Safety of important dermatological drugs (retinoids, immune suppressants, anti androgens and thalidomide) in reproductively active males with respect to pregnancy outcome: A brief review of literature

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Abstract

Paternally transmitted damage to offspring is recognized as a complex issue. Each parent contributes 23 chromosomes to a child; hence, it is necessary to know the effects of both maternal and paternal pre-and peri-conceptional exposure to drugs on pregnancy outcome. While there are many studies on the effects of maternal drug exposure on pregnancy outcome, literature on paternal exposure is scarce. Of late however, paternal exposure has been receiving increasing attention. We present a brief review on the safety of commonly used drugs in dermatology, focused on retinoids, immune suppressants, anti androgens and thalidomide.

Key words: Antiandrogen, immunosuppressive, reproductively active male, retinoid, safety of drugs, thalidomide

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Introduction

According to the Organization of Teratology Information Specialists, paternal exposure refers to anything the father of the baby is exposed to before or during his partner's pregnancy. This includes alcohol, tobacco and other drugs, chemotherapy or radiation treatments, work place exposures and prescription or over-the-counter medicines.[1] Paternal exposure can be pre-, peri-and post-conceptional and can result in an inability to conceive, spontaneous abortions, stillbirths, congenital malformations at birth and conditions detected only months to years after birth. The major mechanisms of male reproductive toxicity are nongenetic (e.g., due to the presence of a drug in seminal fluid leading to negative effects on sperms or its absorption through the vaginal mucosa), genetic (e.g., gene mutation or chromosomal abnormality of sperm DNA) and epigenetic (e.g., involving changes in gene expression without a change in nucleotide sequence). Therapeutic drugs may need

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to be continued for a long time in males of reproductive age, and as humans continue to have intercourse during pregnancy, the fetus may be exposed to drugs in semen at various critical stages of its development. Hence, it is imperative to consider the safety of drugs in reproductively active males with respect to pregnancy outcomes.

Retinoids

Isotretinoin, acitretin and bexarotene are commonly used systemic retinoids. Though there is much concern over the teratogenic potential of retinoids, data regarding safety of their usage in reproductively active males is limited.

Acitretin has not been found to have any genotoxic/mutagenic effects in animal or molecular studies.[2] It does not cause any alteration in sperm parameters.[3-5] Isotretinoin in high doses has been found to adversely affect spermatogenesis in some animal studies.[6,7] However, human studies have shown beneficial effects on spermatogenesis.[8,9] Isotretinoin and bexarotene were non mutagenic in various animal tests.[10,11] It appears that retinoic acid has some role in normal spermatogenesis.[12] A study on 24 men who underwent testicular biopsy found that the intra testicular levels of 13-*cis*-retinoic acid were significantly low in 7 men with abnormal semen analysis compared to 17 others who had a normal semen analysis.[13]

The maximal non teratogenic dose of acitretin in rabbits (the species most sensitive to its teratogenic effects) is 0.2 mg/kg/day.[14] Determination of the maximal non teratogenic dose of retinoids in humans would be unethical. Humans have been retrospectively found to be most sensitive to the teratogenic potential of isotretinoin (maximal nonteratogenic dose – 0.4-1.0 mg/kg).[15] Various studies which looked at drug levels in the ejaculate of men on a retinoid for ≥1 month have concluded that the risk of teratogenicity is negligible, even presuming 100% vaginal absorption of the drug.[5,12,15] Considering 5 ml of ejaculate and 5L blood volume of distribution in a recipient female, the amount of retinoid that reaches the circulation transvaginally in the female is approximately 1/100,000th the oral dose taken by the male. This is considered negligible compared to the physiological levels of endogenous retinoid and much less than the maximal non-teratogenic dose.[4]

Post-marketing surveillance reported 13 pregnancies with known pregnancy outcomes where the father was taking acitretin.[5] Only one fetus had malformations, which were not consistent with retinoid embryopathy. Five mothers delivered healthy neonates. There were six spontaneous abortions, which is not significantly higher than the 30% general incidence of spontaneous abortions.[16] Post-marketing surveillance for isotretinoin included four events with isolated defects compatible with features of a retinoid-exposed fetus; however, two of these reports were incomplete and two cases had other possible explanations.[10] In summary, men on either acitretin or isotretinoin can plan fatherhood. Limited data is

available through post-marketing surveillance for bexarotene, hence the manufacturer recommends the use of condoms for men for at least one month after the last dose.[11]

Corticosteroids

Leydig cells in the seminiferous tubules produce testosterone upon stimulation by luteinizing hormone, and are influenced by glucocorticoid levels in body.[17] Treatment with systemic corticosteroids has an inhibitory effect on luteinizing hormone secretion, as documented in animal studies. Martin and Tremblay in their study on mice found that dexamethasone inhibits the cyclic - adenosine monophosphate (cAMP)-mediated stimulation of steroidogenic genes, thus decreasing testosterone production by Leydig cells.[18] Similar findings have been reported by Bambino and Hsueh.[19] Further, it has been noted that the extent of reduction in testosterone levels varied with steroid used. Reduction was the most with triamcinolone, followed by dexamethasone and cortisol; corticosterone had the least effect on testosterone levels.[19] Other than suppressing luteinizing hormone[20-22] and testosterone production,[17,23] corticosteroids induce apoptosis of Leydig cells and spermatogonia.[24,25]

Contradictory results were documented by Mogilner *et al*. who found that dexamethasone inhibits germ cell apoptosis, thereby improving oligospermia.[26] Low-dose corticosteroids are found to be useful in the treatment of infertility due to antisperm antibodies.[27]

Systemic steroids are known to be non teratogenic with maternal exposure, but whether paternal exposure around the time of conception is teratogenic to the fetus is not known.[28] Conclusive evidence of its effects on male fertility is also lacking. As of now, prospective fathers can only be counseled that there is not enough data to make a recommendation regarding planning pregnancy, but termination of therapy is not recommended.

Methotrexate

Methotrexate inhibits the multiplication of rapidly dividing cells including spermatozoa, and its use causes concern among patients and treating physicians regarding its effects on male fertility and teratogenicity.

Where male fertility while on methotrexate is concerned, current data are conflicting [Table 1]. Methotrexate may lead to oligospermia and even azoospermia. However, some of these patients were simultaneously receiving alkylating agents, which could be responsible for the detrimental effects on the quality and quantity of spermatozoa.[40] The mechanism of methotrexate leading to deleterious effects on spermatozoa is debated, but the most widely accepted hypothesis is that methotrexate inhibits spermiogenesis (transformation of spermatids into mature sperm).[40] Thus, azoospermia is possible during methotrexate therapy and males may be unable to conceive with their partner.

Table 1: Effects of methotrexate on spermatozoa				
Report	Year	Indication for which methotrexate was used	Details of study	Effects on spermatozoa
Günther[29]	1970	Psoriasis	Not available	Nil
Grunnet *et al*.[30]	1977	Psoriasis	Prospective study, included 18 men, of whom 10 received methotrexate	Nil
De Luca *et al*.[31]	1971	Psoriasis	Not available	Nil
Weissbach *et al*.[32]	1974	Testicular tumors	Not available	Reversible sterility (oligospermia)
Hinkes and Plotkin[33]	1973	Acute leukemia	Case report	
Sussman and Leonard[34]	1980	Psoriasis	Case report	
Shamberger *et al*.[35]	1981	Soft tissue sarcoma	Prospective study, included 26 men	
Van Scott and Reinertson[36]	1959	Psoriasis	Prospective study, included 18 men	Oligospermia
Ben Arush *et al*.[37]	2000	Childhood lymphoma	Prospective study on 20 survivors of lymphoma	Oligospermia and azoospermia
El-Beheiry *et al*.[38]	1979	Psoriasis	Prospective study, included 26 men	Nil
Shafik[39]	1993	Testicular seminoma	Case report	Reversible drops in sperm count and motility, and increase in abnormal sperm morphology

Table 2: Effects of paternal exposure to methotrexate on the outcome of pregnancy				
Report	Year	Indication for which methotrexate was used	Details of study	Adverse pregnancy outcomes
French *et al*.[41]	2003	Psoriatic arthritis and rheumatoid arthritis	Compilation of case reports and series	Nil
Weber-Schoendorfer *et al*.[42]	2014	Rheumatic or inflammatory disease	Prospective cohort study comprising 324 methotrexate-exposed pregnancies, 459 disease-matched comparison women, and 1107 comparison women without autoimmune diseases	No significant difference in the rate of major birth defects nor in the risk of spontaneous abortions
Beghin *et al*.[43]	2011		Prospective study on 42 pregnancies involving 40 men treated with methotrexate at the time of conception	
Lee *et al*.[44]	2010		Retrospective cohort study. Of a total of 188,188 counselling requests, 301 pertained to paternal exposure	
Lamboglia *et al*.[45]	2009	Crohn's disease	Case report	Nil
Perry[46]	1983	Reiter's disease	Case report	Nil
Gromnica-Ihle and Krüger[47]	2010	Rheumatic or inflammatory disease	Compilation of case series and surveys	Trisomy 21, atrophy of the hand, small fistula beneath the ear, anomalies of toes

The next major concern is pregnancy outcomes in couples where the male partner was exposed to methotrexate during conception. Again, the outcome reported in different studies are conflicting as summarized in Table 2.[41-47] Earlier, at the Psoriasis Foundation Consensus Conference (2009), it was concluded that conception be avoided during methotrexate therapy and after completion of therapy for at least 3 months in males.[48] However, recent studies by Beghin *et al*. and Weber-Schoendorfer *et al*. found no evidence of increased risk of adverse pregnancy outcome after paternal low-dose methotrexate therapy (≤15 mg per week).[43] Based on current evidence, the authors concluded that paternal methotrexate exposure during conception does not pose any serious hazards to the offspring.

Cyclosporine

Cyclosporine, a calcineurin inhibitor, has immunomodulatory effects on T cells. Dermatologic indications includes psoriasis, atopic dermatitis, chronic idiopathic urticaria, pyoderma gangrenosum and Behçet's disease.[49]

A meta-analysis performed to determine whether cyclosporine exposure during pregnancy is associated with an increased risk of congenital malformations, preterm delivery or low birth weight, found that it does not appear to be a major human teratogen.[50] However, it may be associated with increased rates of prematurity, and more research is needed to evaluate whether cyclosporine increases teratogenic risk.

In men, doses greater than 2 mg/kg/day have been implicated in asthenoteratospermia.[51] No significant difference was seen in men receiving lower doses compared to the control group. Therefore, authors did not recommend discontinuation of the drug (especially at lower doses) if pregnancy is desired. Haberman *et al*. evaluated fertility among 9 young men on cyclosporine A following renal transplantation. Most parameters of semen analysis and testicular hormones were normal in 8 patients. Attempts at conception were successful in three out of four cases.

Table 3: Effects of azathioprine on spermatozoa				
Report	**Year**	**Indication for which azathioprine was used**	**Details of study**	**Effects on spermatozoa**
Dejaco *et al*.[56]	2001	Inflammatory bowel disease	Prospective study on 23 patients	Nil
Xu *et al*.[57]	2008	Renal transplant patients (received azathioprine, cyclosporine and prednisolone concurrently)	Prospective study on 185 patients	Nil

Table 4: Effects of azathioprine on the outcome of pregnancy				
Report	**Year**	**Indication for which azathioprine was used**	**Details of study**	**Adverse pregnancy outcomes**
Rajapakse *et al*.[58]	2000	Inflammatory bowel disease	Prospective cohort of 140 fathers	Spontaneous abortions, missing thumb, acrania with multiple digital and limb abnormalities
Francella *et al*.[59]	2003	Inflammatory bowel disease	Retrospective cohort of 485 patients	No statistically significant adverse outcomes
Nørgård *et al*.[60]	2004	Multiple indications including organ transplant recipients, inflammatory bowel disease	Prospective cohort on 54 exposed pregnancies	Polysyndactyly, oesophagal atresia, hydronephrosis, megaloureter and ventricular septal defect
Teruel *et al*.[61]	2010	Inflammatory bowel disease	Prospective case control study on 130 patients	No statistically significant adverse outcomes
Hoeltzenbein *et al*.[62]	2012	Inflammatory bowel disease, renal transplant, myasthenia gravis	115 prospectively-followed pregnancies after paternal exposure to azathioprine or 6-mercaptopurine, compared to a control group of 341 pregnancies	No significant associations between azathiorpine exposure and specific adverse effects, chromosomal aberrations or congenital malformations
Viktil *et al*.[63]	2012	Multiple indications	Prospective cohort study, 150,000 pregnancies	No statistically significant adverse outcomes
Engeland *et al*.[64]	2013	Multiple indications	Prospective cohort study, 340,000 pregnancies	No statistically significant adverse outcomes

Though cyclosporine does not seem to adversely affect fertility in men,[52] animal studies have documented contradictory results; hence, some caution is warranted. In animal studies, 1–2mg/kg/day of cyclosporine has been associated with reduced weight of accessory sex organs, decreased testicular and epididymal sperm counts and decreased sperm motility (by 50%) and hence, decreased fertility (by 60%).[53] Another study has reported that the toxic effect of cyclosporine on spermiogenesis in rats is by it directly impairing spermiogenic cell development and by impeding Sertoli cell function.[54]

Very little amount (5–20%) of cyclosporine cross placenta and the current evidence does not support its teratogenic potential in humans.[52,53] However, reports on the effects on fetus where the father was on long-term cyclosporine are not available.

Azathioprine

Azathioprine, a purine analogue, reduces T and B cell response and thereby inhibits the synthesis of antibodies. Studies of the effects of azathioprine on male fertility are summarised in Table 3.

Ligumsky *et al*. conducted a study in male mice and found that azathioprine led to an increased risk of resorption of embryos. This was attributed to occult sperm damage.[55]

There is a rising concern that exposure of future fathers to azathioprine might adversely affect pregnancy outcome. There are reports of deleterious outcomes of pregnancy,[58,60] but recent reports suggest that no specific adverse effects are observed after paternal treatment with azathioprine.[59,61-64] [Table 4].

Instances of elective termination of pregnancy after paternal exposure to azathioprine during conception are known.[62] This may be attributed to the apprehension of having a baby with congenital malformations. However, current evidence suggests that conception planning need not be delayed when the future father is on unavoidable azathioprine therapy.[59,61-64] In addition, there is no need to abort the fetus if a chance pregnancy occurs, though in such circumstances, high-frequency serial ultrasound must be carried out to look for any malformations or defects.[62]

Cyclophosphamide

Cyclophosphamide is the most researched chemotherapeutic agent because of its severe effect on human fertility (pregnancy category D).[65] Cyclophosphamide is a pro drug, and its teratogenic effects are mediated through its breakdown products phosphoramide mustard and acrolein.[66] Kirshon *et al*. have reported multiple anomalies, including absent thumbs, cleft palate, low-set ears and multiple eye abnormalities in a neonate born to a mother treated with cyclophosphamide for lupus.[67] In men, cyclophosphamide has been known to induce infertility at cumulative doses above 7500 mg/m². It causes depletion and aplasia of germinal epithelial cells in the testes, resulting in severe oligozoospermia or azoospermia within 90–120 days of treatment, with poor long-term recovery. Arnon *et al*. reported that men who regained spermatogenesis did so after an average interval of 31 months.[65] Gaffan *et al*., in patients of germ cell tumor, reported an insignificant difference in the doses of cyclophosphamide received in the fertile and infertile group (1500 mg m⁻² in the fertile and 1750 mg m⁻² in the infertile).[68]

Animal studies have reported that pre conceptional paternal exposure to cyclophosphamide leads to increases in embryo loss, malformations and behavioral deficits in offspring which are transmissible to subsequent generations.[69] In a study by Hales *et al.*, the progeny of male rats treated with 5.1 mg/kg/day of cyclophosphamide resulted in an F_2 generation (second filial generation- the offspring of the interbreeding F1 generations) with significantly decreased mean fetal weight, omphalocele, generalized edema, syndactyly, gigantism and dwarfism.[70]

Because of these known adverse effects of cyclophosphamide on male fertility and pregnancy outcome, it is advisable for male patients to avoid fathering a child during treatment and for 3 months after treatment with this drug.[71]

Mycophenolate

Exposure to mycophenolic acid products in early pregnancy in female transplant recipients is associated with an increased risk of miscarriage (32–45%) and multiple craniofacial congenital malformations (mycophenolate mofetil-associated embryopathy EMFO tetrad: Ear, Mouth, Fingers, Ocular/Organ malformation, according to The European Network of Teratology Information Services).[72] Hence in 2006, the U.S Food and Drug Administration changed the pregnancy category of mycophenolic acid from category C to D.[73]

Despite a large number of patients being treated with mycophenolic acid products, little clinical data are available concerning its effects on male fertility.[72] Kim *et al*. have reported that there is no evidence of mycophenolic acid impacting male patients' fertility or contributing to birth defects in their offspring. In an animal study, mycophenolate mofetil had no effect on fertility in male rats at a dose equivalent to 200 mg/day in humans, while fetal malformations were noted in female rats at less than a quarter of this dose.[74] Of note, no ill effects on the subsequent generations were observed.[74]

Two registry studies of pregnancies with paternal exposure to mycophenolate derivatives have not identified an increased incidence of fetal malformations compared to the general population (3.1% vs. 3%, 2.1% vs 1.9%).[75,76]

Table 5: National Transplantation Pregnancy Registry data with respect to the effects of mycophenolate

Outcome	NTPR data	General population
Prematurity (%)	10.8	12.18
Low birth weight (%)	4.1	8.16
Very low birth weight (%)	0	1.45
Mean gestational age in weeks (SD)	37 (7.48)	38.6 (2.5)
Mean birth weight in g (SD)	3401.46 (523.05)	3262 (591)
Birth defect rate (%)	3.1	3
Fetal loss rate (%)	6.8	17.1

NTPR: National Transplantation Pregnancy Registry, SD: Standard deviation

National Transplantation Pregnancy Registry (NTPR) data demonstrate that pregnancies fathered by transplant recipients with exposure to mycophenolic acid have outcomes, complication rates and malformations similar to those in the general population. Table 5 compares NTPR outcome data with data for the general population.[76]

In May 2016, the Medicines and Healthcare products Regulatory agency, United Kingdom, gave recommendations for men taking mycophenolate derivatives, that sexually active men exposed to these agents should use condoms during treatment and for 90 days after discontinuation. It also stated that, "female partners of male patients treated with mycophenolate mofetil or mycophenolic acid should use highly effective contraception during treatment and for 90 days after the last dose. However, recommendations do not appear to have high-level scientific evidence, so we may keep our minds open.[75]

Finasteride

Finasteride is a potent type II 5α-reductase inhibitor used in the treatment of androgenetic alopecia and benign prostatic hyperplasia. Its frequent use in reproductively active males raises concerns about potential teratogenicity. Finasteride has been detected in semen. In a study on 35 males taking 1 mg oral finasteride daily for 6 weeks, mean semen finasteride level was 0.26 ng/ml while the highest level achieved was 1.52 ng/ml. Assuming a 5 ml ejaculate volume, the female partner would be exposed to a maximum of 7.6 ng finasteride/day, which is considered insignificant for causing developmental anomalies.[77] In experimental studies, exposures in male monkeys up to 800 ng/day did not result in any developmental anomalies in their off spring. However, administering higher doses (2mg/kg/day, equivalent to 100 times the human dose of 1 mg/day) to pregnant monkeys resulted in anomalies of external genitalia in male fetus. No other anomalies and no effects on female fetuses were observed.[77]

The effect of finasteride on male fertility is controversial and studies have shown conflicting results. In a multicentric study, 1 mg/day of finasteride for 48 weeks did not have any significant effect on sperm concentration, total sperm per ejaculate, sperm motility or sperm morphology.[78] However, a study by Amory *et al*. documented compromise in all semen parameters (except sperm morphology) in patients taking finasteride (5 mg/day) and dutasteride (0.5 mg/day) for 1 year.[79] Inability to conceive while the male partner is on finasteride and conception following discontinuation of finasteride have been documented.[80] Thus, finasteride at 1 mg/day may not impair male fertility, especially if it is used for short periods. However, female partners of males with pre-existing subnormal fertility may not be able to conceive while their partners are on finasteride.[80] Hence, it appears prudent to get a baseline semen analysis before starting finasteride and to discontinue finasteride in males

with oligospermia, as well as in instances of failed attempts at conception.

Some recent reports have noted an increased sperm DNA fragmentation index with chronic use of finastride (1 mg/day).[80,81] This impairment in sperm integrity might result in an inability to conceive and in spontaneous abortions. Improvement in the sperm DNA fragmentation index and successful conception have been observed months after discontinuation of finasteride.

Spironolactone

Spironolactone is an aldosterone receptor antagonist with anti-androgenic actions. Common dermatological indications include female pattern hair loss, hirsutism and acne. Gynecomastia, abnormal menstrual cycles and impotence are frequently noted with prolonged use, which limit its long-term use. In males, it is primarily used for non-dermatological indications though it had been used to treat rosacea in males.[82] Spironolactone at a dose of 400 mg/day impairs spermatogenesis by decreasing testosterone levels[83] However, a study in male rats showed that there were no changes in sperm motility or fertility despite decreases in sperm concentration.[84] More recently, mineralocorticoid receptors have been identified in human sperms.[85] However, their functional importance and the effects of blockade of these receptors by spironolactone are not known.

Mineralocorticoid blockade in pregnant rats has been shown to inhibit fetal organogenesis in (descending order) hind limbs > forelimbs >optic stalk > brain > olfactory pits >otic vesicles.[86] Though human data are not available, this raises concerns about the use of spironolactone in males who are planning to have a child.

Thalidomide

Thalidomide consists of a single central asymmetric carbon atom with a right glutarimide ring and a left pthalidimide ring.[87-89] Sedative effects are mediated by the glutarimide ring whereas the pthalidimide ring leads to teratogenic effects.[90] It was introduced in Europe and Canada in the late 1950s as a non barbiturate sedative hypnotic and antiemetic for treating morning sickness during pregnancy, but by 1962, it was withdrawn from the market due to its teratogenic effects.[91] However, there is a dearth of literature on the effects of thalidomide on paternity and male fertility.

Cecilia Lutwak-Mannin (1964) found some deleterious effects on the progeny of male rabbits fed thalidomide.[92] Teo *et al*. in an animal study found that sperm count, motility and density were not influenced by thalidomide (up to 500 mg/kg) after 8 weeks of dosing.[93] A double-blind, placebo-controlled study performed by Teo *et al*. on HIV-seropositive patients found a significant correlation between plasma and semen thalidomide levels and significantly greater semen levels at higher doses (>100 mg/day). Because the threshold dose

for birth defects due to thalidomide exposure is not known, they advised barrier contraception for male patients.[94] Another study using liquid chromatography-tandem mass spectrometric assays of human semen and plasma, confirmed the presence of the drug in human semen; the concentration achieved in semen is similar to that in plasma.[95]

Because evidence regarding the effects of thalidomide on male fertility and its transmission to future generations are lacking or contradictory, to avoid a repetition of the 1960s tragedy, its marketing and use has been restricted through the mandatory System for Thalidomide Education and Prescribing Safety program that regulates prescribing, dispensing and dosing of thalidomide in United States of America.[87] It is recommended to use barrier contraceptives during thalidomide treatment and for 1 week after stopping treatment.[96]

To summarize, currently available data suggests that the use of retinoids (except bexarotene), methotrexate or azathioprine by prospective fathers is safe. On the other hand, literature does not support the use of cyclophosphamide, mycophenolate mofetil or spironolactone by prospective fathers. However, data for avoidance of mycophenolate mofetil is not sufficiently robust. Among the drugs reviewed above, data for cyclosporine A, corticosteroids, finasteride and thalidomide is not sufficient enough to draw a conclusive opinion regarding its use in prospective fathers.

The role of male partners in mediating drug-induced adverse outcomes of pregnancy is being increasingly recognized. Because the father contributes half the genome in the progeny, it appears prudent that we analyze the effects of drug use by prospective fathers critically. At present, only drug use by females is being tested for teratogenic effects. There is therefore a need to design robust studies evaluating all drugs for potential male-mediated teratogenic effects. Treating dermatologists need to exercise caution and limit the use of drugs by prospective fathers and/or advise contraception till conclusive data regarding the safety of drugs with respect to progeny become available.

Conflicts of interest
There are no conflicts of interest.

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