# Infertility and teratogenicity after paternal exposure to systemic dermatologic medications: A systematic review

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***Background:*** This systematic review assesses effects of paternal exposure to dermatologic medications by using the former US Food and Drug Administration (FDA) pregnancy categories as a benchmark.

***Objective:*** To assess whether systemic dermatologic medications can cause infertility and teratogenicity when taken by men.

***Methods:*** Categories D and X dermatologic medications were identified; a systematic review of the literature and reviews of the FDA Adverse Events Reporting System and prescribing information were performed to identify the effects of these medications on male fertility and teratogenicity. A secondary search was performed to assess for other systemic dermatologic medications causing teratogenicity or infertility following paternal exposure.

***Results:*** A total of 13 medications met the inclusion criteria. Of 1,032 studies identified, 19 were included after a systematic review of the literature. Studies evaluating medication effects with paternal exposure were identified for 10 of the 13 evaluated medications, and evidence of a negative effect was identified for 6 medications.

***Limitations:*** We did not encounter any studies for 3 medications that met the inclusion criteria. Information submitted to the FDA Adverse Events Reporting System may not reflect the incidence of side effects.

***Conclusions:*** Many former pregnancy category D and X systemic dermatologic medications also have effects on male fertility. More research and better-quality studies are required in this area, particularly studies assessing potential teratogenicity. (J Am Acad Dermatol 2019;80:957-69.)

***Key words:*** chromosomal damage; infertility; paternal exposure; pregnancy categories; semen parameters; seminal excretion; spermatogenesis; systemic medications; teratogenicity.

The effects of systemic medications on fertility and fetal development are common concerns among men looking to conceive.[1] Whereas the effects of maternal exposure to many medications are well described, the data surrounding their effects after paternal exposure remain sparse. On the basis of quality of the available evidence, the US Food and Drug Administration (FDA) categorized medications with potential for teratogenicity and infertility from maternal, but not paternal, exposures. This gap in information leads to unease among male patients who take systemic medications and

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hesitance of dermatologists who prescribe them. Moreover, anxiety is further provoked by theoretical guidelines suggesting that men discontinue certain medications before attempting to conceive.

The FDA began phasing out pregnancy categories (Table I) in 2015 to encourage patient-centered discussions regarding medication selection with expecting mothers[2]; however, this legacy classification remains an excellent indicator of availability of evidence on teratogenicity. With use of legacy FDA categories as a benchmark, this systematic review assesses effects of systemic dermatologic medications that were formerly categorized as category D or X after paternal exposure, with particular focus on teratogenicity and infertility.

**CAPSULE SUMMARY**

- Many systemic dermatologic medications can cause teratogenicity after maternal exposure. Some of these medications can cause infertility and may have teratogenic effects after paternal exposure; however, teratogenicity is understudied.
- Information on fertility effects or teratogenicity risk should guide discussions with male patients who are using these medications and looking to conceive.

## METHODS

Medications commonly prescribed by dermatologists and formerly categorized as category D or X for pregnancy by the FDA were identified by using the reference, *Comprehensive Dermatologic Drug Therapy*.[3] Medications were included if they were (1) systemic medications, (2) categorized as category D or X by the FDA as of 2013, and (3) FDA approved for dermatologic indications in male patients.

An electronic literature search of the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases was then performed on January 24, 2018. Articles published from inception of the databases through January 24, 2018, were included in the search. Search terms included the generic names of each medication identified by using the aforementioned criteria separated by using the word *OR* combined with the term *drug effects* and index terms representing parameters affecting male fertility and teratogenicity, including parameters of sperm functions, semen analysis, teratogenicity, and sperm-ovum interactions.

Study selection was performed on the basis of inclusion criteria consisting of (1) full-length clinical or in vitro study of multiple patients; (2) performance of semen analysis or examination of fertility in human males or teratogenic effects in their offspring; (3) a subset of patients taking 1 identified systemic medication in isolation. Studies were excluded if (1) they were duplicate publications; (2) they were reviews or case reports; (3) they were abstracts or presentations; (4) all the subsets of patients included in them took multiple medications; (5) they included patients who were infertile at baseline; (6) all the study subjects were female; (7) they did not include study of any medication meeting the aforementioned medication inclusion criteria; and (8) they used only animal models.

Titles and abstracts were assessed on the basis of these criteria by 2 independent, blinded reviewers (G.A.Z. and C.C.M). If the title or abstract did not include enough information to apply exclusion criteria, the full text was assessed. The reviewers compared results, and any discrepancies were resolved by the senior author (R.H.). The full texts of the remaining manuscripts were reviewed to determine eligibility based on inclusion criteria.

For each medication, prescribing information was reviewed and the FDA Adverse Events Reporting System (FAERS) was queried for teratogenicity and infertility after paternal exposure.

To ensure comprehensive evaluation of all medications with FDA-approved dermatologic indications negatively affecting fertility and teratogenicity, a secondary search was performed by using the aforementioned index terms combined with the term *derm-*.

## RESULTS

In all, 13 systemic dermatologic medications used in males that were formerly classified as belonging to FDA pregnancy category D or X (Table II) were identified. A literature search identified 1032 publications potentially meeting the study criteria. After 124 duplicates were removed, the titles and abstracts of 908 studies were reviewed and 731 publications were excluded (Fig 1). A total of 177 articles were then evaluated by assessing their full text, of which 19 were included.

Studies evaluating medication effect with paternal exposure were identified for 10 of 13 evaluated medications. Evidence of possible teratogenic effects or negative effects on male fertility was identified for 6 medications: colchicine, cyclophosphamide, doxycycline, finasteride, tetracycline, and thalidomide (Table III[4-25]). Evidence against negative effects on fertility was identified for the 4 remaining medications (Table IV[26-37]). Seminal

*Abbreviations used:*

FAERS: FDA Adverse Events Reporting System
FDA: US Food and Drug Administration

excretion (Table V[25,38]) and chromosomal damage were reported with 2 and 1 medications, respectively. Precautions in prescribing information (Tables III,IV, and VI[39-41]) and results of FAERS queries were recorded. A secondary search identified no additional dermatologic medications causing infertility or teratogenicity following paternal exposure.

## Infertility

**Colchicine.** Colchicine inhibits mitosis[42] and has been shown to destroy germ cells in animal models.[43] In an 11-year observational study, 18 married males with familial Mediterranean fever were treated with 0.5 to 2 mg/d of colchicine.[4] Four patients disclosed fertility problems during treatment. Semen analysis of 3 patients revealed normal spermiograms with pathologic sperm penetration analyses, which assess sperm penetration of ova; the fourth patient was azoospermic with reduced ejaculate volume. Two of the 4 men stopped taking colchicine; 1 patient with abnormal sperm penetration analysis conceived after he stopped taking it, whereas the other (who was azoospermic) remained azoospermic 9 months after he stopped taking it.

A second study analyzed semen and serum hormone levels in 31 males with Behçet disease treated with colchicine in a dose of 0.25 to 2 mg/d (n = 6), cyclophosphamide (n = 5), or both (n = 14); 6 patients were untreated controls (4 of whom provided semen samples). Two of the 6 men taking colchicine were found to be oligospermic compared with 1 of the 4 controls who provided sperm samples.[5]

**Cyclophosphamide.** Four studies, including 1 double-blind, randomized, controlled trial,[7] measured semen parameters in adult patients who were given cyclophosphamide—in a dose of 50 to 100 mg/d in 2 studies,[8,9] 25 to 100 mg/d in 1 study,[5] and 1.5 mg/kg/d in 1 study.[7] Of the total of 68 patients, 55 developed azoospermia. Three studies[8-10] reported varying rates of recovery of spermatogenesis after treatment cessation. Buchanan et al demonstrated recovery in 9 of 14 patients treated for less than 18 months and 3 of 12 patients treated for more than 18 months.[8] Mean reappearance of spermatozoa occurred 31 months after cessation of treatment. Anserini et al showed recovery in 8 of 9 patients treated with an average total dose of 200 mg/kg.[10] Fairley et al demonstrated recovery in 3 of 11 patients at 6 months and performed a testicular biopsy in 5 patients: the biopsy demonstrated absence of spermatogenesis but presence of Sertoli cells in 2 patients during treatment and 1 patient 6 weeks after treatment, occasional spermatogonia in 1 patient 12 months after treatment, and normal spermatogenesis with reduced cellularity in 1 patient 16 months after treatment (the patient achieved pregnancy with his wife around the time of the biopsy).[9]

**Table I.** Former FDA pregnancy categories

| Category | Description |
|---|---|
| A | Controlled studies of pregnant women show no risk to the fetus |
| B | No controlled studies have been conducted in humans, and animal studies show no risk to the fetus<br>OR<br>Animal reproduction studies have shown adverse effects, but well-controlled studies in pregnant women have shown no adverse effects to the fetus |
| C | No controlled studies have been conducted in animals or humans<br>OR<br>No controlled studies have been conducted in humans, and animal reproduction studies have shown an adverse effect on the fetus |
| D | Evidence of human risk to the fetus exists; however, benefits may outweigh risks in certain situations |
| X | Controlled studies in both animals and humans demonstrate fetal abnormalities; the risk in pregnancy women outweighs any possible benefit |

Data from Pernia and DeMaagd.[2]
*FDA*, US Food and Drug Administration.

**Table II.** FDA Pregnancy category D and X medications meeting the inclusion criteria

| Category D | Category X |
|---|---|
| Colchicine | Acitretin |
| Cyclophosphamide | Bexarotene |
| Doxycycline | Finasteride |
| Minocycline | Isotretinoin |
| Systemic steroids | Methotrexate |
| Tetracycline | Thalidomide |
| Voriconazole | |

*FDA*, US Food and Drug Administration.

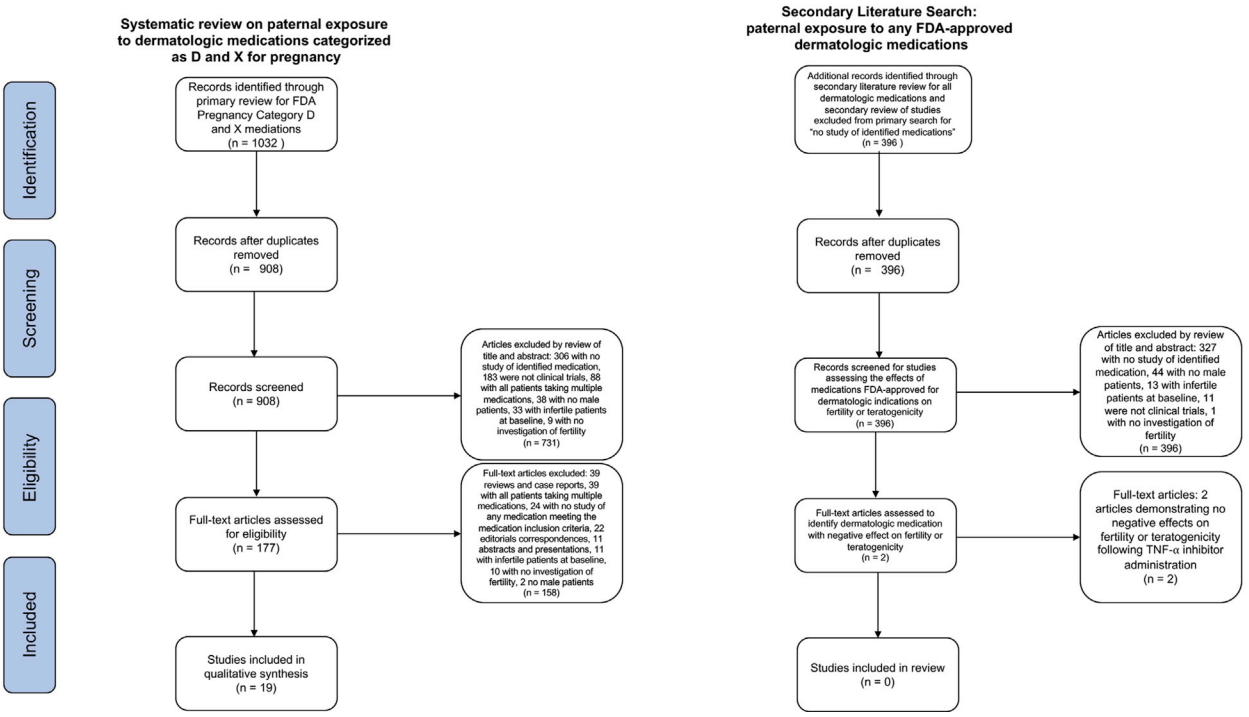


**Fig 1.** Search methodology and results of literature search on paternal exposure to systemic dermatologic medications. *FDA*, US Food and Drug Administration.

Studies of adults who were treated with cyclophosphamide as children have shown persistent effects on fertility. At an average of 13 years' post-treatment follow-up, Watson et al found that 4 of 30 patients were azoospermic and 9 were oligospermic.[11] The remaining normospermic patients had lower percentages of normal forms and decreased motility relative to the controls. Similarly, Trompeter et al showed that compared with controls, adults treated as children had decreased sperm density and motility, an increased percentage of abnormal spermatozoa, and decreased serum androgens.[12] Long-term gonadotoxicity may be dose dependent; Lentz et al[13] found that 6 of 7 patients who were receiving high-dose therapy (>365 mg/kg) developed persistent azoospermia compared with 0 of 11 who were receiving low-dose therapy (<365 mg/kg).

**Finasteride.** Finasteride is an inhibitor of 5-α reductase enzymes,[44] which convert testosterone to dihydrotestosterone[45] (the biologically active androgen at most end organs,[46] including the prostate, seminal vesicles, and epididymis).[47] Finasteride is typically dosed differently for benign prostatic hyperplasia (5 mg/d) and androgenic alopecia (1 mg/d).

In a double-blinded, randomized controlled trial of 99 healthy men that compared semen parameters, patients were treated with 5 mg/d of finasteride (n = 34), 0.5 mg/d of dutasteride (n = 33), or placebo (n = 32) for 52 weeks. At 26 weeks, significant reductions from baseline in semen volume (21.1%) and sperm count (34.3%), concentration (21.5%), and motility (10.5%) occurred during finasteride treatment. Except for sperm motility, these reductions were no longer significant after 52 weeks of continuous treatment, and the parameters returned to baseline values at 24 weeks after treatment. One patient had his sperm count reduced to less than 10%; however, it rebounded to 18.8% at 24 weeks after treatment, suggesting that some patients exhibit greater sensitivity to finasteride's effects.[18]

A second double-blind, randomized controlled trial evaluating 1-mg dosing in 91 healthy men suggested a dose-dependent response to finasteride.[19] Analysis showed no effect on sperm concentration, total sperm per ejaculate, sperm motility, sperm morphology, or ejaculate volume at 48 weeks or 60 weeks after treatment compared with placebo. This study suggests negligible effects of finasteride on fertility at the indicated dermatologic dosage.

**Tetracycline.** Tetracycline is distributed to various tissues and has been shown to bind human sperm in vitro,[21] which may affect sperm function and fertility. In semen samples incubated with increasing concentrations of tetracycline, a

**Table III.** Summary of drugs with possible evidence of teratogenic effects or evidence of negative effects on fertility

| Medication | No. of studies | LOE* | Side effect reported as first- or second-degree outcome or adverse event | No. taking drug in highest-LOE study | Dosage in highest-LOE study | Half-life, h | Summary of highest-LOE studies | Reported evidence of effects on male fertility in prescribing information | Prescribing information comments on teratogenicity after treatment of males |
|---|---|---|---|---|---|---|---|---|---|
| Colchicine | 2[4,5] | 4 | First-degree | 6 | 0.25-2.0 mg/d | 27-31[6] | An observational study of 31 patients with Behçet disease identified 2 of 6 patients as oligospermic on semen analysis[5] | Human studies demonstrating negative effects[6] | NA |
| Cyclophosphamide | 9[5,7-14] | 1b | Second-degree | 18 | 1.5 mg/kg/d | 3-12[15] | A prospective, double-blinded study of 121 patients with rheumatoid arthritis assigned to a 48-wk regimen of azathioprine, gold, or cyclophosphamide found that all patients on cyclophosphamide became azoospermic[7] | Human studies demonstrating negative effects[15] | Recommends that male patients who are sexually active with a female partner who is or may become pregnant use condoms during treatment for ≤4 mo after completion of therapy (no evidence cited)[15] |
| Doxycycline | 1[16] | 4 | First-degree | 16 | 1 × 200-mg dose | 18-22[17] | A prospective study of the semen plasma 16 men given a single dose of doxycycline of 200 mg demonstrated detectable levels of doxycycline within 24 h; doxycycline reached a maximum prostatic fluid—to— blood plasma ratio of 0.6[16] | Fertility not studied[17] | NA |
| Finasteride | 2[18,19] | 1b | First-degree | 34[18]<br>91[19] | 5 mg/d[18]<br>1 mg/d[19] | 3-16[20] | 2 double-blind, randomized placebo-control trials of healthy men described different fertility effects depending on dose of finasteride. No changes in semen parameters, except for reduced volume, were identified in healthy men taking a dose of 1 mg daily,[18] | Human studies demonstrating negative effects[20] | Reports no developmental abnormalities observed in the offspring of untreated females mated with finasteride-treated male rats that received 488 times the recommended human dose[20] |

Continued

**Table III.** Cont'd

| Medication | No. of studies | LOE* | Side effect reported as first- or second-degree outcome or adverse event | No. taking drug in highest-LOE study | Dosage in highest-LOE study | Half-life, h | Summary of highest-LOE studies | Reported evidence of effects on male fertility in prescribing information | Prescribing information comments on teratogenicity after treatment of males |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | whereas decreases in sperm count, concentration, and motility and volume of semen were identified in healthy men taking a 5-mg daily dose[19] | | |
| Tetracycline | 2[21,22] | In vitro | First-degree | NA | NA | 6-11[23] | An in vitro study of human semen incubated with tetracycline at varying concentrations demonstrated that tetracycline caused an arrest of sperm motility without a change in sperm viability[22] | Animal studies demonstrating no negative effects[23] | NA |
| Thalidomide | 1[24] | 1b | Second-degree | 2 | 100 mg/d × 8 wk | 5.5-7.3[25] | A double-blind, placebo-controlled study assigned 7 men with HIV to take either thalidomide or placebo for 8 wk. Investigators found detectable levels of thalidomide in 2 of 2 patients who took the medication and provided semen samples[24] | Animal studies demonstrating "slight" negative effects[25] | Recommends that men taking thalidomide use a latex condom during any sexual contact with women of childbearing potential even if they have undergone a vasectomy, as the drug is present in the semen of patients receiving the drug (no evidence cited)[25] |

*LOE,* Level of evidence; *NA*, not available.

*According to the 2009 Centre for Evidence-Based Medicine LOE, a level of 1a means a systematic review of RCTs, a level of 1b means an individual randomized controlled trial, a level of 2a means a systematic review of cohort studies, a level of 2b means an individual cohort study, a level of 3a means a systematic review of case-control studies, a level of 3b means an individual case-control study, and a level of 4 indicates a case series.

**Table IV.** Summary of drugs with evidence against possible teratogenic effects or negative effects on fertility

| Medication | No. of studies | LOE* | Side effect reported as first- or second-degree outcome or adverse event | No. taking drug in highest-LOE study | Dosage in highest-LOE study | Half-life, h | Summary of highest-LOE studies | Reported evidence of effects on male fertility in prescribing information | Prescribing information comments on teratogenicity after treatment of males |
|---|---|---|---|---|---|---|---|---|---|
| Acitretin | 1[26] | 4 | First-degree | 10 | 50 mg/d × 6 wk, then 25-50 mg/d × 6 wk | 33-96[27] | A prospective study of 10 subjects taking acitretin found no impairment in semen parameters during or after a 12-wk regimen of acitretin[26] | Human studies demonstrating no negative effects[27] | Reports that trace acitretin has been reported in seminal fluid, reaching a maximum of 12.5 ng/mL (1/200,000 of a single 25-mg capsule) (no study cited); however, it is asserted that residual acitretin in seminal fluid possesses little, if any, risk to a fetus, and postmarketing surveillance results indicate no reproductive safety risk[27] |
| Isotretinoin | 2[28,29] | 4 | First-degree | 81 | Total dose of 120 mg/kg over 6 mo | 1[30] | A prospective study of 81 male patients with severe acne treated with isotretinoin for 6 mo demonstrated a positive change from baseline in all parameters on spermiogram[29] | Animal studies demonstrating no negative effects[30] | Reports isotretinoin is found in the semen of male patients, but the amount delivered to a female partner would be 1 million times lower than a typical oral dose (no study cited). A total of 20 y of postmarketing reporting has identified only 4 isolated defects |

Continued

**Table IV.** Cont'd

| Medication | No. of studies | LOE* | Side effect reported as first- or second-degree outcome or adverse event | No. taking drug in highest-LOE study | Dosage in highest-LOE study | Half-life, h | Summary of highest-LOE studies | Reported evidence of effects on male fertility in prescribing information | Prescribing information comments on teratogenicity after treatment of males |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | compatible with retinoid exposure; 2 reports were incomplete and 2 had alternative explanations. Despite this, the package insert recommends that male patients use a condom with a female patient who may be pregnant for 1 mo in the event that the patient took a higher dose than that prescribed[30] |
| Methotrexate | 1[31] | 2b | First-degree | 10 | Mean total dose of 3824 g over a mean of 4.5 y | 3-15[32] | A study comparing semen parameters from 10 men treated with methotrexate for severe psoriasis with those of 10 men using topical steroids found that those taking methotrexate were significantly more likely to have normal semen parameters[31] | Reported negative effects in humans without cited studies[32] | Recommends that pregnancy be avoided for a minimum of 3 mo after therapy for male patients (no evidence cited)[32] |
| Steroids | 1[33] | 3b | First-degree | 48 | NA | 2-3 (prednisone)[34] | A retrospective study of 70 men with | Prednisone: fertility not studied[34] | NA |

| | |
|---|---|
| Crohn's disease using sulfasalazine and/or steroids showed no difference in number of offspring between patients taking and not taking steroids | Methylprednisolone: reported negative effects in humans without cited studies[35]<br>Dexamethasone: reported negative effects in humans without cited studies[36]<br>Hydrocortisone: reported negative effects in humans without cited studies[37] |

*LOE*, Level of evidence; *NA*, not available.
*According to the 2009 Centre for Evidence-Based Medicine LOE, a level of 1a means a systematic review of RCTs, a level of 1b means an individual randomized controlled trial, a level of 2a means a systematic review of cohort studies, a level of 2b means an individual cohort study, a level of 3a means a systematic review of case-control studies, a level of 3b means an individual case-control study, and a level of 4 indicates a case series.

concentration of 2.5 μg/mL reduced spermatozoa motility; sperm from some individuals were observed to exhibit greater sensitivity to tetracycline's effects.[22]

### Potential teratogenicity

**Finasteride.** Although we did not identify studies demonstrating this effect, 7 reports of teratogenicity following paternal exposure to finasteride were identified through our FAERS query. Of these, 3 described malformation patterns compatible with finasteride-induced teratogenicity; however, 2 cases were incompletely recorded, whereas the third occurred following 5-mg dosing.[48] Furthermore, an animal study identified through review of finasteride's prescribing information similarly suggests teratogenicity to be unlikely.[20] Nonetheless, spontaneous abortion has been frequently reported to the FDA following paternal exposure and may be a risk associated finasteride use.

### Chromosomal damage

**Cyclophosphamide.** An in vitro study performed by Watanabe and Kamiguchi demonstrated clastogenic effects of cyclophosphamide metabolites on spermatozoa through use of interspecific fertilization assay.[14] After metabolic activation and incubation with human semen, the authors found a significant increase in structural chromosomal aberrations (37%). This may explain the aforementioned in vivo observations regarding effect on fertility; however, whether spermatozoa with cyclophosphamide-induced DNA damage could fertilize human ova or result in fetal malformations is unclear.

### Seminal excretion

**Doxycycline.** Doxycycline is a tetracycline antibiotic used to treat acne; however, it is also used for many infections of the urogenital tract and can improve semen parameters in these patients.[49] Doxycycline may also improve idiopathic leukocytospermia.[50] Despite this, we did not identify evidence of its effect on men with normal baseline semen parameters. However, we did identify 1 study of 16 healthy men that described the detection of doxycycline in semen. Concentrations reached peaks of 2.0 μg/mL 6 hours after 200-mg oral dosing,[16] which may have implications for men with pregnant partners, as doxycycline may be absorbed during sexual intercourse.

**Thalidomide.** Thalidomide acts primarily through modulation of E3 ubiquitin ligase complexes, which mediate protein degradation.[51] Teratogenicity with

**Table V.** Medications with evidence of excretion in semen

| Medication | Dose | Peak levels in semen | Peak seminal plasma–to–blood plasma ratio | Time from first dose to measurement of peak levels | Teratogenic effect | Trimester of peak teratogenicity |
|---|---|---|---|---|---|---|
| Doxycycline | 200 mg × 1 dose | 2.0 μg/mL | 1.0 | 6 ho | Tetracyclines are implicated in the disruption of tooth and bone development[38] | Second, third[38] |
| Thalidomide | 100 mg/d × 8 wk | Mean of 185.5 ng/g | 0.6* | 4 wk | Thalidomide can cause mortality at birth; amelia; phocomelia; hypoplasticity of bones; absence of bones; external ear abnormalities; congenital heart defects; and alimentary, urinary, and genital tract malformations[25] | First, second, and third[25] |

*Calculated as the average peak seminal plasma concentration divided by the average blood concentration at the same interval.

thalidomide is well described and can occur in women at doses as low as 25 mg/d for 2 to 3 days or a single dose of 50 mg.[52]

A double-blind, placebo-controlled study evaluated 7 male patients with HIV who were taking either 100 mg of thalidomide or placebo. Two patients taking thalidomide provided 7 semen samples over 8 weeks, and all the samples had detectable levels of thalidomide; however, the effects of this finding on offspring has not been explored.[24]

### Evidence against infertility

**Acitretin.** Acitretin is a second-generation retinoid used for antiproliferative effects in the skin. We found evidence against similar inhibitory effects on spermatogenesis. In a single prospective study of 10 patients who were taking acitretin, the authors found no impairment in semen parameters during or after a 12-week regimen of acitretin compared with baseline.[26]

We were unable to identify evidence of the effects of this medication on teratogenicity after paternal exposure. However, postmarketing surveillance suggests that no such risk exists.[33]

**Isotretinoin.** Isotretinoin is also used for its inhibitory effects on cellular proliferation. We identified 2 studies suggesting that isotretinoin may have the opposite effect on spermatogenesis. The first was a prospective study of 81 male patients that demonstrated positive changes from baseline in all parameters on semen analysis after treatment for severe acne with a cumulative dose of 120 mg/kg of isotretinoin over 6 months.[29] Similarly, a study of 13 patients with severe acne treated with 1 mg/kg/d of isotretinoin for 16 weeks demonstrated increased sperm motility from baseline.

Although isotretinoin may improve fertility parameters in males, we did not identify any studies demonstrating safety with regard to teratogenicity following paternal exposure. On the basis of postmarketing surveillance, 4 cases of fetal anomalies and 25 uncomplicated births have been recorded following paternal exposure. Moreover, manufacturers have reported that the amount of isotretinoin delivered via semen is 1,000,000 times lower than with an oral dose.[30] Despite this, manufacturers continue to recommend barrier contraception for men engaging in intercourse with females who are or might become pregnant.

**Methotrexate.** Methotrexate mediates antiproliferative effects primarily by inhibiting folic acid metabolism. Despite this, we found 1 study suggesting that these antiproliferative effects do not affect spermatogenesis. In this study, semen parameters of 10 men treated with methotrexate for severe psoriasis were compared with those of 10 men who were using topical steroids. The authors found that the methotrexate group was significantly more likely to have normal parameters.[31] However, interpretation of these results may have been complicated by high rates of abnormal semen parameters among the 2 groups.

We did not identify any studies addressing teratogenicity after paternal exposure to methotrexate. The manufacturer does recommend discontinuation 3 months before attempting conception[32]; however, no evidence is cited for this recommendation.

**Systemic corticosteroids.** Systemic corticosteroids are commonly used and may decrease testosterone levels.[53] We identified a single retrospective study of 48 married men with Crohn's disease treated with sulfasalazine, corticosteroids, and/or azathioprine; the study assessed number of offspring among patients. Regardless of treatment, all patients with Crohn's disease were less fertile after

**Table VI.** Summary of drugs with no identified evidence

| Medication | No. of studies | LOE* | Side effect reported as first- or second-degree outcome or adverse event | No. taking drug in highest-LOE study | Dosage in highest-LOE study | Half-life, h | Summary of highest-LOE studies | Reported evidence of effects on male fertility in prescribing information | Prescribing information comments on teratogenicity after treatment of males |
|---|---|---|---|---|---|---|---|---|---|
| Bexarotene | 0 | NA | NA | 0 | NA | 7[39] | NA | Animal studies demonstrating possible negative effects[39] | Recommends that male patients with sexual partners who are pregnant or could become pregnant use condoms during sexual intercourse (no evidence cited)[39] |
| Minocycline | 0 | NA | NA | 0 | NA | 15-23[40] | NA | Reported negative effects in humans without cited studies[40] | Recommends that minocycline not be used by men who are attempting to conceive a child (no evidence cited)[40] |
| Voriconazole | 0 | NA | NA | 0 | NA | Dose-dependent (nonlinear pharmacokinetics)[41] | NA | Animal studies demonstrating possible negative effects[41] | NA |

*LOE*, Level of evidence; *NA*, not available.
*According to the 2009 Centre for Evidence-Based Medicine LOE, a level of 1a means a systematic review of RCTs, a level of 1b means an individual randomized controlled trial, a level of 2a means a systematic review of cohort studies, a level of 2b means an individual cohort study, a level of 3a means a systematic review of case-control studies, a level of 3b means an individual case-control study, and a level of 4 indicates a case series.

diagnosis compared with before diagnosis and compared with 53 married controls; however, there was no difference in fertility based on medication taken. Moreover, the authors reported no difference in fertility among those receiving corticosteroids for more than 6 months (n = 21) and all other patients (n = 27).

Unfortunately, we did not identify any studies addressing the teratogenic effects of paternal exposure, nor did we encounter guidelines regarding teratogenicity for male patients in the prescribing information for 4 different systemic steroids.[34-37]

## CONCLUSION

The information in this review was curated to guide treatment discussions among male patients taking systemic dermatologic medications. Information on dosage, treatment duration, and desired fertility time line should be reviewed with patients to determine individual risk. In addition, potential options to preserve fertility, such as cryopreservation, should be discussed when considering these medications. For patients already suffering from drug-induced infertility, intracytoplasmic sperm injection may be an option.

Evidence of chromosomal damage and medication excretion into seminal fluid is also valuable. Though potential teratogenicity of semen with aberrant chromosomes and medications present in semen is understudied, patients using these mediations should use barrier protection during intercourse with pregnant partners. Further research is required to assess seminal excretion of medications and absorption following receptive sexual intercourse.

Although no studies with evidence against teratogenicity were identified, postmarketing surveillance data suggest that teratogenicity following paternal exposure is unlikely for the included medications.

Unfortunately, we were unable to identify studies for 3 medications that met our inclusion criteria (Table VI). Furthermore, the design of some of the included studies may limit their generalizability. Finally, FAERS may not fully reflect the incidence of teratogenicity, as adverse event reporting by clinicians is voluntary. There may also be discordance between the FAERS data and identified studies, particularly for infertility with methotrexate and corticosteroids. Despite these limitations, the data in this review may help clarify potential risks associated with these medications and ease patient and physician anxiety when patients are looking to conceive.

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