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Original Research

New changes in pregnancy and lactation labelling: Review of dermatologic drugs

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ABSTRACT

Background: The U.S. Food and Drug Administration has published new pregnancy and lactation labelling rules that set standards on the presentation of information with regard to drug usage during pregnancy and breastfeeding, as well as the effects on fertility. These guidelines became effective June 30, 2015, and classified the risks of using prescription drugs during pregnancy in three detailed subsections: Pregnancy, Lactation, and Females and Males of Reproductive Potential. These sections describe the risks within a real-world context of caring for these patients.

Objective: In this study, we reclassified and categorized drugs and treatments commonly used in dermatology according to these new guidelines.

Methods: We performed a search of the medical literature about the use of relevant prescription drugs during pregnancy and breastfeeding and their effect on fertility. The search included prospective and retrospective studies, review articles from PubMed-indexed journals (from inception to November 2018), U.S. Food and Drug Administration records, pregnancy exposure registries, relevant information and studies provided in drug labeling by companies, and updated pharmacologic texts and guidelines up to 2018.

Results: Topical immunomodulators, systemic immunomodulators (including biologics), systemic antipruritic agents, antimicrobials, as well as acne, hair, and cosmetic agents were included. We have made best attempts to review and consolidate existing and new data and include them in our guide.

Conclusion: This new narrative format facilitates prescribing by considering a variety of factors. One previously overlooked aspect was the impact on the reproductive potential of both male and female patients. Rather than depending on overly simplistic letter risk categories, dermatologists will now need to make prescribing decisions based on each patient and the information provided, which will allow for better decision making and patient care.

Introduction

Dermatologists often encounter pregnant or breastfeeding women seeking professional advice on skin disorders. Female patients may become pregnant during the course of treatment of their dermatological conditions. Hence, dermatologists must be familiar with the potential effects of common medications on the fetus and nursing infant.

However, the generalizations of the old category system (i.e., A, B, C, D, and X), together with the lack of safety data, make assessments of risks versus benefits difficult. Therefore, the U.S. Food and Drug Administration (FDA) established and implemented a new pregnancy and lactation labelling rule as of June 30, 2015. The new format includes three sections: Pregnancy, lactation, and a new section on the reproductive potential in men and women. The rule also includes information on contraception recommendations, pregnancy testing, and information on infertility, as applicable.

Safety data in medications exclusively used in dermatology may be limited. We have reviewed the medical literature and consolidated available data from Medline, Cochrane databases, and eligible studies published in English between 1980 and 2018 relevant to common dermatologic therapies in this guide.

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Topical immunomodulators

Topical corticosteroids

Most large, population-based studies have not found any significant associations between maternal use of topical corticosteroids and pregnancy outcomes. Mild-to-moderate potency topical corticosteroids are preferred, and usage should be limited to a short duration because large amounts of very potent topical steroids during pregnancy has been associated with low-birth-weight babies (Chi et al., 2016). It is recommended that lactating mothers avoid application to the breast and nipple-areolar area until nursing ceases.

Non-steroid immunomodulators

Information on topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus), imiquimod, calcipotriene, and crisaborole is shown in Table 1.

Systemic immunomodulators

Information on systemic immunomodulators is shown in Table 2.

Systemic corticosteroids

Use of the lowest effective steroid dose is recommended (Briggs et al., 2014). These drugs should be avoided during the first trimester when the fetus's hard palate is forming. The use of corticosteroids during lactation is deemed "usually compatible" by the American Academy of Paediatrics if justified by a potential benefit to the mother. Delaying nursing until 3 to 4 hours after treatment with high doses is recommended to minimize infant exposure.

Other systemic immunomodulators

Hydroxychloroquine, cyclosporine, and sulfasalazine are relatively low risk during pregnancy and lactation. Acitretin, methotrexate, cyclophosphamide, mycophenolate mofetil, and thalidomide should be avoided under all circumstances. We recommend two forms of contraception per the FDA black box warning guidelines. In addition, male patients on thalidomide should also use a latex condom during sexual contact with women of childbearing potential, even after a successful vasectomy. Counseling should be offered in the event of inadvertent exposure. The use of systemic therapy with conditions such as psoriasis should be discussed extensively with the pregnant patient because psoriasis may improve spontaneously in up to 60% of pregnant women.

We also included the new Janus kinase inhibitor tofacitinib, which is currently indicated for psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis. Apremilast, a phosphodiesterase 4 inhibitor, is currently indicated for moderate-to-severe plaque psoriasis and psoriatic arthritis.

Table 1
Nonsteroidal immunomodulators

	Pregnancy	Lactation	Fertility (man)	Fertility (woman)
Tacrolimus and pimecrolimus	Limited data on female reproduction.	Limited clinical data available on the effects of topical tacrolimus and pimecrolimus during pregnancy, lactation, and reproduction. Due to its large molecular size, pimecrolimus is theoretically poorly absorbed systemically. When no alternatives exist, topical use on small surfaces is permissible (Murase et al., 2014). Oral tacrolimus is associated with low birth weight and premature birth; hence, avoidance in topical form is recommended.	Excretion of both drugs in breast milk is less than levels used for infantile organ rejection; however, the effects on infants are unknown and caution is advised. Using sparingly and avoiding application on the nipple are recommended (Butler et al., 2014).	Data based on animal rodent studies from manufacturer indicate altered sex hormone functions with pimecrolimus at high doses (20-40 times maximum human exposure after dermal application), and reduced sperm function was noted in male rats at high subcutaneous doses of tacrolimus.
Imiquimod	Data are limited, but teratogenicity has not been demonstrated in studies.*	Unknown if imiquimod is excreted in breast milk.	No limitations on male or female fertility based on animal studies. Human clinical data are limited.	No limitations on male or female fertility based on animal studies. Human clinical data are limited.
Calcipotriene	Animal studies have shown altered calcium homeostasis; however, no studies exist on safety during human pregnancies.* Topical usage on small surfaces is allowed.	Compatible with breastfeeding, advise for use only in localized areas to reduce the risk of significant systemic absorption.†	Rodent studies showed no change in reproduction and fertility in both males and females (Suzuki et al., 1996). Limited clinical data are available in humans.	Rodent studies showed no change in reproduction and fertility in both males and females.‡ Limited clinical data are available in humans.
Crisaborole (Eucrisa package insert, 2016)	No available data with crisaborole in pregnant women to inform of drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, no adverse developmental effects were observed with the oral administration of crisaborole in pregnant rats and rabbits during organogenesis at doses up to 5 and 3 times, respectively, the maximum recommended human dose	No information available on the presence of crisaborole in human milk, effects of the drug on the breastfed infant, or effects of the drug on milk production after topical application of crisaborole to women who are breastfeeding. Crisaborole is systemically absorbed.	Limited data are available.	Limited data are available.

* Murase et al., 2014.
† Butler et al., 2014.
‡ Suzuki et al., 1996.

Table 2
Systemic immunomodulators

	Pregnancy	Lactation	Fertility (male)	Fertility (female)
Systemic corticosteroids	Lowest effective steroid dose (Murase et al., 2014) and avoidance during first trimester when hard palate of the fetus is forming recommended. Recent studies have not shown increased risk of cleft deformities (Bandoli et al., 2017). Exposure during pregnancy may increase risk of premature rupture of membrane, placental insufficiency, low birth weight, and intrauterine growth restriction in babies.*	Systemic corticosteroids are excreted into breast milk. Use of corticosteroids during lactation is deemed "usually compatible" by AAP if justified by potential benefit to the mother (Butler et al., 2014). Nursing delay recommended for 3-4 hours after high doses to minimize infant exposure.	Possible theoretical reversible decrease in sperm production and motility; however, discontinuation not necessary in male patients trying to conceive (Semet et al., 2017).	Limited data on women; however, oral corticosteroids are used as part of in vitro fertilization and infertility treatments for women.
Azathioprine	Conflicting results from transplant and inflammatory bowel disease studies. Use if benefit of immunosuppression appears to outweigh risks.	May be compatible with breastfeeding. Recommendation to wait 4 hours after ingesting medication and monitor infant full blood count.†	No recommendation to discontinue for male patients while trying to conceive. Case series on 18 patients did not show decrease in sperm quality (Dejaco et al., 2001).	Limited data.
Acitretin	**U.S. boxed warning**: Contraindicated, known teratogen. Two forms of contraception advised, with avoidance of pregnancy 3 years after discontinuation.	Excreted in breast milk. Avoid due to potential cumulative toxicity.†	No reported infertility cases; no alterations in sperm counts/motility (Millsop et al., 2013).	Limited data available.
Cyclophosphamide	Risk of teratogenicity in humans high, especially if used during first trimester (Briggs et al., 2014). Causes cyclophosphamide embryopathy (growth restriction, ear and facial abnormalities, absence of digits, hypoplastic limbs, and developmental delay).	Excreted in breast milk. Avoid.	High risk of permanent azoospermia. Cryopreservation of sperm necessary before treatment (Silva et al., 2010).	Risk of infertility related to cumulative dose and age (Janssen and Genta, 2000).
Cyclosporine	No increased rate of fetal major malformations compared with the general population.‡ Animal data suggest low risks. Associated with low birth weight and prematurity in babies of patients with complicated health status. If used, minimum dose should be administered with close monitoring of maternal blood pressure and renal function.	Enters breast milk, not recommended by AAP.	No recommendation to discontinue for male patients while trying to conceive.‡ Study showed normal semen parameters and testicular function (Haberman et al., 1991).	Limited data available.
Hydroxychloroquine	Can be continued during pregnancy and lactation to prevent disease flares.	Deemed compatible by AAP.	Limited data available, not well studied.	Limited data available.
Hydroxyurea	Contraindicated. Teratogenicity and embryotoxicity in animals. No adequate human studies.	Excreted in breast milk. Avoid.	Small retrospective study in male patients showed potentially irreversible decreased sperm motility and spermatogenesis (Grigg, 2007).	Limited data on female fertility.
Intravenous immunoglobulin	Compatible in pregnancy.* Limited studies have shown intravenous immunoglobulin to be a safe therapy in pemphigus and pemphigoid gestationis (Ahmed and Gurcan, 2011).	Excreted in breast milk. Probably compatible.†	No impact on male fertility.‡	Improves fertility rates in in vitro fertility studies.
Leflunomide	**U.S. boxed warning:** Leflunomide is contraindicated in pregnant women because of potential for fetal harm. Following treatment, pregnancy should be avoided until undetectable serum concentrations (<0.02 mg/L) are verified. May use cholestyramine for enhanced drug elimination.	Unknown if excreted in breast milk. Avoid.‡	Limited data. Preclinical animal studies demonstrate toxicity on animal reproductive organs; manufacturer recommends contraception and washout prior to conception.†	No influence on fertility; perform washout before planning pregnancy.
Methotrexate	**U.S. boxed warning**: May cause fetal death and/or congenital abnormalities. Stays in the liver for up to 116 days after exposure, so recommendation for discontinuation at least 3 months before attempts to conceive.	Excreted in breast milk. Contraindicated.†	Possibility of reversible impairment of spermatogenesis. Discontinue at least 3 months before planning pregnancy. ‡	Discontinue 3 months before planning pregnancy.
Mycophenolate mofetil	Contraindicated. Teratogenic effects; associated with miscarriages and congenital anomalies.	Excreted in breast milk. Avoid.	No effect on male fertility or spermatogenesis, but male patients advised to discontinue medication for 3 months before attempting to conceive due to teratogenicity (Uptodate, 2019).	Limited data.

Table 2 (*continued*)

	Pregnancy	Lactation	Fertility (male)	Fertility (female)
Sulphasalazine	Mixed findings. Case reports of cleft lip and palate, hydrocephalus, coarctation of aorta. Based on other data, increase in fetal malformations has not been observed after maternal use of sulfasalazine to treat inflammatory bowel disease or ulcerative colitis. Folic supplementation recommended.	Enters breast milk. Use with caution; bloody stools or diarrhea have been reported in nursing infants. May cause kernicterus in newborns.	Reversible oligospermia, asthenozoospermia, and teratozoospermia in male patients (Toovey et al., 1981). Recommendation to discontinue treatment for 3 months before planning pregnancy with male patients.	Limited data.
Thalidomide	**U.S. boxed warning**: May cause severe birth defects or embryo-fetal death. Avoid pregnancy 4 weeks prior, during, and ≥4 weeks after therapy is discontinued.	Unknown if excreted in breast milk. Avoid.	Limited data. Animal studies report testicular degeneration in rabbits.‡	Limited data. Animal studies report no adverse effect on male and female fertility.
Tofacitinib	Indicated for psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis. Limited data. Manufacturer suggests avoiding use in pregnant women.	Unknown if tofacitinib is present in breast milk. Manufacturer does not recommend breastfeeding during treatment and for at least 18 hours after last dose of immediate-release tofacitinib or 36 hours after last dose of tofacitinib extended release. Some guidelines recommend avoiding breastfeeding.	Limited data.	Limited data. Preclinical animal studies from manufacturer data suggest reduced fertility in women of reproductive potential. Unknown if effect is reversible.
Apremilast (Otezla package insert, 2017)	Adequate and well-controlled studies with apremilast have not been conducted in pregnant women. In animal studies, the administration of apremilast to cynomolgus monkeys during organogenesis resulted in dose-related increases in abortion/embryo-fetal death at dose exposures of 2.1× MRHD, and no adverse effect at an exposure of 1.4× MRHD. In mice, no apremilast-induced malformations were observed at exposures up to 4.0× MRHD. Incidences of malformation and pregnancy loss in human pregnancies have not been established for apremilast.	Unknown whether apremilst or its metabolites are present in human milk; however, apremilast was detected in milk of lactating mice.	In fertility study of male mice, apremilast at oral doses up to approximately 3× MRHD produced no effects on male fertility.	In fertility study of female mice, apremilast was administered at oral doses of 10, 20, 40, or 80 mg/kg/day. At doses ≥1.8× MRHD, estrous cycles were prolonged due to lengthening of diestrus, resulting in longer intervals until mating. Mice that became pregnant at doses of ≥20 mg/kg/day also had increased incidences of early postimplantation losses. No effect of apremilast approximately 1.0× MRHD

AAP, American Academy of Pediatrics; MRHD, maximum recommended human therapeutic dose.

* Briggs et al., 2014 and Murase et al., 2014.

† Semet et al., 2017 and Butler et al., 2014.

‡ Briggs et al., 2014 and Silva et al., 2010.

Biologics

Biologics (Table 3) are relatively new, specific systemic therapies. Although there are no large scale studies, an increasing body of evidence suggests that biologics can be used in the treatment of patients with psoriasis during pregnancy and lactation because psoriasis as a disease itself is a risk factor for adverse pregnancy outcomes. Anti-tumor necrosis factor (TNF) alpha agents are preferred over IL-12/23 and IL-17 inhibitors due to the increased availability of long-term data. Recommendations include using anti-TNF alpha agents during the first half of pregnancy and discontinuing during the third trimester due to risks of disseminated infection in infants who receive live vaccinations. Anti-TNF alpha agents (except certolizumab) are IgG1 antibodies or receptors attached to an Fc portion of an IgG1. In the third trimester, there is a marked increase in IgG1 placental transfer (Eworuke et al., 2019). Adalimumab and infliximab are both IgG1 immunoglobulins, but etanercept is a fusion protein with considerably less transplacental transport.

Certolizumab is an Fc-free, PEGylated TNF-alpha inhibitor that is approved for treatment of moderate-to-severe plaque psoriasis and psoriatic arthritis. Certolizumab has an FDA label update indicating minimal active placental and breastmilk transfer due to its lack of the Fc region. It should be considered for pregnant women who require a biologic.

Breastfeeding is generally acceptable during treatment with anti-TNF alpha agents because these agents are minimally excreted in breast milk. Live vaccines should be avoided for 6 months in infants whose mothers have been continuously exposed to biologics, due to increased risks of infections (Porter et al., 2017).

We also included newer biologics such as guselkumab, ixekizumab (indicated for psoriasis), and dupilumab (indicated for treatment of atopic dermatitis and asthma).

Systemic antipruritics

Antihistamines

The preferred choices in pregnancy is diphenhydramine and chlorpheniramine due to their long history of relatively uneventful use during pregnancy. Loratadine is preferred as a nonsedating antihistamine as it poses no major teratogenic risk. Otherwise, cetirizine may also be considered. Observation for symptoms of sedation, tachycardia, or dry mouth in the nursing infant is recommended.

There are no published animal studies examining the effects of antihistamines on male fertility, and current available literature on humans reports conflicting findings. There are a few case reports of gynecomastia, low sperm motility, and inability to conceive associated with chronic antihistamine use, and these effects were reversible 3 months after antihistamine discontinuation. However, a

Table 3
Biologics

	Pregnancy	Lactation	Fertility (male)	Fertility (female)
Adalimumab	No apparent evidence of increased embryotoxicity, teratogenicity, or pregnancy loss based on data from >500 pregnancies (Grunewald and Jank, 2015). Manufacturer recommends contraception during therapy and within 5 months after end of treatment.	Case reports show no adverse effects on infants (Butler et al., 2014).	Limited clinical data suggest no negative impact on male/female fertility.	Limited clinical data suggest no negative impact on male/female fertility.
Etanercept	Multiple studies (cohort, case controls, registry data, case reports) of >300 pregnancies conclude no patterns of malformation or prematurity (Götestam Skorpen et al., 2016). Generally preferred over other anti-tumor necrosis factor alpha agents due to its fusion protein makeup. An exception to these general conclusions is 1 case report of an infant with VACTERL* association in a mother on etanercept during pregnancy (Carter et al., 2006).	Concentration excreted in breast milk minimal; no adverse events reported.	No negative effects on fertility. In men, spermiogram parameters remained unchanged (Clark, 2010).	No negative effects on fertility.
Infliximab	Multiple studies of >1000 pregnancies do not show patterns of malformation or prematurity (Ostensen, 2014). Manufacturer recommends contraception during therapy and for 6 months after last infusion.	Case reports show no adverse effects on the infant.†	In vitro experiments show decreased sperm motility and sperm integrity (Perdichizzi et al., 2007). However, normal ejaculate findings remained unchanged in patients on infliximab (Villiger et al., 2010) and a small case series have described births of healthy children to fathers who were on infliximab during the time of conception (Paschou et al., 2009).	Limited clinical data. Does not appear to be affected.
Ixekizumab	Extremely limited clinical data, no human studies. One animal study showed no harmful effects on the fetus when medication was administered during the first 20 weeks of gestation; week 20 to birth was associated with increased neonatal deaths (Clarke et al., 2015).	Excretion in breast milk unknown.	Limited data. Preclinical animal studies do not show impairment on male and female fertility.	Limited data. Preclinical animal studies do not show impairment on male and female fertility.
Omalizumab	Limited data in pregnant women; use has been mainly reported in population with asthma.	Excretion in breast milk unknown.	Limited data. Preclinical animal studies show no effect on male/female fertility.	Limited data. Preclinical animal studies show no effect on male/female fertility.
Rituximab	Not recommended. Counseling recommended for women to avoid pregnancy for at least 12 months after exposure due to long retention time.‖	Excreted in breast milk. Avoid.†	Limited data. Eight case reports in literature of men on rituximab at the time of conception; 7 of 8 pregnancies resulted in healthy children, and 1 was a spontaneous abortion (Ostensen, 2014).	Limited data available.
Secukinumab	Limited clinical data. Developmental toxicity studies from manufacturer in monkeys and mice found no evidence of harm to fetus.	Excretion in breast milk unknown; not recommended.	Limited data. Preclinical animal studies do not show impairment on male and female fertility.	Limited data. Preclinical animal studies do not show impairment on male and female fertility.
Ustekinumab	Other agents are preferred over ustekinumab due to limited data. Manufacturer recommends contraception for women of childbearing potential at least 15 weeks after therapy.	Excretion in breast milk unknown; not recommended.	Preclinical animal studies do not show impairment on male and female fertility.	Preclinical animal studies do not show impairment on male and female fertility. Older/more thoroughly investigated tumor necrosis factor alpha inhibitor recommended instead.
Certolizumab	Preferred choice during pregnancy. Registry data of 1137 patients show no teratogenicity or increased risk of fetal death (Clowse et al., 2018).	Concentration excreted in breast milk minimal; no adverse events reported.	Limited data. Preclinical animal studies do not show impairment on male and female fertility.	Limited data. Preclinical animal studies do not show impairment on male and female fertility.
Guselkumab	Monoclonal IgG antibody. Human IgG is known to cross the placenta; therefore, exposure to the fetus may occur if administered to pregnant women.	Unknown if guselkumab is present in breast milk. However, guselkumab is a monoclonal IgG antibody; human IgG is known to be present in breast milk.	Limited data.	Limited data.
Dupilumab	Indicated for atopic dermatitis and asthma. Dupilumab is a monoclonal IgG antibody; IgG molecules are known to cross the placenta; therefore, exposure to the fetus during pregnancy may occur.	Unknown if dupilumab is present in breast milk; however, maternal IgG molecules are present in breast milk.	Limited data.	Limited data.

IgG, immunoglobulin G

Table 4
Antimicrobials

	Pregnancy	Lactation	Fertility (male)	Fertility (female)
Antibacterial				
Azithromycin	No reported increase risk in pregnancy, compatible (Murase et al., 2014).	Excreted in small amounts in breast milk, but studies have not shown any adverse effects. Compatible (Butler et al., 2014).	No impairment of fertility based on animal studies.	No impairment of fertility based on animal studies.
Cephalosporin	No issues identified in fetus when used during second and third trimesters in general. Older cephalosporins preferred.	Deemed compatible by AAP.†	No impairment of fertility based on animal studies.	No impairment of fertility based on animal studies.
Clindamycin	No association with teratogenicity; compatible.*	Deemed compatible by AAP.†	No impairment of fertility based on animal studies.	No impairment of fertility based on animal studies.
Clofazimine	Safe for both mother and child. Leprosy is exacerbated during pregnancy, so standard multidrug therapy should be continued during pregnancy (World Health Organization, 1998).	Small amount enters breast milk and may cause skin discoloration of the infant, which may be reversible.	Limited data available.	Limited data available.
Dapsone	Use during pregnancy does not seem to present major risks to the fetus or newborn baby; use with caution.*	AAP recommendation to avoid in infants with known G6PD deficiency.†	Limited data in humans. Per manufacturer, animal studies in rats showed reduced sperm motility and reduced embryo implantations at oral doses much higher than systemic exposure in humans (17×).	Limited data in humans. Per manufacturer, animal studies in rats showed reduced sperm motility and reduced embryo implantation at oral doses much higher than systemic exposure in humans (17×).
Erythromycin	Antibiotic of choice throughout pregnancy, along with penicillins. Erythromycin estolate causes maternal hepatotoxicity during second trimester, and contraindicated during pregnancy.	Deemed compatible by AAP.†	Human clinical study on 78 men showed no significant effect on semen quality (Baker et al., 1984).	Limited data available.
Fluoroquinolones (ciprofloxacin, ofloxacin)	Generally avoided during pregnancy and lactation because they are toxic to developing cartilage in experimental animal studies, but not found in human pregnancy.* Accidental administration should not be indication for abortion.	Ciprofloxacin and ofloxacin considered safe for lactation by AAP; watch for diarrhea.	Per manufacturer, animal studies with high doses (13×) showed decreased spermatogenesis and impaired fertility in male rats. However, multiple studies have demonstrated antibiotic therapy recommendations for testicular infections and epididymis (Briggs et al., 2014).	No effects on fertility observed in female rats.
Metronidazole	Human data suggest low risks. Topical usage is permissible (Burtin et al., 1995).	Deemed compatible.†	Animal studies on rats showed male infertility at high doses (el-Nahas and el-Ashmawy, 2004). Limited clinical data in humans.	Limited data available.
Mupirocin (topical)	Low dose use has not been associated with teratogenicity in small studies.	Compatible. Topical antibiotic of choice during lactation.	Limited clinical data in humans. Animal studies show no effect on fertility.	Limited clinical data in humans. Animal studies show no effect on fertility.
Penicillins (penicillin G, penicllin V, amoxicillin, ampicillin, cloxacillin)	Antibiotic of choice during pregnancy.	Excreted into breast milk in low concentrations. Reports of loose stools and rash in nursing infants. Use with caution.	In vitro studies showed no effect on sperm characteristics at low doses. Impairment in viability at higher doses.	Limited data available.
Retapamulin (topical)	Animal studies have shown minor effects on fetal growth and incomplete ossification after oral administration. However, very low plasma concentration suggests little to no risks with topical application.‡	Excretion in breast milk unknown.	Animal studies showed no impairment of male/female fertility.	Animal studies showed no impairment of male/female fertility.
Rifampicin	Compatible; not a proven teratogen.*	Deemed compatible.†	Limited clinical data.	Limited clinical data.
Sulfonamides, sulfamethoxazole-trimethoprim	Possible increased risk of congenital malformations, preterm births. Avoid in G6PD deficiency.*	Excreted in breast milk; use with caution.	Mixed results in male in vitro studies (Samplaski and Nangia, 2015). No impairment on fertility based on animal studies.	No impairment on fertility based on animal studies.
Tetracyclines	Contraindicated; risk of congenital defects.*	Recommendation to avoid prolonged usage for >3 weeks to prevent infant dental staining.†	In vitro study showed reversible impairment of sperm movement and viability (Millsop et al., 2013).	Limited data available.
Topical antifungal				
Ciclopirox (topical)	Likely compatible.*	Minimal systemic absorption.†	Animal studies show no effect on fertility.	Animal studies show no effect on fertility.
Clotrimazole (topical, pessary)	Topical antifungal of choice.*	Best studied; first line therapy.	Animal studies showed no impairment of male/female fertility.	Animal studies showed no impairment of male/female fertility.
Miconazole	Adverse human fetal events not noted in topical form.*	Excretion in breast milk unknown.	Limited data available.	Limited data available.
Ketoconazole (topical)	Permissible. Not detectable in plasma serum after chronic use of shampoo form.	No human data available, but deemed minimal risk.	Limited data available.	Limited data available.

Table 4 (*continued*)

	Pregnancy	Lactation	Fertility (male)	Fertility (female)
Nystatin	Extensive data on intravaginal and topical nystatin during pregnancy do not indicate toxicity. Drug of choice for superficial candida infection.*	Compatible with lactation.	Limited data available.	Limited data available.
Selenium sulphide (topical)	No animal or human studies conducted, risk to fetus unknown. Recommendation for local application for a limited time.*	Compatible; no adverse events reported.†	Limited data available.	Limited data available.
Terbinafine (topical)	Permissible. Systemic absorption is limited after topical application.	Systemic absorption is limited after topical application. Avoid over nipple areas.	Systemic absorption is limited after topical application.	Systemic absorption is limited after topical application.
Systemic antifungal				
Griseofulvin	Case report of conjoined twins. Avoid.*	Avoid due to tumorigenic potential.†	Mixed findings in animal studies. Available human studies are limited and have not shown that griseofulvin is deleterious to male fertility. Manufacturer recommends male patients wait at least 6 months after completing griseofulvin to father a child. Potential fathers should be counseled on possible adverse effects of griseofulvin on male fertility.	Limited data available.
Itraconazole	Dose-related embryotoxicity and teratogenicity in first trimester. In case of exposure, obtain detailed fetal ultrasound.*	Alternatives preferred.†	Animal studies show no effect on male and female fertility.	Animal studies show no effect on male and female fertility.
Ketoconazole	Dose-related embryotoxicity and teratogenicity during first trimester. In case of exposure, obtain detailed fetal ultrasound. *	Deemed compatible by the AAP.†	Ketoconazole may decrease serum testosterone concentration. Consider discontinuing ketoconazole prior to planning conception.‡	Animal rodent studies showed decreased pregnancy rates and inhibition of ovulation at high doses. Consider discontinuing ketoconazole prior to planning conception.
Terbinafine	Animal data suggest low risk.*	Excreted in breast milk. Avoid.†	Animal studies show no effect on fertility.	Animal studies show no effect on fertility.
Antiviral				
Acyclovir	No reported association with adverse fetal effects in human pregnancy (Stone et al., 2004).	Deemed compatible by AAP.†	Manufacturer's animal studies using high doses of acyclovir showed largely reversible adverse effects on spermatogenesis. Limited data in humans.	Manufacturer's animal rodent studies show no effect in female fertility. Limited data in humans.
Famciclovir	Limited data available. Use when potential benefit clearly outweighs fetal risk in human pregnancy. Acyclovir and valacyclovir preferred.	Excretion in breast milk unknown.	Testicular toxicity noted in manufacturer's animal studies. No effect on sperm count and morphology in human male clinical study.	No effect on fertility in manufacturer's female rodent animal studies.
Valacyclovir	Prodrug of acyclovir. Guidelines for use as in acyclovir.	Second-line therapy.	Manufacturer product information showed no effect on fertility in animal studies.	Manufacturer product information showed no effect on fertility in animal studies.
Antiscabetic/antipediculocide				
Benzyl benzoate (topical)	Banned in United States because benzyl alcohol is a metabolite. Benzyl alcohol associated with neonatal fatal intoxication or "gasping syndrome" from rinsing venous catheters. No evidence of adverse outcomes in pregnancy.‡	Limited data available.	Limited data available.	Limited data available.
Crotamiton (topical)	Minimal data on human and animal studies; likely safe.	Limited data available.	Limited data available.	Limited data available.
Ivermectin	Teratogenic in animals at high doses. Recommended for use only if resistant to topical treatment/compelling indication.*	Secreted in low concentrations. Manufacturer recommends treatment only if benefits outweigh risks.	Animal rodent study showed slight male fertility disturbances (el-Nahas and el-Ashmawy, 2008). Rodent animal studies by manufacturer did not show any impairment of fertility.	Limited data available.
Lindane (topical)	Avoid; potential teratogenicity.*	Enters breast milk. Avoid.†	Clinical study showed possible decline in semen quality.	Animal rodent studies on use as a pesticide suggest disruption of estrogen cycle in female rats and delay in ovulation.
Malathion (topical)	Avoid, if possible.*	Excreted in breast milk. Avoid.†	Animal rodent studies on use as pesticide suggest toxic effects to male reproductive system (Choudhary et al., 2008).	Limited data available.
Permethrin (topical)	Drug of choice. No evidence of adverse outcomes during pregnancy.*	Compatible with lactation.†	Animal studies show no effect on fertility.	Animal studies show no effect on fertility.

* Murase et al., 2014.
† Butler et al., 2014.
‡ Briggs et al., 2014.

Table 5
Acne, hair, and cosmetic agents and miscellaneous agents

	Pregnancy	Lactation	Fertility (male)	Fertility (female)
Topical acne preparations				
Azelaic acid	No adequate and well-controlled studies of topically administered azelaic acid in pregnant women. Animal studies indicate potential for effects with respect to pregnancy, embryo-fetal development, parturition, or postnatal development. However, dose levels without observed adverse effects in animals ranged across studies from 3-32 times the maximum recommended human dose based on body surface area (Skinoren package insert, 2016). Amount of azelaic acid available systemically after topical administration is minimal (<4%); hence, deemed low risk (Uptodate, 2019).	Unknown if azelaic acid is excreted in breast milk. Amount of azelaic acid available systemically after topical administration is minimal (<4%); significant change from baseline azelaic acid levels in breast milk is not expected.†	Animal studies have shown no adverse effects on fertility.	Animal studies have shown no adverse effects on fertility.
Benzoyl peroxide	Animal studies have not been conducted. Estimated 2% of applied dose is expected to be absorbed systemically, but considered safe (Murase et al., 2014).	Unknown if benzoyl peroxide is excreted in breast milk. Caution should be exercised when administering to nursing women.	Limited data.	Limited data.
Adapalene	Limited safety data available. Not recommended according to experts.* Case report of cerebral and ocular malformations in exposed fetus, which resulted in termination of pregnancy (Autret et al., 1997).	Excretion in breast milk is unknown. Recommendation to use with caution.	Animal studies have not shown adverse effects on fertility.	Animal studies have not shown adverse effects on fertility.
Tretinoin	Studies suggest that usage in small body surface areas are likely safe; however, not recommended according to experts.*	Minimal amounts found in breast milk, not thought to be harmful to infants (Butler et al., 2014).	Animal studies showed no effects on fertility and general reproductive performance. No specific contraceptive precautions are necessary for men using topical tretinoin.	Animal studies showed no effects on fertility.
Isotretinoin	Isotretinoin is contraindicated in women of childbearing potential. Patients should be on two forms of contraception or abstinence at least 1 month prior, during, and 1 month after discontinuation. Associated with major fetal abnormalities, spontaneous abortions, premature births, and low IQ scores. Embryopathy has been reported even with single doses.	Excreted in breast milk. Not recommended during lactation.	No reported effects on sperm parameters and no recommendation to male patients for discontinuation when trying to conceive (Briggs et al., 2014).	Limited data available on female fertility.
Hair agents				
Minoxidil (topical)	Case reports of newborns with birth defects (Smorlesi et al., 2003); hence, suggested to avoid during pregnancy.	Deemed safe by AAP.‡	Manufacturer's animal rodent studies have shown reduction in conception rates; Limited data available in humans.	Limited data available in humans.
Finasteride	Pregnant women are advised to avoid crushed or broken finasteride tablets and contact with semen from male partners exposed to finasteride, although it has been shown that pregnant women are exposed to only a negligible amount of finasteride in their male partner's semen.	N.A.	Human studies show slight decrease in ejaculate volume and counts and motility of spermatozoa, but morphology remains unaffected. Effects are reversible. Recommendation to discontinue treatment prior to conception.‡	N.A.
Spironolactone	Spironolactone crosses the placenta and should be avoided during the first trimester due to antiandrogenic effects.‡	Possible suppression of milk; however, deemed compatible by AAP and WHO.†	Rodent studies showed decreased sperm concentration but no reduction in sperm motility and fertility. In humans, gynaecomastia, impotence, and reduced sperm motility and density may occur with spironolactone at doses >100mg/day due to decreased testosterone levels (Millsop et al., 2013).	Limited data.

Table 5 (*continued*)

	Pregnancy	Lactation	Fertility (male)	Fertility (female)
Dutasteride	Currently FDA approved for benign prostatic hyperplasia but not alopecia; approved in South Korea and Japan for alopecia. Contraindicated in pregnancy. Pregnant women are advised to avoid contact with crushed or broken tablets and the semen from a male partner exposed to dutasteride.	Unknown if dutasteride is excreted in breast milk. Use is contraindicated in women of childbearing potential.	Abnormalities of external male genitalia were reported in animal reproduction studies.	Limited data.
Cosmetic agents				
Botox and fillers	In general, cosmetic therapy (e.g., botulinum toxin) should be avoided during pregnancy, even though data exist to suggest that risk to fetus is low. No case reports have examined outcomes of pregnant women and their children after use of hyaluronic acid, poly-L-lactic acid, calcium hydroxylapatite, or collagen fillers during pregnancy.	Use in lactating mothers is unknown.	Limited data.	Limited data.
Hydroquinone (topical)	Studies on reproduction and fertility have yielded conflicting results. Based on available data, hydroquinone use during pregnancy does not appear associated with increased risk of major malformations or other adverse effects (Decaprio, 1999). However, because of substantial absorption compared with other products, it is best to minimize exposure until further studies can confirm safety.	Excretion in breast milk is unknown.	Animal studies have yielded conflicting results with regard to reproduction.	Animal studies have yielded conflicting results with regard to reproduction.
Analgesics				
Paracetamol	Analgesic of choice during pregnancy	Deemed compatible by AAP	Epidemiological studies have shown that in utero exposure may be associated with cryptorchidism in offspring (Kilcoyne and Mitchell, 2017).	No known effects; however, recent studies with animals and human embryonic stem cells have shown that intrauterine exposure at levels commonly observed in pregnant women may compromise female reproductive health (Holm et al., 2016).
Aspirin	Low-dose aspirin permissible during pregnancy; avoid during third trimester due to risk of fetal harm.	Salicylates cross the placenta and enter fetal circulation. Low dose permissible; however, alternative drugs should be considered for analgesic use.	A meta-analysis showed efficacy of low-dose aspirin in improving pregnancy rate for in vitro fertilization (Wang et al., 2017).	Human study on 7 healthy male volunteers showed possible adverse effects on fertility with high doses of aspirin (Kershaw et al., 1987).
Nonsteroidal anti-inflammatory agents[†]	Considered safe for use up until third trimester due to risk of premature closure of ductus arteriosus.	Limited information available. Ibuprofen is preferred due to most information available. Ibuprofen is secreted into breast milk in small amounts.	Conflicting data with regard to risks of spontaneous abortion during first trimester. Women who plan to conceive should be cautioned.	Limited data available.
Local anesthetics				
Lidocaine	Preferred choice during pregnancy.	Deemed compatible by AAP.	Limited data available.	Limited data available.
Prilocaine	Adverse events have not been observed in animal studies.	Excretion in breast milk is unknown.	Limited data available.	Limited data available.
Miscellaneous				
Colchicine	Colchicine is not associated with increased teratogenic risk during pregnancy (Both et al., 2012).	Excreted in breast milk; however, no adverse effects reported in infants during breastfeeding with mothers who receive 1.5 mg/day.	Meta-analysis showed no demonstrable negative effect on fertility.	Meta-analysis showed no demonstrable negative effect on fertility (Both et al., 2012).
Salicylic acid (topical)	Use of topical salicylic acid on limited areas for limited time is generally acceptable;[*] however, occlusive dressings should be avoided. No studies on the effects of salicylic acid on human pregnancy, but other salicylates have been associated with birth abnormalities.	Deemed safe by American Academy of Dermatology.[‡]	No apparent effects on both male and female fertility.	No apparent effects on both male and female fertility.

Table 5 (*continued*)

	Pregnancy	Lactation	Fertility (male)	Fertility (female)
Podophyllin (topical)	Podyphyllin is absolutely contraindicated in pregnant and lactating patients. Reports in pregnant women have shown evidence of fetal abnormalities, fetal death, and stillbirth.‡	Contraindicated	Animal studies have not shown any influence on fertility. Limited data available in humans.	Limited data.
Coal tar (topical)	In general, should be avoided during pregnancy due to presence of mutagenic and carcinogenic aromatic hydrocarbons.*	Avoid.†	Limited data.	Limited data.
Methyl aminolevulinate (topical)	Limited clinical data available. Fetal ossification irregularities observed in animal studies.	Excretion in breast milk is unknown.	Animal studies did not show effect on male and female fertility.	Animal studies did not show effect on male and female fertility.
Psoralen	Psoralen is a known mutagen; recommended to avoid psoralen and ultraviolet A light phototherapy treatment during pregnancy.*	Excretion in breast milk is unknown.	Animal studies indicate decreased sperm count and fertility in male rodents.	Animal studies indicate ovarian toxicity in female rodents (Diawara and Kulkosky, 2003).

AAP, American Academy of Pediatrics; FDA, U.S. Food and Drug Administration; N.A., xxx; WHO, World Health Organization.

human in vitro study demonstrated that histamine had spermicidal properties, and low doses of H1 antihistamines prevented this spermicidal action (Millsop et al., 2013).

A few reported cases of improved sperm count and motility with the use of H1 antihistamines also exist. Due to insufficient data, there are no recommendations to avoid antihistamine use when planning to conceive.

Doxepin

Doxepin has been associated with fetal ileus and hypotonia in newborns when used during the third trimester; however, no congenital human malformations have been reported with use during early pregnancy. Doxepin is secreted in breast milk, and there is a case report of drowsiness, vomiting, poor feeding, and muscle hypotonia in a nursing infant after maternal use of doxepin (Frey et al., 1999). Animal studies have reported risks of impaired fertility with high doses of doxepin (Sinequan package insert, 2007).

Antimicrobials

Information on antimicrobial agents is shown in Table 4.

Antibacterials

The choice of antibiotic in pregnancy should be governed by antibiotic sensitivities whenever possible. In general, penicillins and the erythromycin group have a history of safety during pregnancy, except for erythromycin estolate, which has risks of hepatotoxicity during the second trimester. Mupirocin is the topical agent of choice during pregnancy and lactation.

Antifungals

Oral anti-fungal agents should be avoided during pregnancy. Superficial cutaneous infections can be treated with topical agents unless the mother's health or function is severely impaired by the condition. Vulvovaginal candidiasis during pregnancy should be treated with topical agents. Treatment for onychomycosis should be best left until after pregnancy.

Antivirals

Acyclovir is preferred for the treatment of genital herpes in pregnant women because more data are available. However, valacyclovir may also be considered due to its simplified dosing schedule. Breastfeeding should be avoided if herpetic lesions are on the breast to prevent transmission to the infant.

Antiscabietics

Permethrin, topical precipitated sulphur, benzyl benzoate, and crotamiton are all considered safe for scabies therapy. The choice of treatment during pregnancy and lactation is permethrin.

Acne, hair, and cosmetic agents, and miscellaneous agents

Information on acne, hair, and cosmetic agents, and miscellaneous agents are shown in Table 5. Topical acne agents include azelaic acid, benzoyl peroxide, adapalene, and tretinoin. Azelaic acid and benzoyl peroxide have been considered safe to use during pregnancy. Isotretinoin is contraindicated in women of childbearing potential and is associated with major fetal abnormalities, with embryopathy reported even with a single dose. Isotretinoin is excreted in breast milk and thus not recommended during lactation.

Topical and oral agents used to treat female pattern hair loss (e.g., minoxidil, finasteride, spironolactone, and dutasteride) should be avoided during pregnancy.

Lidocaine (Lignocaine) and prilocaine are not contraindicated during pregnancy and lactation for topical or intradermal use in routine biopsies and excisions. There are no studies to document prenatal fetal lidocaine levels after maternal cutaneous injection. Therefore, the usual recommended maximal doses can be used with closer monitoring. The lowest possible doses of adrenaline should be used with lidocaine.

Paracetamol is the analgesic of choice during pregnancy and lactation. Aspirin should be avoided during the third trimester due to risks of premature closure of the ductus arteriosus and excessive blood loss during delivery. Nonsteroidal anti-inflammatory agents are associated with an increased risk of spontaneous abortion during the first trimester, neonatal renal failure, and premature closure of the ductus arteriosus if used during the last trimester; hence, they should be avoided during pregnancy and lactation.

Conclusion

This new FDA ruling provides patients and prescribers with additional information to guide decision making to provide the best standard of care for both the mother and child during pregnancy and breastfeeding, as well as for patients of childbearing age. The guidelines will affect and change current practices and policies as

supported by clinical data. However, this may imply increasing the responsibility of physicians to safeguard the wellbeing of their patients. Rather than depending on overly simplistic letter risk categories, dermatologists now need to make prescribing decisions based on each patient and new information provided. Ideally, pregnant patients and those who are breastfeeding or of childbearing potential should also be able to make informed decisions with regard to these issues. Overall, this new rule aims to improve safety and patient care.

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