	Quinolones (Ciprofloxacin/Ofloxacin/ Norfloxacin)	C	B:3	B:3	2	2	2	Use only in complicated cases of antibiotic resistant infection(IV)[10]	L3	Observe for diarrhea; case of pseudomembrane colitis(IV)
	Tetracyclines	D	D	D	2	X	X	Contraindicated if >15wks b/c ↓ bone growth/teeth discoloration(III)[10]	L2-4	May cause ↓bone growth with prolonged exposure (>3wks)(IV)
Topical anti-fungals	Nystatin	Ctopical, Avaginal	A	A	1	1	1	Topical anti-fungal of choice(IV)[10]	L1	Best studied:1st therapy(IV)
	Clotrimazole	B	A	A	2	1	1	Topical anti-fungal of choice(IV)[10]	L1	Best studied: 1st therapy(IV)
	Terbinafine	B	B:1	B1	Min data: no known increased risk			Animal data suggests low risk(IV)[10]	L2	Min systemic absorption(IV)
	Ciclopirox	B	A	–	Min data: no known increased risk			Probably compatible(IV)[10]	L3	Min systemic absorption(IV)
	Selenium sulfide	C	A, B:3	–	Local application is acceptable			Local application for limited time(IV)[10]	L3	Safe, case of lactation suppression(IV)
Systemic anti-fungals	Griseofulvin	C	–	B3	2	2	2	Avoid, case of conjoined twins(IV)[118]	L2	Min data: avoid(IV)
	Fluconazole	C	B:3	D	2	2	2	Human data suggest risk(III)[119]	L2	Best studied, compatible, safe in preterm infants(IV)
	Ketoconazole	C	B:3	B3	2	2	2	Human data suggests risk(IV)[10]	L2	Min data: probably compatible(IV)
	Itraconazole	C	B:3	B3	2	2	2	Human data suggests risk(IV)[10]	L2	Can concentrate in milk(IV)
	Terbinafine	B	B:1	B1	Min data: avoid			Postpone tx of onchomycosis(IV)[10]	L2	Avoid prolonged use(IV)
Systemic anti-virals	Acyclovir	B	B:3	B3	1	1	1	1st line for herpes; prophylaxis begins at 36 wks gestation(Ib)[127]	L2	Compatible(IV)
	Famciclovir	B	B:2	B1	Min data			3rd line(IV)[10]	L2	3rd line(IV)
	Valacyclovir	B	B:3	B3	More data than famciclovir			2nd line(IV)[10]	L1	2nd line(IV)
Topical anti-virals: Warts	Trichloroacetic acid	–	–	–	Possible tx for condylomata acuminata			2nd line after destructive therapy(IV)[10]	–	Min data: prob compatible(IV)
	Squaric acid	–	–	–	–	–	–	Min data in animals/humans	–	Min data: prob compatible(IV)
	Salicyclic acid	C	C	–	Use on limited areas for limited time is acceptable			Local application for limited time(IV)[10]	L3	Compatible for local, topical use(IV)
	Podophyllin	X	–	–	Absolutely contraindicated			Maternal/fetal death; heart/ear/ extremity defects; psych sxs(IV)[10]	L3	Uncertain if advisable(IV)
	Podofilox	C	B:1, C	–	–	–	–	Min data in animals/humans	L3	Uncertain if advisable(IV)
	Cantharidin	C	–	–	–	–	–	Min data in animals/humans	–	Uncertain if advisable(IV)
	Imiquimod	C	B:1	B1	–	–	–	Min data, no teratogenicity(III)[7#]	–	Min data: prob compatible (IV)
Scabies & Lice	Lindane	C	–	B3	T	T	T	Avoid; teratogen(IV)[10]	L4	Avoid; may cause ↑LFTs, seizures & hypersensitivity(IV)
	Benzyl benzoate (Banned in US)	C	B:2	B2	1	1	1	Used in Europe(IV)[10]	–	Prob compatible(IV)
	Permethrin	B	B:1	B2	2% absorbed with topical use			1st line for scabies; 2nd line for lice (1st line occlusive tx)(III)[10]	L2	1st for scabies: apply head to toe (infants) & neck down (adults)(IV)
	Pyrethrin	C	–	B2	1	1	1	2nd line for lice (1st line occlusive tx)(IV)[10]	L2	2nd line for lice (1st line occlusive tx)(IV)
	Crotamiton	C	–	B2	<1% is absorbed with topical use			Min data: likely safe	–	Min data: likely safe(IV)
	Malathion	B	B:1	B2	–	–	–	Pesticide, avoid if possible	L4	Min data: avoid; may cause respiratory depression(IV)
	Precipitated sulfur	C	–	–	–	–	–	Min data: likely safe	–	Min data: likely safe(IV)
	Ivermectin	C	–	B3	Only use for compelling indication			Min data: systemic tx for scabies if resistant to topical tx(IV)[41]	L3	If topical permethrin fails, ivermectin can be used(IV)

Disclaimer: This material is intended to serve as an initial reference, *not* as a complete resource. It does not include information concerning every therapeutic agent, laboratory, or diagnostic test or procedure available. It is intended for physicians and other competent healthcare professionals who will rely on their own discretion and judgment in medical diagnosis and treatment.

Fig 1. Continued.

Table I. Definition of the pregnancy risk categories used by the United States Food and Drug Administration, the Swedish Catalogue of Approved Drugs, and the Australian Drug Evaluation Committee

Comparison of drug risk classification systems*		
US FDA	**FASS**	**ADEC**
A—Clinical data show no evidence of risk to the fetus (4%)	A—Reliable clinical data indicate no evidence of disturbance of the reproductive process (22%)	A—Extensive clinical experience in pregnant women and women of childbearing age has shown no increase in the frequency of malformations or other harmful effects on the fetus (27%)
B—Clinical data are limited or not available, but animal studies show no evidence of risk to the fetus, or clinical data show no evidence of risk to the fetus, but animal studies show adverse effects to the fetus (23%)	B—Clinical experience of use in pregnant women is limited or insufficient. Classification is based on animal data, by allocation to 3 subgroups (B:1, B:2, and B:3)	B—Human data are lacking or inadequate. Limited use in pregnant women and women of childbearing age has shown no increase in the frequency of malformation or other harmful effects on the human fetus. Classification is based on available animal data into 3 subcategories (B:1, B:2, and B:3). Note: allocation to category B does NOT imply greater safety than category C
	B:1—Animal experiments have not given evidence of an increased incidence of fetal damage; similar to FDA category B (11%)	B:1—Studies in animals have not shown evidence of an increased occurrence of fetal damage; similar to FDA category B (8%)
	B:2—Animal experiments are inadequate; similar to FDA category C (12%)	B:2—Studies in animals are inadequate or lacking, but available data show no evidence of an increased occurrence of fetal damage; similar to FDA category C (19%)
	B:3—Reproduction toxicity studies in animals have revealed an increased incidence of fetal damage, the significance of which is considered uncertain in humans; similar to FDA category C (12%)	B:3—Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans; similar to FDA category C (11%)
C—Clinical data are not available and animal studies are not available, or clinical data are not available, but animal studies show adverse effects to the fetus (45%)	C—Data suggest pharmacologic effects may have adverse effects on the reproductive process (30%)	C—Drugs which, owing to their pharmacologic effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible (24%)
D—Positive evidence of risk to the fetus from clinical data (22%)	D—Data indicate an increased incidence of malformations in humans (13%)	D—Drugs which have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacologic effects. Note: drugs in category D are not absolutely contraindicated in pregnancy. In some cases, the D category has been assigned on the basis of suspicion (10%)
X—Contraindicated based on animal studies or clinical data (6%)		X—Contraindicated in pregnancy (1%)

ADEC, Australian Drug Evaluation Committee; *FASS*, Farmaceutiska Specialiteter i Sverige (Swedish Catalogue of Approved Drugs); *FDA*, Food and Drug Administration.

*For each organization, the percentage of medications that fall within each pregnancy category is indicated in parentheses (according to Addis et al[133]).

completely contraindicated in pregnancy. Women of childbearing age should be discouraged from taking acitretin because it is necessary to avoid pregnancy for 3 years after discontinuing use.

PHOTOTHERAPY

Narrow- and broadband ultraviolet B light phototherapy

Both narrowband (NBUVB) and broadband (BBUVB) ultraviolet B light phototherapy are considered safe options in pregnancy. Phototherapy may worsen melasma, so advise facial shielding depending on patient skin type. Folic acid levels have been shown to decrease with both NBUVB and BBUVB, and folate deficiency in the first trimester could predispose to the development of neural tube defects (NTDs).[34,35] NTDs have been demonstrated in three patients with sunbed exposure in early pregnancy.[36] Core temperature readings in a small cohort suggested that phototherapy is unlikely to result in hyperthermia, but cooling measures and avoidance of high doses of heat is advisable. Measure folic acid levels in phototherapy patients considering pregnancy, and initiate appropriate folic acid supplementation during phototherapy.[36,37]

Psoralen plus ultraviolet A light phototherapy

Psoralen plus ultraviolet A light phototherapy has not been shown to increase risk of congenital malformations or infant mortality, but there was a marked increase in low birth weight babies.[38,39] Because psoralen is a known mutagen and teratogen, it is recommended to avoid psoralen plus ultraviolet A light phototherapy treatment during pregnancy.

OTHER SYSTEMIC ANTIINFLAMMATORY DRUGS

Systemic corticosteroids

Prednisone, a nonfluorinated corticosteroid, is the preferred choice because placental enzymes limit passage to the embryo.[40] Studies note a 3-fold increased risk of orofacial clefts 4 weeks before conception to 12 weeks after conception; lip formation occurs during weeks 5 to 7 and palate formation during weeks 8 to 12. The absolute risk is low given that the baseline risk is 1 in 1000 live births. Prednisone also may result in premature delivery, premature membrane rupture, intrauterine growth retardation, gestational diabetes, hypertension, preeclampsia, and eclampsia, so many clinicians recommend prolonged use limited to 7.5 mg/day and the avoidance of >20 mg/day.[1,41,42]

Hydroxychloroquine

Hydroxychloroquine (HCQ) is considered a first-line therapy for pregnant mothers with active lupus, and published studies have not found the maternal use of HCQ to increase the risk of congenital, neurologic, or auditory abnormalities.[43-47] Although adults may be monitored for retinal toxicity with long-term use of HCQ, literature has not suggested similar risk in fetuses.[48,49] In a large prospective study, those who stopped HCQ had a higher degree of lupus activity and those who continued were able to lower their prednisone dose.[50] Other beneficial effects include reducing the risk of cardiac neonatal lupus and protection against maternal osteoporosis.[43,51] Published reviews continue to support the safety of HCQ during pregnancy.[43,46,50]

Dapsone

Literature on dapsone, which is used extensively for leprosy and malaria chemoprophylaxis, does not indicate major fetotoxicity or congenital anomalies. Animal studies in high doses reveal that it is not a teratogen, but the tolerability of dapsone in pregnancy makes meaningful risk assessment difficult.[52,53] Glucose-6-phosphate dehydrogenase levels should be measured before initiating therapy because of the risk of maternal anemia, and neonatal hyperbilirubinemia and hemolytic anemia have been attributed to gestational exposure.[54,55]

Mycophenolate mofetil

Mycophenolate mofetil (MMF) was reclassified from class C to D in 2007 because the FDA acted proactively in response to postmarketing studies indicating potential increased risk of first-trimester miscarriage, microtia, external auditory canal atresia, cleft lip/palate, and finger, cardiac, renal, ocular, and central nervous system abnormalities.[56-58] MMF should not be used in pregnancy, and women should use nonhormonal contraception until 6 weeks after stopping therapy, because MMF compromises the efficacy of the birth control pill.[59]

Azathioprine

The main risks associated with azathioprine are preterm and low birth weight infants, and sporadic anomalies and hematologic toxicities have been reported. There are safety data supporting its use in organ transplant patients, autoimmune bowel disease, and rheumatic disease. There is no clear pattern of congenital malformation, outside of a possibly increased risk of atrial or ventricular septal defects.[60] To prevent the development of leukopenia and thrombocytopenia in newborns, a protocol was

initiated to halve the dose at 32 weeks' gestation if the mother's leukocyte count was <1 standard deviation below the mean.[61] Patients taking azathioprine should not use intrauterine devices as contraception because several patients have become pregnant with their intrauterine device in place.[62]

Intravenous immunoglobulin

Limited studies have shown intravenous immunoglobulin (IVIG) to be a safe therapy in pemphigus and pemphigoid gestationis.[63,64] Interestingly, in patients with antibody-mediated disease—thought to contribute to up to 10% of cases of infertility—IVIG can improve the chance of in vitro fertilization resulting in pregnancy.[65] A study of anti-Ro/La^{+} pregnant women also found that IVIG was safe during pregnancy and was effective in preventing recurrent neonatal lupus.[66] Nonspecific risks specific to pooled human plasma, such as anaphylaxis, viral infections, and hypercoagulability, need to be weighed. IVIG crosses the human placenta in significant amounts only at >32 weeks' gestation and is not embryotoxic.[67]

Rituximab

Rituximab is not recommended during pregnancy and has been associated with an increased risk of neonatal hematologic abnormalities. Placental passage is minimal during the first trimester, moderate during the second, and extensive during the third, and can affect fetal B-cell development. Women should be counseled to avoid pregnancy for at least 12 months after rituximab exposure.[68]

SYSTEMIC ANTIPRURITICS

Antihistamines

A large number of pregnancies exposed to first-generation antihistamines have been studied, and there is no definitive increased teratogenic risk. Diphenhydramine was associated with an increased risk of cleft palate in 1 study, but this was not confirmed in multiple later studies.[69] Both chlorpheniramine and diphenhydramine are considered safe during the first trimester and are first-line agents. Exposure to hydroxyzine during the first trimester has been linked with a slightly increased risk (5.8%) of congenital anomalies.[41] First-generation are preferred over second-generation antihistamines because of the preponderance of safety data. The increased risk of hypospadias initially reported with loratidine has not been confirmed in multiple subsequent studies.[70] Loratidine remains the first choice and cetirizine the second choice among second-generation antihistamines.[10,71]

Antihistamines should be used judiciously peripartum. One study of premature infants found that the use of antihistamines within 2 weeks of delivery doubled the risk of retrolental fibroplasia.[72] Overdose and the intravenous use of antihistamines can stimulate uterine contractions and increase the risk of fetal hypoxia.[73] Withdrawal symptoms (ie, tremulousness, irritability, poor feeding, and diarrhea) have been reported in infants up to 4 weeks old with regular maternal use of antihistamines; 1 newborn developed tonic–clonic seizures with 150 mg daily maternal hydroxyzine use.[74,75]

Doxepin

Doxepin was not teratogenic in animal models, and there are no reports definitively linking its use with human malformations. In 1 study of 118 newborns, 12 major birth defects were seen with first-trimester exposure (4.5 expected), including oral clefts, cardiovascular defects, and polydactyly.[41] Antihistamines would be preferable over doxepin for pruritus during pregnancy, but human data suggest low risk.

ACNE, COSMETICS, AND SURGERY

Lidocaine and epinephrine

Both lidocaine and epinephrine are considered safe in small amounts for local anesthesia. Both cross the placenta; animal reproductive studies of lidocaine reveal no evidence of harm to the fetus, but there is 1 study that suggested an increase in malformations when mothers were exposed to systemic epinephrine during the first trimester.[76,77] Because epinephrine's alfa-adrenergic properties may lead to vasoconstriction of placental blood vessels, fetal tachycardia, and decreased uteroplacental blood flow, the addition of this compound is not generally accepted to be of advantage in obstetric procedures.[78] However, local vasoconstriction prolongs the duration of anesthesia and reduces both maternal blood levels of lidocaine and placental transfer of lidocaine, so in dermatologic surgery the benefits of using small controlled amounts of epinephrine seem to outweigh potential risks.[78-80]

Minoxidil

Topical minoxidil is most frequently used as therapy for androgenetic alopecia. Concentrations in the serum are far below therapeutic levels in adults, but there have been case reports of cardiac, neurodevelopmental, gastrointestinal, renal, and limb malformations with topical use.[81-83] Because there are no conclusive studies, minoxidil is not recommended during pregnancy.

Botulinum toxin A

In general, cosmetic therapies, such as botulinum toxin A facial intramuscular injection, should be avoided during pregnancy, even though there are limited data to suggest that the risk to the fetus is low. Up to 1200 units of botulinum toxin have been used for various medical conditions without adverse effects.[84,85] There are 5 reports of mothers with systemic botulism in the second or third trimesters, and none of the infants were affected. The only movements in a paralyzed mother were those of the fetus, so it is unlikely that the toxin crosses the placenta.[86-90]

Hydroquinone

Hydroquinone, a cosmetic therapy, is not recommended during pregnancy, although available data indicate low risk. Topical use results in 35% to 45% systemic absorption.[91] High potency exposure in rats did not lead to increased rates of malformation.[92] It is estimated that two-thirds of women in sub-Saharan Africa use a skin lightening agent during pregnancy; in a small cohort, hydroquinone alone without a high-potency cortisone did not increase risk of malformations, prematurity, or low birth weight.[8]

Topical retinoids

The safety data regarding adapalene and tretinoin are limited. Early case reports suggested that the use of topical tretinoin during pregnancy resulted in ear, cerebral, and cardiac malformations that are typically associated with the use of systemic retinoids in pregnancy.[93-96] However, larger studies have not found an increased risk of retinoid embryopathy or other major birth defects with the topical use of tretinoin.[97-99] Although these studies suggest that use in limited body surface area is likely safe, most experts do not recommend the topical application of tretinoin to pregnant patients.

Tazarotene

Tazarotene causes retinoid-like malformations in experimental animals, so is contraindicated in pregnancy (class X). It is highly bound to plasma protein (>99%) and maternal plasma concentrations are low, so placental transfer is unlikely. Healthy infants were delivered in several cases of inadvertent exposure.[41,100,101]

Isotretinoin

Isotretinoin is absolutely contraindicated in pregnancy because of increased first-trimester pregnancy loss and increased birth defects, such as cleft palate, hydrocephalus, cardiac outflow tract defects, microtia, and external ear canal stenosis.[102] Any patient in the United States taking isotretinoin must enroll in iPLEDGE, a national registry that requires monthly pregnancy tests before a woman is able to obtain refills of the medication. However, numerous studies have observed that the program has not significantly decreased fetal exposure to the medication, so it is necessary to counsel patients at each visit about the dangers of becoming pregnant while taking isotretinoin.[103]

Spironolactone

Spironolactone's antiandrogen effects—inhibiting 5-alfa reductase and antagonizing androgen receptors—aid in the treatment of hormonal acne and hirsutism. This medication should not be used during pregnancy because it may increase the risk of hypospadias and feminization in a male fetus.[41]

TOPICAL ANTIBIOTICS

In general, topical antibiotics used for skin infection, acne vulgaris, and rosacea therapy are considered safe during pregnancy. The 5% of benzoyl peroxide that is absorbed by the skin is metabolized within the skin to benzoic acid, a food additive. Exposure to benzoic acid in the diet is greater than exposure from topical application.[101,104]

SYSTEMIC ANTIBIOTICS

Beta-lactam antibiotics

Penicillins, amoxicillin, and all cephalosporins are pregnancy class B and are considered compatible with pregnancy. Animal reproductive studies found no malformations with many times the human dose. A surveillance study revealed 317 (3.7%) malformations in 8538 newborns exposed to amoxicillin (363 expected), 27 (3.7%) in 722 exposed to cefadroxil (30 expected), and 176 (4.9%) in 3613 exposed to cephalexin (154 expected).[41] Safety data support the use of amoxicillin for severe acne rosacea and cefadroxil for severe acne vulgaris. Because elimination is faster in pregnancy, it may be necessary to adjust the dose when treating infections.[105]

Macrolides

Erythromycin, azithromycin, and clarithromycin are all second-line antibiotics to the beta-lactam antibiotics, but are considered compatible with pregnancy. Erythromycin, with data on 7000 first-trimester exposures, is the drug of choice in this class. One study indicated an increase in atrial and ventricular septal defects (1.8%) and pyloric stenosis (0.2%), but these risks are still uncertain.[106] Erythromycin estolate is associated with hepatotoxicity during the second trimester in 10% of

pregnancies, so erythromycin base or erythromycin ethylsuccinate should be prescribed.[107,108]

Clindamycin

Clindamycin is compatible with pregnancy and has not been shown to increase the risk of malformation. It can cause pseudomembranous colitis with both oral and intravaginal use, so it is second-line therapy to beta-lactam antibiotics.[109] The laboratory must perform a D-test to rule out inducible resistance to clindamycin when treating methicillin-resistant *Staphylococcus aureus*.

Rifampin

Rifampin is not associated with an increased risk of malformations and is the treatment of choice for tuberculosis in pregnancy. Prophylactic vitamin K must be administered to infants exposed late in pregnancy to prevent hemorrhagic disease.[110] Rifampin may interfere with efficacy of oral contraceptives.[111]

Sulfonamides/Trimethoprim

Sulfonamides and trimethoprim both increased the risk of cleft palate in rats at very high doses—an effect not seen in human studies, but the combination increased the risk of cardiovascular defects with first-trimester exposure, preterm birth and low birth weight, and miscarriage.[41,112,113] The primary danger is use near delivery, when the risk of neonatal hyperbilirubinemia increases. Trimethoprim induces folate depression in high doses or in folate-depleted individuals, so appropriate folic acid supplementation in the first trimester limits risk of NTDs.[114]

Quinolones

Quinolones should be reserved only for complicated infections, notably ciprofloxacin or norfloxacin, which have been studied the most extensively. Animal experiments indicate that quinolones can damage fetal cartilage, but they are not associated with an increased risk of malformations or musculoskeletal defects in humans.[10,41,115]

Tetracyclines

Tetracyclines are contraindicated after 15 weeks' gestation because of maternal hepatitis, brown discoloration of deciduous teeth, and the inhibition of bone growth. Inadvertent first-trimester exposure is common and has not been associated with congenital malformations.[10,116] There are possible associations with inguinal hernia, hypospadias, and limb hypoplasia, but no definitive patterns of malformations have been identified.[41]

TOPICAL ANTIFUNGALS

Extensive data regarding the intravaginal and topical application of nystatin in pregnancy do not indicate any toxic effect, so it is the drug of choice for superficial candida infection. Second-line options include clotrimazole and miconazole, which did not show embryotoxic potential.[117] Safety data are more limited for topical ciclopirox and terbinafine. Selenium disulfide in local application for a limited period of time is acceptable.[10]

SYSTEMIC ANTIFUNGALS

Griseofulvin and terbinafine

Both griseofulvin and terbinafine have extremely limited safety data and are not prescribed for life-threatening infections, so neither are recommended in pregnancy. Conjoined twins were reported with griseofulvin. Teratogenicity was not seen in animal or humans with terbinafine.[10,41,118]

Oral imidazole derivatives

First-trimester exposure of fluconazole, ketoconazole, and itraconazole increases the risk of cardiovascular, skeletal, craniofacial, and neurodevelopmental defects. Patients with first-trimester, low-dose, short-term exposure for vaginal candidiasis can be reassured that increased risk has not been shown, but they should obtain a detailed fetal ultrasound.[119-122] Imidazoles may disrupt estrogen production in pregnancy and ketoconazole inhibits testosterone synthesis, but the effect on fetal corticosteroid synthesis is unknown.[10,123,124]

Systemic antivirals for herpes simplex and varicella-zoster virus

Disseminated herpes simplex virus and varicella-zoster virus are important to treat intravenously during pregnancy; both are *t*oxoplasmosis, *o*ther (syphilis, varicella-zoster, parvovirus B19), *r*ubella, *c*ytomegalovirus, and *h*erpes (TORCH) infections, which potentially produce a syndrome characterized by microcephaly, sensorineural deafness, chorioretinitis, hepatosplenomegaly, and thrombocytopenia. Acyclovir is preferred because it has been studied the most extensively, although famciclovir and valacyclovir have not shown an increased risk.[10] Primary herpes simplex virus and severe recurrences should be treated at 400 mg 3 times daily for 7 to 14 and 5 days, respectively. Prophylaxis can be started at 36 weeks' gestation to minimize the risk of cesarean section, but its effect on neonatal herpes incidence is unknown. Neonatal transmission risk is high (30-50%) if women acquire genital herpes near delivery and low (<1%) if

acquired in the first half of pregnancy or in women with a history of recurrent genital HSV.[125,126]

Topical antivirals

Liquid nitrogen is safe and is a first-line treatment for warts. Trichloroacetic acid is a second-line therapy for condylomata acuminata.[10] Data are limited for imiquimod, but teratogenicity has not been shown in either animals or humans.[127] Podophyllin is pregnancy class X because high doses cause heart, limb, and ear malformations, psychiatric issues, and fetal and maternal death.[10] Podofilox should also be avoided, even though the risk of systemic absorption is low. Squaric acid was not a mutagen in biologic assays, but it lacks safety data in both animals and humans.[128] Cantharidin, potentially a potent tumor promoter, should be avoided since this also lacks safety data.[129]

Salicylic acid

Salicylism has occurred using methyl salicylate ointments and high concentrations of salicylic acid on widespread areas of hyperkeratotic skin, but there are no known cases resulting from salicylic acid acne or wart products.[130] There is no cause for concern if used on limited areas and for limited periods of time.[10]

Scabies and lice

Permethrin, topical sulfur, benzyl benzoate, and crotamiton are all considered safe for scabies therapy. One case report of a pregnant woman with arachnophobia who abused aerosolized pyrethroids was associated with congenital leukemia, but no adverse effects with topical use were seen when studied.[131,132] Benzyl benzoate was banned in the United States because its metabolite, benzyl alcohol, was associated with neonatal fatal intoxication or "gasping syndrome" from rinsing venous catheters; this has not been reported with topical use, and benzyl alcohol is available over the counter in the United States.[10] Ivermectin was teratogenic in animals at high, maternally toxic doses, but no teratogenicity has been shown in humans.[41] Lindane is potentially neurotoxic and should not be used. For lice, occlusive therapy with coconut oil or moisturizer is considered to be a first-line therapy.

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