Medicines Adverse Reactions Committee

Meeting date	11/06/2026	Agenda item	3.2.2
Title	**Paternal exposure to low-dose methotrexate**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**	**Formulation**	**Sponsor**
methotrexate	Trexate	tablet	Rex Medical
	DBL Methotrexate	solution for injection	Pfizer
	Methotrexate Sandoz	prefilled syringe	Sandoz
	Methotrexate Ebewe	concentrate for injection	Sandoz
PHARMAC funding	All products above are funded on both community and hospital schedules		
Previous MARC meetings	No		
Prescriber Update	No		
International regulatory guidance	EMA recommendations on duration of contraception for genotoxic medicines US FDA recommendations on reproductive toxicity and testing for oncology medicines		
Classification	Prescription medicine		
Usage data	Approximately 30,617 people were dispensed methotrexate from a community pharmacy in 2024		
Advice sought	**The Committee is asked to advise:** • If the current advice in the methotrexate data sheets for male patients to use effective contraception during treatment and for a minimum of three months after stopping treatment is sufficient. The Committee may wish to consider whether there are differences in the risk of paternal exposure for low-dose vs. high-dose methotrexate, and whether additional context for advice in the data sheets is needed (eg, data from observational studies).		

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1 PURPOSE

Methotrexate is used as an antineoplastic agent and in autoimmune conditions. For autoimmune conditions such as psoriasis and rheumatoid arthritis, low doses (typically ≤25 mg/week) are generally prescribed compared to the higher doses used in cancer indications. The methotrexate data sheets currently recommend that males should use effective contraception or avoid conception during treatment and for at least 3 months after stopping treatment. This recommendation does not differentiate between low- vs. high-doses, nor between indications.

A specialist clinician has asked that the MARC reviews the risks of paternal exposure to low-dose methotrexate because the data sheet advice is not supported by more recent evidence. International rheumatology and dermatology guidelines no longer recommend methotrexate cessation in men planning conception. In addition, other treatment options have a less favourable safety profile.

Alongside clinical guidelines, there are also regulatory guidelines on the duration of contraception for genotoxic medicines published by the EMA and US FDA. The EMA recommend male patients should use contraception until the end of systemic exposure to the genotoxic medicine including potential genotoxic metabolites (ie, five half-lives after the last dose) plus 90 days. These recommendations should apply to any genotoxic active substance regardless of its therapeutic indication. The US FDA's guidance on the duration of contraception is the same as the EMA's, but is specific for genotoxic medicines intended for use in cancer.

This paper reviews information on the recommended duration of contraception in male patients using low-dose methotrexate, and outcomes of pregnancies following paternal exposure to low-dose methotrexate.

2 METHOTREXATE

2.1 Products

Methotrexate-containing products (oral and parenteral formulations) that are currently approved and marketed in New Zealand are shown on the cover page. All of these products are funded by Pharmac on both the community and hospital schedules.

Methotrexate was first approved by Medsafe as a solution for injection formulation in 1977. A tablet formulation was subsequently approved in 1982. These product approvals occurred before international harmonisation of regulatory requirements were established, for example, the International Council for Harmonisation (ICH) was established in 1990. There are now ICH guidelines for genotoxicity testing, and reproductive toxicology.

Information provided in the subsections below comes predominantly from the methotrexate NZ data sheets:

- Trexate tablets (Rex Medical): reference 1
- DBL methotrexate solution for injection (Pfizer): reference 2
- Methotrexate Ebewe concentrate for injection (Sandoz): reference 3
- Methotrexate prefilled syringes (Sandoz): reference 4

2.2 Indications and dose

Low-dose methotrexate is given in once weekly doses to treat the following severe autoimmune conditions:

- Psoriasis: Dose for a 70 kg adult is generally between 10 and 25 mg/week [1-4].
- Rheumatoid arthritis: Initial dose of 7.5 mg once weekly and can be increased to 15 mg/week after six weeks, and further increased to 20 mg/week to achieve optimal response [1, 2, 4].
- Juvenile idiopathic arthritis (children and adolescents): 10-15 mg/m^2 body surface area (BSA) per week. Weekly dose can be increased up to 20 mg/m^2 BSA in refractory cases [4].

The use of methotrexate via the parenteral route for psoriasis or rheumatoid arthritis is generally considered in individuals with an inadequate response to oral therapy, who do not tolerate oral administration, who exhibit inadequate absorption of the oral form, or when high doses are required. When changing from oral to parenteral administration, a dose reduction may be needed due to the variable bioavailability of methotrexate after oral administration [1].

Methotrexate is also used as an antineoplastic agent in certain cancers (eg, breast cancer, gestational choriocarcinoma). Doses are usually calculated per m^2 BSA and given IV, IM or intrathecally.

Comments:

'Low-doses' of methotrexate are generally considered to be doses lower than cancer doses, typically ≤25 mg/week.

According to Dermnet, psoriasis affects 2-4% of males and females with onset peaking at 15-25 years and 50-60 years.

According to Healthify, rheumatoid arthritis affects about 40,000 New Zealanders with onset peaking between the ages of 25 and 50 years. It affects females more often than males.

2.3 Pregnancy and fertility

Only information relevant to use in males is included here.

Fertility

Methotrexate has been reported to cause impairment of fertility, defective spermatogenesis and oligospermia (low sperm count) in humans, during and for a short period after stopping treatment [1-4].

Men treated with methotrexate should use contraception and not father a child during and for 3 months after treatment. Methotrexate may be genotoxic and has caused increased number of abnormal and immobile spermatozoa in clinical studies [1-4].

Since treatment with methotrexate can lead to severe and possibly irreversible disorders in spermatogenesis, men should seek advice about the possibility of sperm preservation before starting treatment [1-3]. Men should not donate sperm during therapy or for 3 months following discontinuation of methotrexate [1-4].

Pregnancy

Both male and female patients should be fully counselled on the serious risk to the fetus if pregnancy occurs while undergoing treatment and counselled regarding pregnancy prevention and planning [1-4].

Pregnancy should be avoided and reliable effective contraception used if either partner is receiving methotrexate, during and for a minimum of three months after therapy has ceased for men. The optimal time interval between the cessation of methotrexate treatment of either partner and pregnancy has not been clearly established [1-4].

Comments:

The recommended duration of contraception in the NZ data sheets for male patients is during treatment and for 3 months after treatment. There is no differentiation between doses or indications. This is aligned with Australia, the EU and the US.

The UK data sheet states limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-doses (<30 mg/week). However, the recommended duration of contraception is during and for 6 months after treatment which is longer than the NZ data sheet.

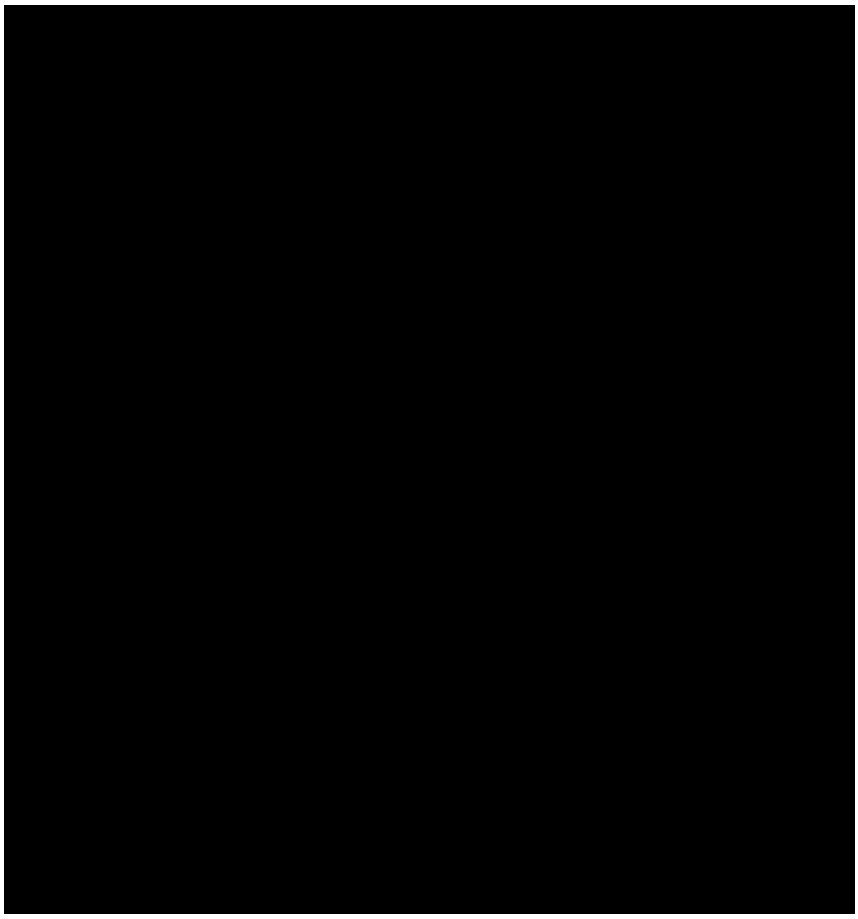
The Canadian data sheet states published literature recommendations for time intervals between cessation of methotrexate treatment and pregnancy vary from 3 months to one year.

2.4 Mechanism of action

Methotrexate (MTX) is sometimes considered a prodrug. As shown in Figure 1, after entering a cell, it is converted by folylpolyglutamate synthetase (FPGS) into polyglutamyl derivatives which are then preferentially retained within cells [5]. This is a dynamic process with γ-glutamyl hydroxylase (γ-GH) controlling the removal of glutamate residues [6]. Methotrexate polyglutamates are highly potent irreversible inhibitors of dihydrofolate reductase (DHFR) [7] which is the enzyme that reduces folic acid to tetrahydrofolic acid [1-4]. Inhibition of tetrahydrofolic acid results in interference with DNA synthesis and cellular reproduction [1-4].

Methotrexate also increases intracellular deoxyadenosine triphosphate which inhibits ribonucleotide reduction and polynucleotide ligase activity, an enzyme involved in DNA synthesis and repair [1, 4].

Figure 1: Mechanism of methotrexate's cytotoxic effect



Source: Figure 3 of Zarou et al (2021) [7]
MTX = methotrexate; FPGS = folylpolyglutamate synthetase; γ-GH = gamma-glutamyl hydroxylase; $MTX(Glu)_n$ = methotrexate polyglutamates; DHFR = dihydrofolate reductase

Malignant cells, bone marrow, fetal cells, dermal epithelium, buccal and intestinal mucosa, spermatogonia, urinary bladder cells and other actively proliferating tissues are typically more sensitive to the pharmacological effects of methotrexate [1-4].

When methotrexate is used in low-doses for the treatment of autoimmune conditions, it is thought the anti-inflammatory effects are mediated via adenosine pathways, and inhibition of nucleic acid synthesis in activated T-cells and keratinocytes account for some of its immunomodulatory effects [6].

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased compared to normal skin. This differential in reproductive rates provides the basis for use of methotrexate to control the psoriatic process [2-4].

In rheumatoid arthritis, it is thought methotrexate's effects are via immunosuppressive and/or anti-inflammatory actions [8].

Comments:

Methotrexate exerts its cytotoxic effect by inhibiting dihydrofolate reductase. However, when used in low doses to treat autoimmune conditions such as rheumatoid arthritis and psoriasis, its exact mechanism of action is not fully understood.

Actively proliferating cells and tissues (eg, spermatogonia as stated in the Trexate tablets data sheet), are more sensitive to the pharmacological effects of methotrexate. Therefore, there is concern that sperm germ cells undergoing differentiation would be affected.

2.5 Pharmacokinetics

A summary of the pharmacokinetics of methotrexate is shown in Table 1, by formulation. This information was obtained from NZ data sheets.

Table 1: Pharmacokinetics of methotrexate (oral, parenteral)

	Oral [1]	**Parenteral**
Absorption	Peak serum levels within 1 to 4 hours of oral administration. It is rapidly absorbed from the GI tract but absorption is erratic when administered at higher doses.	Peak serum levels within 0.5 to 2 hours following IV or IM administration [2, 3].
Distribution	Actively transported across cell membranes into tissue cells with highest concentrations in the kidneys, gallbladder, spleen, liver and skin. Even a single dose results in methotrexate being retained for several weeks in the kidney and several months in the liver.	Approximately 50% bound to serum proteins [2-4]. High concentrations particularly in liver, kidneys and spleen in the form of polyglutames which can be retained for weeks or months [2, 4]. Also distributes into third-space accumulation of fluid (eg, ascites or pleural effusions) [2, 4].
Metabolism	Methotrexate does not appear to undergo significant metabolism at low doses.	Does not appear to be appreciably metabolised [2].
Elimination	After low oral doses, the terminal half-life of methotrexate is between 3 and 10 hours. There is wide intra-individual variation in clearance with average total clearance of 12 L/h. Delayed clearance is one of the major contributors to toxicity. Methotrexate is primarily excreted through the kidneys by glomerular filtration and active transport but this is influenced by dose. It is eliminated slowly from third-space compartments which can result in a prolonged terminal phase half-life and increased risk of toxicity.	Predominantly excreted by the kidneys [2, 3] and small amounts appear in the faeces [2]. Excretion of methotrexate is reduced in the presence of impaired renal function [2, 4]. Average terminal half-life is 6-7 hours with considerable variation (3-17 hours). May be prolonged up to 4 times the normal length in patients with third-space accumulation (eg, pleural effusion, ascites) [4].

Comments:

For this paper, the most relevant pharmacokinetic component is elimination because the half-life is used by medicine regulators (eg, EMA, US FDA described in section 3.1 of this report) to calculate the duration of contraception for genotoxic medicines.

The terminal half-life of orally administered low doses of methotrexate is between 3 and 10 hours. The terminal half-life is prolonged in patients with third-space accumulation and excretion is reduced in patients with impaired renal function.

2.6 Preclinical safety information

Methotrexate has been shown to induce chromosomal damage in animal somatic cells and human bone marrow cells [1-4].

In several preclinical tests, methotrexate was genotoxic [1, 2, 4]. There is evidence of a teratogenic risk in humans (craniofacial, cardiovascular and extremital malformations) and in several animal species [2, 4]. Methotrexate has been shown to be toxic to male reproductive organs, embryotoxic and teratogenic in mice, rats and rabbits [1].

Comments:

A genotoxic medicine is an agent that can damage DNA or chromosomes within cells potentially causing mutations (mutagenicity), cancer (carcinogenicity), or inherited defects (teratogenicity).

2.7 Usage

The number of people who have received an initial dispensing of Pharmac-funded methotrexate from a community pharmacy overall is shown in Table 2, and by individual product in Table 3.

The following are noted:

- The use of methotrexate is increasing over time.
- Because this is community pharmacy dispensing data, oral tablets are used more than injectable forms.
- Although the indications for use are unknown, it could be assumed that oral forms are predominantly used to treat autoimmune non-cancer conditions.
- It is unknown whether these people are male or female.

Table 2: Number of people with an initial dispensing of Pharmac-funded methotrexate from a community pharmacy, overall

Year	Number of people
2020	25,436
2021	26,793
2022	27,774
2023	29,225
2024	30,617

Source: Pharmaceutical Data web tool (extracted 22 April 2026)

Table 3: Number of people with an initial dispensing of Pharmac-funded methotrexate from a community pharmacy, by individual product

	2020	2021	2022	2023	2024
10 mg tablet	19,199	20,634	21,700	23,325	24,953
2.5 mg tablet	9523	9689	9752	10,097	10,304
7.5 mg prefilled syringe	73	85	100	94	83
10 mg prefilled syringe	465	496	497	528	516
15 mg prefilled syringe	515	559	540	534	533
20 mg prefilled syringe	843	892	951	911	879
25 mg prefilled syringe	285	308	334	343	304
30 mg prefilled syringe	21	28	26	42	27
2.5 mg/mL, 2 mL injection	<6	<6	<6	6	7
25 mg/mL, 2 mL vial	21	16	10	7	9
25 mg/mL, 20 mL vial			<6		
100 mg/mL, 10 mL injection	<6				
100 mg/mL, 50 mL vial			<6		

Source: Pharmaceutical Data web tool (extracted 25 March 2026)

3 PATERNAL EXPOSURE

3.1 Regulatory guidance for genotoxic medicines

3.1.1 EMA

The EMA's recommendations on the duration of contraception following the end of treatment with a genotoxic drug were first published 1 Apr 2020 and last updated 24 Apr 2023. Relevant sections are summarised below.

3.1.1.1 Background

The EMA consulted a working party to give advice on the duration of contraception in male and female patients after cessation of treatment with a genotoxic medicine for both clinical trials and approved medicines.

The objective is to support a harmonised EU position and facilitate sponsors to introduce consistent recommendations within relevant sections of the data sheet.

The working party was asked the following questions:

- What should be the recommended duration of contraception following the end of treatment with a genotoxic medicine for male patients?
- What should be the recommended duration of contraception following the end of treatment with a genotoxic medicine for female patients?
- Would these recommendations apply only to genotoxic anticancer medicines, or to any genotoxic active substance regardless of its therapeutic indication?

3.1.1.2 Recommendation for male patients

The recommended duration of contraception in male patients should be until the end of relevant systemic exposure to the genotoxic medicine including potential genotoxic metabolites (ie, **five half-lives after the last dose) plus 90 days**.

For substances with five half-lives of ≥7 days the additional time period should be rounded up to at least 1 month and increased thereafter on a per month time as shown in Table 4.

Table 4: EMA working group recommendations on duration of contraception for male patients

Source: EMA working group recommendations for genotoxic medicines

Genotoxicity/genetic damage at the level of the germ cell and/or conceptus is important due to its potential irreversible nature. This is independent of the therapeutic indication. Therefore, the recommendations should apply to any genotoxic active substance regardless of its therapeutic indication. However, these recommendations should not apply to active substances whose mechanism of genotoxicity is known to have a threshold which is not expected to be attained in patients.

Sperm DNA damage and its recovery may also depend on the disease, concomitant medicines, the dose and duration of treatment. The SmPC could give recommendations on seeking advice for cryopreservation of sperm prior to treatment and/or to use individual genetic counselling for patients intending to have children after treatment with a genotoxic medicine.

Comments:

The terminal half-life of methotrexate as stated in the oral Trexate data sheet is between 3 and 10 hours. Using 10 hours, five terminal half-lives is 50 hours equivalent to 2.08 days. Using the EMA's recommendations, the duration of contraception for male patients is therefore 92 days after stopping methotrexate.

Due to irreversible effects, these recommendations apply regardless of the indication unless the mechanism of genotoxicity has a threshold that is not reached in patients.

3.1.1.3 Scientific information

Genotoxic substances may have an impact on male fertility and can induce adverse effects on the offspring. These adverse outcomes include spontaneous abortion, birth defects and childhood cancer. The mechanism by which genotoxic medicines may affect progeny outcome is via a detrimental effect on sperm DNA.

Spermatogenesis starts in the male testis with puberty. This comprises the entire development of the spermatogonia up to sperm cells and is divided into 3 stages: spermatogonial proliferation, meiosis, and spermatogenesis.

Genotoxic agents may induce both single gene and chromosomal mutations in germ cells, both of which can cause genetic disease in offspring.

Animal studies have shown that spermatozoa damaged by paternal exposure to genotoxic cancer medicines can lead to adverse effects in the offspring, including heritable translocations, mutations and malformations such as hydrocephaly and micrognathia in the F1 progeny.

The susceptibility of the germ cell to DNA insult is stage specific during spermatogenesis in the testis and maturation in the epididymis (Figure 2).

Figure 2: Sequence of spermatogenic cells, sensitivities and resilience

Source: Meistrich et al, 2009 [9]

Damaged sperm cells have three options:

- Repair the damage
- Activate the apoptotic process causing cell death
- Tolerate the damage resulting in mutations which could be transmitted to future generations.

Due to down-regulation of DNA repair mechanisms that occurs during late spermatogenesis, spermatogenic cells further along the differentiation pathway cannot repair incurred DNA damage, nor are they capable of undergoing complete apoptosis. As a result, the ejaculated spermatozoa may harbour extensive genomic damage that could theoretically be transmitted to an embryo. However, repair of DNA damage may also be possible in the oocyte to some extent.

Mutations induced exclusively in the later stages of spermatogenesis will yield a risk period for the production of genetically compromised sperm that is limited to the time it takes for the entire spermatogenic cycle to complete (about 3 months).

Spermatogonial stem cells have the capacity to repair induced mutations by inherent DNA repair mechanism or by complete removal of the damaged cell via apoptosis. However, as these spermatogonial cells represent the progenitors from which all future germ lines are derived, any sustained mutations in these cells that escape repair or elimination will continue to be transmitted, resulting in the possible production of mutation-carrying sperms for the duration of a male's lifetime.

Animal studies indicate that differentiating germ cells are more sensitive to induction and transmission of mutations than stem spermatogonia.

Human data on the effects of genotoxic agents on spermatogenesis, on the time period for recovery and outcomes of pregnancies after paternal exposure to genotoxic agents, are limited. Most data are available from cancer treatments with genotoxic compounds.

Some literature reports of cancer treatment-induced sperm DNA changes indicated increased sperm chromatin damage for up to 2 years after end of treatment. The damage was more marked in advanced cancer stages and was also influenced by treatment type and dose. However, cancer treatment is in the majority a combination treatment of several cytotoxic and genotoxic compounds, often in combination with radiotherapy. Therefore, more pronounced effects are likely. Additionally, studies in lymphoma patients and testicular cancer patients have also shown that cancer patients had altered sperm DNA before treatment with anticancer agents or an increased risk of congenital malformations in offspring.

The incidence of adverse effects in offspring of fathers treated with anticancer agents has been reviewed. There are contradictory reports of the incidence of any effects in the offspring of fathers treated with antineoplastic therapies. Most authors did not find any increased risk of congenital or genetic abnormalities, perinatal death, low birth weight or preterm birth in the children of male cancer survivors treated with chemotherapy or radiotherapy. However, others reported an increased risk of congenital abnormalities, at their peak in children born within 2 years of their father's cancer diagnosis.

A study in children of fathers with testicular germ-cell cancer did not show evidence of more frequent abnormalities in offspring after treatment with radio- or chemotherapy. However, all these studies have some limitations and the exact interval between the end of cancer treatment and safe conception is still not known precisely.

Nevertheless, it can be assumed that mutational risk will be highest when a pregnancy occurs during or within several months after the male is exposed to the genotoxic agent. After this time, the incidence of mutations declines to a lower level.

Therefore, the time period for use of contraception measures for male patients after treatment with genotoxic agents should last until the end of relevant systemic exposure (generally defined as five half-lives after the last dose) plus at least 90 days (ie, 60-75 days for sperm production plus 10-14 days for transport to the epididymis). In the case of encapsulated medicines (eg, liposomes) an additional time period for elimination from the body should be added to the 3 months (ie, time period for complete release of substance from liposomes plus five half-lives of the free fraction).

This recommendation will significantly reduce the risk of transmission of damaged DNA to the F1 generation.

In the more theoretical case of treatment of males with a pure aneugenic pharmaceutical (ie, a substance that induces an abnormal number of chromosomes), the recommended duration of contraception should be the same.

Comments:
From animal studies, differentiating spermatogonia are more sensitive to mutations compared to stem spermatogonia.
For males, the recommended duration of contraception for genotoxic medicines is at least 90 days (60-75 days for sperm production + 10-14 days for transport to the testicles).

3.1.1.4 General statement

The EU SmPC (data sheet) aims to provide recommendations to healthcare professionals on the safe and effective use of a medicine. However, the final decision regarding the additional time period of 3-months contraception for males should be taken by the doctor and/or the patient.

3.1.2 US FDA

The US FDA's Oncology pharmaceuticals: Reproductive toxicity testing and labelling recommendations (Guidance for industry) was published in May 2019. Relevant sections are summarised below.

3.1.2.1 Background

The purpose of this guidance is to assist sponsors in evaluating reproductive toxicity (mainly for effects on embryo-fetal development, EFD) for oncology pharmaceuticals and to provide recommendations for product labelling on duration of contraception following cessation of treatment to minimise potential risk to a developing embryo or fetus.

This guidance provides information for development of pharmaceuticals that are intended to treat patients with cancer.

3.1.2.2 Recommendation for male patients

Genotoxic medicines

Genotoxic pharmaceuticals may cause DNA damage in sperm, potentially resulting in adverse effects in the embryo or fetus. Although there are no reports of increased malformation in offspring of men treated with oncology pharmaceuticals, no report has adequately examined effects on children born within the first year after cessation of therapy. In addition, adverse embryo-fetal effects have been observed in animals when males treated with genotoxic pharmaceuticals were mated with untreated females. Use of contraception for a period of 3 months after cessation of therapy will minimise the risk of adverse embryo-fetal effects from genotoxic pharmaceuticals (Table 5). The 3-month period covers spermatogenesis and epididymal maturation.

Table 5: FDA recommendation on duration of contraception for genotoxic medicines

Source: Table 1 of FDA guidance for industry on reproductive toxicity with oncology pharmaceuticals

Nongenotoxic medicines

A hypothetical risk of teratogenicity or embryo-fetal lethality exists because of the transfer of a pharmaceutical (or its metabolites) through the seminal fluid to a woman. Although reports indicate that there is no increased malformation rate in the offspring of males exposed to oncology pharmaceuticals, no report has adequately examined effects on children born within the first year after cessation of therapy.

Scientific articles indicate that pharmaceuticals administered intravaginally, including thalidomide, at clinically relevant concentrations did not cause malformation in the fetus. However, an earlier study showed adverse embryo-fetal effects when male rabbits were administered thalidomide. Although thalidomide does not accumulate in the semen, many small-molecule pharmaceuticals do. Given data gaps for small-molecule teratogenic pharmaceuticals, FDA recommends a contraception period of 5 half-lives (Table 6). However for teratogenic biological products, no duration of contraception is necessary because these products have not been seen to accumulate in semen, have limited absorption, and may undergo proteolytic degradation caused by the presence of vaginal and cervical enzymes.

Table 6: FDA recommendation on duration of contraception for nongenotoxic medicines

[redacted]

Source: Table 2 of FDA guidance for industry on reproductive toxicity with oncology pharmaceuticals

Comments:

Unlike the EMA's recommendations which apply to all genotoxic medicines regardless of indication, the FDA's recommendations are specific for the treatment of cancer.

The FDA also groups their recommendations based on the type of medicine:

- Genotoxic: 5 half-lives plus 90 days
- Nongenotoxic small molecule: 5 half-lives (minimum of 1 week)
- Nongenotoxic biologics: none

3.2 Clinical practice and guidelines for methotrexate

3.2.1 New Zealand

A dermatologist is asking that the MARC reviews and considers updating the advice in the methotrexate data sheets and CMI (Annex 1). They note the following:

- Wording should be more proportionate and better aligned with contemporary human data for accurate risk communication and clinical decision-making.
- EMA recommendations do not distinguish between low-dose and high-dose use.
- Methotrexate used to treat skin and rheumatological inflammatory diseases is predominantly through an anti-inflammatory/immunomodulatory mechanism rather than immunosuppressive.
- In dermatology, methotrexate is widely used as first-line systemic therapy for multiple inflammatory conditions including eczema, psoriasis, lichen planus, sarcoidosis, pityriasis rubra pilaris, nodular prurigo, and other chronic skin conditions. Alternative treatments include ciclosporin, azathioprine, mycophenolate, systemic corticosteroids, and biologic or targeted therapies (eg, TNFα inhibitors, secukinumab, upadacitinib).
- For eczema, avoiding methotrexate would increase reliance on systemic corticosteroids and ciclosporin both of which have less favourable long-term safety profiles. Compared with methotrexate, medicines such as ciclosporin, azathioprine, upadacitinib and prolonged systemic corticosteroids are associated with higher risks of immunosuppression, infection, metabolic toxicity, photosensitivity and malignancy.
- For psoriasis, treatment options are relatively limited. Avoiding methotrexate would require increased use of ciclosporin and earlier escalation to biologic therapy. Earlier use of biologics has implications for treatment durability, health system cost, and the risk of secondary loss of response over time.
- Several observational studies and a meta-analysis (Bo Jensen et al [10], Grosen et al [11], Eck et al [12], Weber-Schoendorfer et al [13], Winter et al [14]) have examined pregnancy outcomes following paternal methotrexate exposure typically defined as use within approximately 90 days prior to conception. Across these studies, there has been no demonstrated increase in the rate of major congenital malformations or other consistent adverse pregnancy outcomes, although small risk increases cannot be entirely excluded.
- Dermatologists are receiving increasing queries from GPs and patients requesting alternative systemic treatment options due to concerns on paternal use of methotrexate. These concerns are largely driven by the current package-insert wording. This places clinicians in a challenging position as patients request avoiding methotrexate despite the absence of adverse pregnancy outcomes from paternal exposure in the available human data.

- With updating the methotrexate product information, consideration could be given to wording that explicitly acknowledges the precautionary basis of current recommendations noting that human observational studies to date have not demonstrated an increased risk of major congenital malformations associated with paternal methotrexate exposure.

Other relevant information sources note the following:

- **bpac^{nz}**: A 2014 article on the safe prescribing of methotrexate notes that international treatment guidelines recommend the use of contraception for male patients taking methotrexate. The reference for this is the British rheumatology DMARD guidelines in consultation with dermatologists reported by Chakravarty et al 2008 [15]. However, recent evidence suggests that paternal use of methotrexate does not increase the risk of miscarriage or birth defects (Weber-Schoendorfer et al [13]).
- **Dermnet**: The methotrexate webpage states that for many years men were advised not to father children while they were on methotrexate and for at least 3 months afterwards because methotrexate had been reported to cause a reduction in sperm count. The current expert view is that the risks are very low, and this precautionary approach is not necessary.
- **NZ Rheumatology Association**: The methotrexate prescribing position statement for family planning (August 2015) states multiple studies including meta-analysis of paternal methotrexate use have not shown any negative association with quality of sperm or evidence of fetal harm. Active autoimmune rheumatic disease is more likely to have a detrimental effect on fertility, therefore, males on methotrexate hoping to father children should be advised to continue on methotrexate. Multiple international guidelines on reproductive health endorse continuation of methotrexate in males. No references are cited.
- **NZF**: The patient advice section in the methotrexate monograph includes that for males of reproductive potential, contraception must be used during treatment with methotrexate and for at least 3 months after stopping treatment.
- **Healthify**: Advice for patients on methotrexate tablets for inflammatory conditions is for males to use effective contraception for at least 3 months after stopping treatment.

Comments:

The dermatologist is not requesting a change to the data sheet recommendation for males to use effective contraception during and for 3 months after stopping methotrexate. Their suggestion is to add more context from observational studies that haven't found an increased risk of major congenital malformations.

The Chakravarty et al article referenced in the bpac^{nz} article contains 11 key statements when monitoring a DMARD. One of these statements is that pregnancy and related issues such as breastfeeding must be addressed when patients are receiving a DMARD. However, it was published in 2008 and there is no specific advice for contraception requirements in male patients.

It is worth noting there is a high rate of unintended pregnancy in New Zealand. The 2014/2015 New Zealand Health survey found 54% of all women's most recent pregnancies were planned, 32% were ambivalent, and the remaining 14% were unplanned [16]. The Growing Up in New Zealand study found 40% of mothers reported their pregnancies were unplanned [17].

3.2.2 Australia

The **Council of Australian Therapeutic Advisory Groups (CATAG)** is an expert, consensus-based collaboration of representatives from all Australian state and territory therapeutic advisory groups. CATAG published a position statement on the use of low-dose methotrexate in October 2020. This statement provides guidance to healthcare professionals on dispensing and administering low-dose methotrexate (oral tablets and prefilled syringe subcutaneous formulations).

- Low-dose methotrexate is defined as between 5 mg and 25 mg of methotrexate per week, although doses up to 30 mg may be used.

- Methotrexate performs two distinct therapeutic functions at different doses:
    - Low-dose methotrexate given once weekly is an immunomodulator. Although the pharmacology is unclear, low-dose methotrexate does not appear to exert its effects through its antineoplastic effect. Low-dose methotrexate is NOT considered chemotherapy and as such does not require handling as for antineoplastic medicines.
    - At all other doses when used as an antineoplastic medicine, methotrexate works as a folic acid antagonist. When preparing methotrexate for use as chemotherapy, precautions for handling are required in both preparing and administering.
- The risk of harm from occupational exposure during the dispensing/administering of whole tablets is low. Precautions intended for handling antineoplastic medicines are not necessary for the dispensing or administering of low-dose methotrexate (intact whole tablets). A 'non-touch' technique should be used as with all medicines.
- Women who are pregnant or trying to conceive shouldn't handle any dose forms of methotrexate. Pregnant women do not need to avoid social contact with people who are taking low-dose methotrexate for an inflammatory or autoimmune condition.
- The risk from taking low-dose methotrexate in men trying to conceive is considered negligible based on recent literature (Bo Jensen et al [10], Eck et al [12], Mouyis et al [18] and Crohn's & Colitis UK [19]). Men trying to conceive are able to continue handling low-dose methotrexate tablets.

Comments:
CATAG considers the risk of taking low-dose methotrexate in males who are trying to conceive is negligible.

3.2.3 Europe

The **European Alliance of Associations for Rheumatology (EULAR)** is a non-profit organisation that represents rheumatology patients, healthcare professionals, researchers and scientific societies of all European countries. EULAR published their recommendations for use of antirheumatic drugs in reproduction, pregnancy, and lactation (2024 update) [20]. A systematic literature review was conducted for the use of antirheumatic medicines during pregnancy etc. including paternal drug safety:

- Treatment with azathioprine, mercaptopurine, colchicine, cyclosporin, hydroxychloroquine, chloroquine, intravenous immunoglobulin, leflunomide, methotrexate ≤25 mg/week, mycophenolate, NSAIDs, prednisone, prednisolone, sildenafil, sulfasalazine, tacrolimus, TNF-inhibitor biologic DMARDs and non-TNF-inhibitor biologic DMARDs has not demonstrated a clinically relevant impact on offspring and can be continued in male patients trying to conceive.
- Given that high disease activity itself may impair male fertility, controlling rheumatic diseases with compatible medicines is the best strategy. Current evidence suggests that all the above medicines have no negative impact on birth outcome and can be continued in male patients trying to conceive. This also applies to medicines that would be discontinued in women before attempting pregnancy (eg, methotrexate, leflunomide, mycophenolate) since data in men showed no evidence of an increased risk for birth defects (Mouyis et al [18], Andersen et al (on teriflunomide) [21], Perez-Garcia 2020 [22], Grosen et al 2022 [23], Perez-Garcia 2023 [24], Meserve et al [25], and the EMA teriflunomide SmPC [26].

Comments:
EULAR states current evidence suggests methotrexate ≤25 mg/week can be continued in male patients trying to conceive.

3.2.4 Great Britain

The **British Society for Rheumatology** guidelines on prescribing immunomodulatory anti-rheumatic drugs and corticosteroids in pregnancy and breastfeeding published in 2023 (Russell et al [27]) is an update to the 2016 guideline (Flint et al [28, 29]). The following are noted (Table 7):

- Previous low-quality evidence contained in the 2016 guideline for outcomes of pregnancies after paternal exposure (n=263) to predominantly low-dose methotrexate did not find any adverse effects [28].
- An additional 6 studies were identified (n=2026) with paternal exposures to methotrexate within 3 months of conception that similarly found no increased risk of adverse fetal outcomes when compared with unexposed controls (n=4,700,599) (Winter et al [14], Egeberg et al [30], Andersen et al poster presentation [31], Friedman et al [32], Weber-Schoendorfer et al [13], and Eck et al [12]).
- Overall, paternal exposure to low-dose (≤25 mg/week) methotrexate is considered compatible with pregnancy (GRADE 1B indicating a strong recommendation based on moderate-quality evidence).

Table 7: Summary of pregnancy outcomes after paternal exposure to methotrexate

[redacted]

Source: Portions of Table 4 of the guidelines [27]

The **British Association of Dermatologists** guideline for the safe and effective prescribing of methotrexate for skin disease was based on relevant literature up to October 2015 (Warren et al [6]).

- Controversy exists around the safety of men fathering a pregnancy while taking methotrexate, and the general advice based on data for high-dose methotrexate is to wait for at least 3 months after the last dose (Fransen et al 2010 [33], UKTIS 2016 version [34]).
- Low-dose methotrexate may induce oligospermia (Sussman & Lenoard 1980 [35]) and evidence from animal studies suggests methotrexate induces damage to spermatogenesis (Sukhotnik 2013 rat study [36]) but this has not been examined in humans.
- Prospective observational studies comprising between 42 and 139 men taking low-dose methotrexate have not found an increased risk of spontaneous abortion or fetal malformations (Weber-Schoendorfer et al [13], Beghin et al [37], Wallenius et al [38]). Therefore, there is no evidence to support interruption of pregnancy following impregnation by a man taking low-dose methotrexate. However, it is prudent to advise men to delay planning their family for at least 3 months following their last dose of methotrexate [37].

Comments:

The rheumatology guidelines consider paternal low-dose methotrexate (≤25 mg/week) is compatible with pregnancy.

The dermatology guidelines suggest unplanned pregnancies from males taking low-dose methotrexate can be continued. However, for planned pregnancies males should wait for 3 months after their last dose of methotrexate. Some of the references are older (eg, Fransen et al 2010, Sussman & Leonard 1990 reporting a case of oligospermia in a patient with severe psoriasis treated with low-dose methotrexate).

UKTIS (UK teratology information service) is also referenced. The most recent 2024 version notes methotrexate manufacturers recommend male partners use reliable contraception and wait 3 months after cessation before attempting conception. Since there is no conclusive evidence of adverse fetal effects, where a couple is planning a pregnancy and the male's condition is well-controlled with methotrexate, an

assessment and discussion of the benefits and risks of continuing treatment vs. stopping treatment should be undertaken. The risks to the fetus are theoretical and not supported by available human data.

4 PUBLISHED LITERATURE

A Pubmed search of (methotrexate) AND (paternal) yielded 54 results. Those that are relevant are summarised below along with references provided by the dermatologist and relevant references from the CATAG and EULAR guidelines.

Study types have been grouped into 4 subsections (reviews, cohort/registry studies, teratology information service (TIS) studies, effects on sperm/fertility) and there is a summary table of findings at the end of each subsection. The majority of studies in each subsection are shown in order of publishing year (older to newer).

4.1 Reviews

4.1.1 Rademaker et al 2017 – Australasian Psoriasis Collaboration (APC) review [39]

Title: The Australasian Psoriasis Collaboration view on methotrexate for psoriasis in the Australasian setting

The Collaboration reviewed methotrexate in the management of psoriasis in the Australian and New Zealand setting. This article is based on expert opinion and a literature review.

Low-dose methotrexate (<0.4 mg/kg/week) has a slow onset of action and has moderate to good efficacy, together with an acceptable safety profile. A standard dermatological dose is 15-25 mg once per week (range 5-40 mg/week).

The mechanism of action is anti-inflammatory by inhibiting 5-aminoimidazole-4-carboxamide ribonucleotide transformylase, rather than immunosuppressive through inhibition of tetrahydrofolate reductase.

Although methotrexate is a potential teratogen post-conception, there is little evidence for this pre-conception. Post-conception, there are risks of spontaneous abortion (42%, 95% CI 29.2-58.7), major birth defects (adjusted OR 1.8, 95% CI 0.6-5.7), and developmental delay (unknown rate but possibly increased). There are a few reports of oligospermia (low sperm count) but no effect on the quality of sperm, and no increased risk of congenital abnormalities due to spermatogenesis.

Comments:

The recommendations and comments in this article are listed in bullet points with minimal explanation, which is deliberate. The authors note that for psoriasis low doses are used and methotrexate's mechanism of action is anti-inflammatory rather than immunosuppressive, which implies minimal effects on DNA synthesis, DNA repair and cell replication.

4.1.2 Gutierrez & Hwang 2017 – Expert opinion [40]

Title: The toxicity of methotrexate in male fertility and paternal teratogenicity

This paper reviewed the evidence for current recommendations for methotrexate use and male fertility, and aimed to educate health professionals so they can provide appropriate counselling to males of reproductive age. The authors conducted a literature search of peer-reviewed studies from Pubmed searches and the references included in these studies.

Studies of men receiving methotrexate have demonstrated varied testicular effects, with some patients experiencing reversible oligospermia, while a majority experience no measurable effects on immediate fertility or future progeny outcome. However, these small case studies have largely examined patients using standard semen evaluations, which are insensitive to small but potentially meaningful changes in the sperm that may impact fertility and the health of future offspring. The known incidence of severe oligospermia in multiple

patients demonstrates the potential for important molecular alterations in the sperm of men receiving methotrexate. However, molecular alterations need to be better quantified.

The recommendation to stop methotrexate 3 months before conception to allow for mutagenic spermatozoa to be replaced appears safe but is based on the timeframe of spermatogenesis rather than evidence of germline mutations resulting in clinically significant changes in offspring. This recommendation should be based on a discussion between a patient and healthcare professional, rather than a strict recommendation.

The discussion should consider the patient's disease state and risks and benefits of continuing treatment with methotrexate. For example, in patients with disease processes that may influence fertility such as psoriasis, IBD and other inflammatory conditions, the physician and patient must weigh the potential toxicity of methotrexate and importance of maintaining remission of the disease. Given the paucity of clear evidence and the poor predictability of post-therapy fertility status, the patient can only be advised as to the potential of adverse effects of methotrexate. It is essential that patients are informed of the availability and possibility of sperm cryopreservation.

Duration of contraceptive use during methotrexate treatment and up to 3 months after cessation should be left up to the patient's preference given the lack of evidence of clinically significant mutagenic effects.

For patients who conceive while the male is being treated with methotrexate, the patient may reasonably be reassured given the very few number of reported adverse outcomes and the number of small studies that have found no reported adverse pregnancy outcomes among fathers treated with methotrexate at the time of conception.

Comments:
The authors recommend that the need to stop methotrexate 3 months before conception is discussed between patients and prescribers. This should include their current disease state and the risks and benefits of continuing/stopping treatment with methotrexate.
For unplanned pregnancies, patients can be advised that available data indicate a low chance of adverse pregnancy outcomes.

4.1.3 Grosen et al 2017 – Systematic literature review [11]

Title: The influence of methotrexate treatment on male fertility and pregnancy outcome after paternal exposure

The authors performed a systematic literature search to investigate the influence of methotrexate on male fertility and pregnancy outcomes. A total of 53 papers were included in the review, including 17 animal studies and 36 human case reports.

Animal studies

- Animal studies have shown adverse effects on spermatogenesis and chromosomal abnormalities in sperm after methotrexate exposure.
- One small animal study on pregnancy outcomes found that male treatment with methotrexate resulted in fewer litters with no other information (eg, miscarriage, biochemical pregnancies) reported.

Human studies

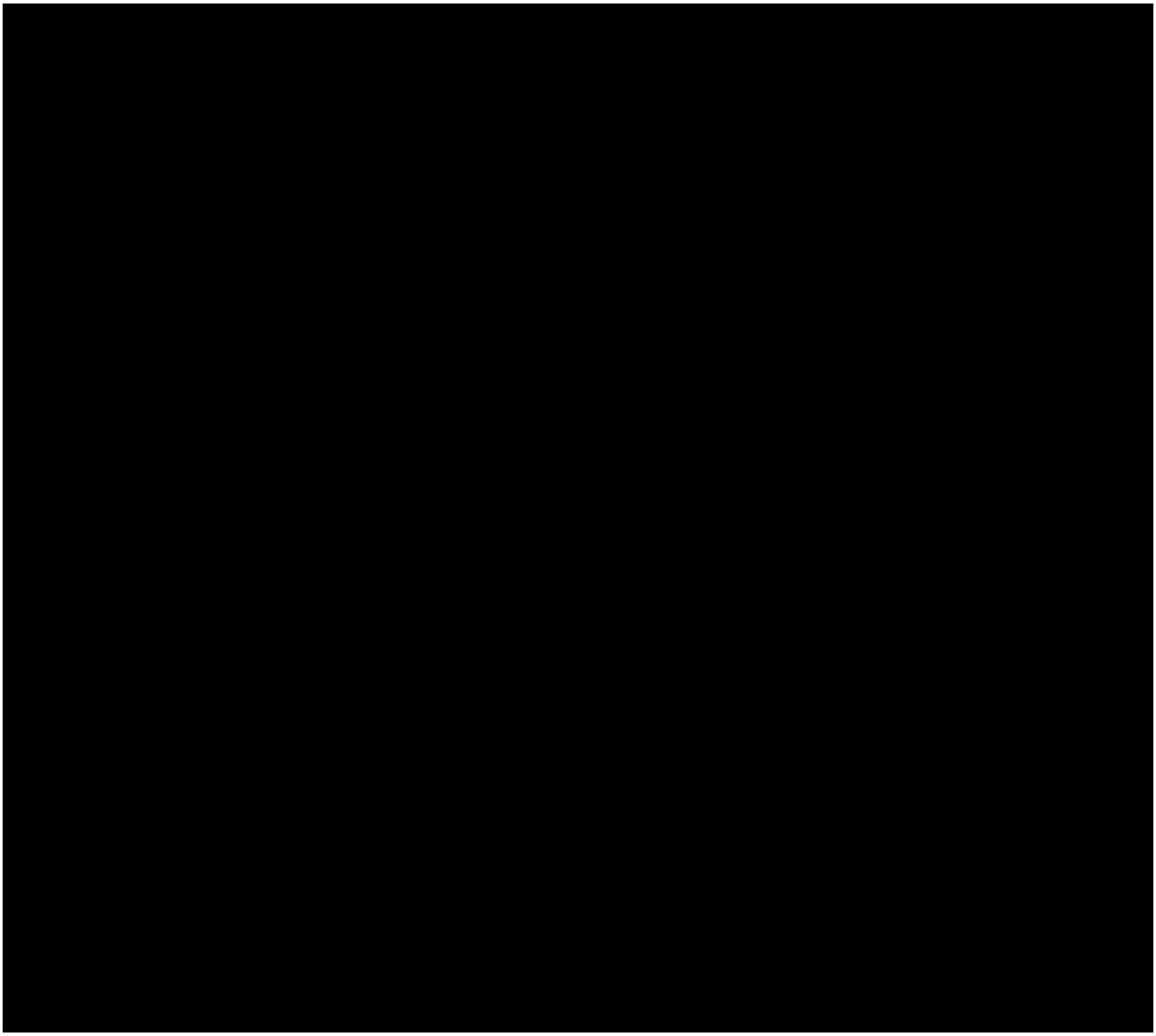
Sperm quality:

- A transient adverse effect on sperm quality with low-dose methotrexate has been reported, but several other cases have not found harmful effects of methotrexate.
- Methotrexate has not been measured in human sperm ejaculates. The risk of a direct toxic effect on the fetus through methotrexate-contaminated seminal plasma seems negligible.

Pregnancy outcome:

- A total of 284 pregnancies with known paternal methotrexate exposure during or 3 months before conception have been published (Table 8). They resulted in 248 live births, 19 spontaneous abortions, 16 elective terminations, and one pregnancy with unknown outcome.
- 13 congenital malformations were reported. Amniocentesis was performed in 18 cases and one chromosomal aberration was diagnosed (trisomy 16). The malformations were manifold and not specific for methotrexate embryopathy.
- Studies that compared exposed individuals with control groups found no increased risk of major congenital malformations, spontaneous abortions or elective terminations.
- Studies reporting exposure during organogenesis found no increased risk of congenital abnormalities during this sensitive period with a potential risk of exposure through contaminated seminal fluids.
- Gestational age at delivery and birth weight were comparable with control groups.
- Children who were conceived >3 months after cessation of methotrexate given in combination with other chemotherapeutic agents did not have an increased frequency of congenital malformations.

Table 8: Summary of results from studies on pregnancy outcomes after paternal methotrexate exposure during or 3 months before conception



The authors conclude that given the limited data, a conservative approach would be to advise withdrawal of methotrexate 70 days before conception in men wanting to father children. If continuation is crucial for disease control, the decision should be made on a case-to-case basis keeping in mind the limited literature in this field, with mainly positive clinical outcomes. The use of condoms during pregnancy seems unnecessary because the potential risk to the fetus is considered negligible.

Comments:

This review is in the context of the use of methotrexate for inflammatory bowel diseases (ulcerative colitis, Crohn's disease). This is not an approved indication in New Zealand but is a low-dose treatment where approved.

Most patients were receiving other concomitant medicines which contribute to adverse outcomes. The majority of the human studies were case reports, and some observational studies didn't have a comparator group.

The authors recommend a conservative approach of stopping methotrexate 70 days before conception.

4.1.4 Garritsen et al 2017 – Critically appraised topic [41]

Title: Pregnancy and fetal outcomes after paternal exposure to azathioprine, methotrexate or mycophenolic acid: A critically appraised topic

Oral immunosuppressive medicines are increasingly being prescribed to patients with chronic skin diseases. In clinical practice, there are concerns about prescribing these medicines to young men.

A systematic search in Pubmed, Embase, GREAT and the Cochrane central register of clinical trials (CENTRAL) was conducted on 19 October 2015. Studies on the effects of paternal use of azathioprine (AZA), methotrexate (MTX), mycophenolic acid (MPA) and mycophenolate mofetil (MMF) on pregnancy and fetal outcomes were included. Studies in which immunosuppressants were given for non-dermatological conditions were included as well.

After screening the full text of 82 studies, 20 were selected for critical appraisal. An additional 6 relevant articles were found by searching references of related articles and citations of the 20 included studies, therefore 26 articles were included for data extraction.

There were 13 studies identified for methotrexate which included 279 pregnancies (Table 9). Adverse pregnancy outcomes included preterm birth (n=10) and spontaneous abortion (n=19). Adverse fetal outcomes included congenital malformations (n=13).

Table 9: Summary of outcomes

Source: Table 3 of Garritsen et al 2017 [41]

The study of Weber-Schoendorfer et al had the greatest validity. A total of 113 pregnancies were described with no increased risk of major birth defects (OR 1.02, 95% CI 0.05-7.0) or spontaneous abortion (HR 1.19, 95% CI 0.65-2.17) in methotrexate exposed pregnancies compared with pregnancies not exposed to methotrexate. The other studies were of lower quality.

The authors conclude most of the included studies compared outcomes to a healthy population and there was no increase in adverse pregnancy or fetal outcomes. Nevertheless, preterm birth, spontaneous abortion, low

birthweight and congenital malformations have been described with varying incidence. Therefore, a possible risk of adverse pregnancy and fetal outcomes when using these medicines cannot be excluded.

Clinicians could discuss the results of this critical appraisal with patients, highlight the discrepancies between studies in reviews and guidelines and discuss the benefits and risks of treatment. If possible, preference should be given to the use of cyclosporin.

Comments:

There were 13 studies comprising 279 pregnancies with paternal exposure to methotrexate included in this review. Using the statistical rule of three, it could be concluded that any effect is rarer than 1 in 100. Most of the included studies compared outcomes with the general population, rather than a disease comparator group.

The authors note there was no increase in adverse pregnancy or fetal outcomes, but the possible risk of adverse outcomes with the use of these medicines cannot be excluded.

4.1.5 Bo Jensen et al 2019 – Poster presentation [10]

Title: THU0670 Paternal use of methotrexate and congenital malformations: A systematic review and meta-analysis

The authors performed a systematic search in PubMed, Embase, Cochrane Central, and Cinahl on 1 March 2018. Studies with an English abstract that assessed major or all malformations following any paternal exposure to methotrexate that included a control group were included in the meta-analysis.

36 studies were identified of which 20 contained original data. Five studies met the inclusion criteria for the meta-analysis: 3 studies from Denmark had a major overlap in study populations, one study from Norway, and one German study. All studies were cohort studies using national registries except the German that used structured interviews and phone interviews. Because of the overlapping Danish studies, only the largest Danish study for each of the outcomes were included.

A total of 265 fathers exposed to methotrexate and 1,004,834 controls were included. Among offspring of the methotrexate-exposed 7 (2.64%) had a major malformation compared to 33,816 (3.37%) among the unexposed. Pooled odds ratios were 1.02 (95% CI 0.48-2.20) for major malformations and 1.02 (95% CI 0.62-1.66) for all malformations.

The authors conclude they found no association between preconception paternal methotrexate use and major or all congenital malformations. The current recommendations to avoid paternal methotrexate use before conception do not appear to be supported by evidence and paternal treatment with methotrexate could be continued when planning a pregnancy.

Comments:

The abstract of this systematic review and meta-analysis was published as part of a set of poster presentations for the 2019 European congress of rheumatology and 2018 American college of rheumatology annual meetings. No further information, aside from the abstract and shown here, is available.

This article has been included because it was one of the references provided by the dermatologist and is also referenced in the Australian CATAG guidelines.

Meta-analyses of safety data have limitations: Efficacy outcomes, not safety, are usually the primary focus of clinical trials; there are often differences in definitions and measurement of adverse events between studies; and pooling data for adverse events that are rare could generate unstable results.

4.1.6 Mouyis et al 2019 – Systematic review of anti-rheumatic medicines [18]

Title: Safety of anti-rheumatic drugs in men trying to conceive: A systematic review and analysis of published evidence

The authors conducted a systematic search of Pubmed and Embase up to September 2017 to find relevant peer-reviewed papers, using keywords for fertility/spermatogenesis/conception, men, and disease modifying or biologic medicines commonly prescribed in patients with rheumatic disease.

The search yielded 724 papers and a total of 84 papers were included in the final analysis which covered the impact on fertility of over 611 male exposures to relevant medicines and over 5986 pregnancies conceived during paternal exposure to (or within 3 months of stopping) these medicines. Of the 84 papers, 35 had a comparator or control group.

Overall, aside from the known adverse impact of cyclophosphamide and sulfasalazine on spermatogenesis, there was no firm evidence of harm to fertility or pregnancy outcomes with paternal exposure to anti-TNF therapies, abatacept, rituximab, azathioprine, cyclosporin A, hydroxychloroquine, leflunomide, methotrexate or mycophenolate mofetil. There was no evidence found on the effects of male exposure to IVIG, tacrolimus, golimumab, anakinra or belimumab on fertility or pregnancy outcomes.

For pregnancy outcomes with methotrexate, there were 1511 peri-conception paternal exposures (Table 10).

- One cohort study reported 3 periconception exposures to methotrexate in 2 fathers and included one 1st trimester therapeutic abortion due to hydrocephalia [42].
- 17 studies (n=1508 exposed pregnancies) did not find a link between paternal methotrexate exposure and adverse pregnancy outcomes or congenital malformations. Where outcomes were specified, there were 264 live births to 34 pregnancy losses (including spontaneous and elective abortions, but early pregnancy losses were not accurately captured by all studies).
- In studies where congenital malformations were reported, there were 967 healthy babies with 78 congenital malformations. The two largest studies to assess this issue raised no concerns about the malformation rate. One by Eck et al reported 127 live births including 4 babies with congenital malformations (3.2%) which was a lower rate than the unexposed group (3.4%, OR 0.93) [12]. In another study by Egeberg et al, 72 congenital abnormalities were reported amongst 864 live births and the rate was not significantly elevated compared to the control group (OR 1.12, 95% CI 0.87-1.3) [30]. In this study, the odds ratios for low birth weight and preterm birth were 0.86 (95% CI 0.62-1.19) and 1.02 (0.74-1.42), respectively.
- Another large population-based cohort study by Friedman et al looked at longer term outcomes in 209 children following paternal exposure to methotrexate (with 1,056,524 controls). This study concluded there was no negative impact of paternal preconception use of methotrexate on selected outcomes (malignancies, autism spectrum disorders/schizophrenia/psychosis, and ADHD) [32].

Table 10: Results of systematic study of paternal exposure to methotrexate in men trying to conceive

The authors state since the British rheumatology guidelines which was based on limited evidence low-dose methotrexate may be compatible with paternal exposure, further evidence is accumulating with an additional 1248 reported exposures to support this view. These results provide further reassurance as to the safety of many DMARDs for men trying to conceive and will be useful when counselling men about risks of anti-rheumatic medicines to fertility and pregnancies, and following accidental conception.

Comments:
This review included findings from the Danish registry studies and support the current recommendations in the British rheumatology guidelines that low-dose methotrexate is compatible with paternal exposure.

4.1.7 Perez-Garcia et al 2020 – Systematic review of immunosuppressants [22]

Title: The effect of paternal exposure to immunosuppressive drugs on sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes: A systematic review

A systematic literature search was performed in Embase, Medline, Ovid, Cochrane, and Web of Science. Google Scholar and clinical trial registries of Europe and US were also included. The searches combined keywords on male sexual function and fertility, pregnancy outcomes and offspring health with a list of immunosuppressive medicines. For pregnancy outcomes, publications were included if paternal exposure to an immunosuppressive medicine took place in the 6 months before or around the time of conception.

A total of 5867 references were identified of which 161 articles met eligibility criteria. Of these, 50 included pregnancy and offspring outcomes and 130 included sexual health outcomes. Except for large Scandinavian cohorts, most of the identified articles had a small number of participants.

While a clear negative effect on sperm quality was evident for sulfasalazine and cyclophosphamide, a dubious effect was identified for colchicine, methotrexate and sirolimus. Information on pregnancy and offspring outcomes was scant but no large negative effect associated with paternal immunosuppressive exposure was reported.

Six studies reporting fertility outcomes in patients exposed to methotrexate were identified (Table 11). These studies included a total of 47 cases (40 men with psoriasis, 7 with immune-mediated disease), and 1912 controls all from one study. In patients exposed to methotrexate, sperm concentration decreased in 3 studies, no differences were reported in 2 studies, and sperm quality of one group of patients diagnosed with psoriasis and exposed to methotrexate was better than in patients treated with high dose glucocorticoids.

Table 11: Summary of methotrexate study characteristics and main findings for sperm quality, sexual function and reproductive hormone outcomes

[redacted]

For pregnancy and child outcomes with methotrexate (Table 12), 3 case reports from before 2000 reported only healthy liveborn children (Perry; Griggs & Schwartz; Lamboglia et al). More recent case series and cohort studies (169 pregnancies and 193 liveborn children) found no increased risk of birth defects associated with paternal methotrexate exposure (Beghin; Engeland; Weber-Schoendorfer; Winter; Drenches). This also applies to the rate of spontaneous abortions, preterm birth and small for gestational age (SGA). A study using Danish registries to look at long-term outcomes found no negative impact of paternal preconception use of methotrexate (Friedman et al).

Table 12: Summary of methotrexate study characteristics and main findings for pregnancy and child outcomes

[redacted]

[redacted]

Source: Portions of table 2 of Perez-Garcia et al 2020 [22]

The authors suggest evidence on the safety of immunosuppressive medicines in men with a wish to become a father is inconclusive. The lack of standardisation on how to evaluate and report male sexual function, fertility and reproduction as study outcomes in men exposed to immunosuppressive medicines is an important contributor to this result.

Comments:
The authors note that the more recent case series and cohort studies, including the large Danish registry studies, found no increased risk of birth defects with paternal methotrexate exposure.

4.1.8 Uysal et al 2025 – Systematic review and meta-analysis [43]

Title: Pregnancy outcomes following paternal methotrexate exposure: A systematic review and meta-analysis

The objective was to explore whether there is an association between major congenital malformations and other pregnancy outcomes following paternal methotrexate exposure through a systematic review and meta-analysis.

Pubmed, Web of Science, and Reprotox databases were searched through December 2023. Cohort and case-control studies with paternal exposure to methotrexate were included. The primary outcome of interest was major congenital malformations following paternal methotrexate exposure during preconception and at conception.

Seven cohort studies that fulfilled inclusion criteria were identified (Weber-Schoendorfer et al, Winter et al, Eck et al, Wallenius et al, Egeberg et al, Zarén et al). Among the outcomes, only major congenital malformations, stillbirth, and preterm birth were eligible for quantitative analysis. The adjusted analysis for major congenital malformations is shown in Figure 3. No significant increases in the risk of major congenital malformations (aOR 1.05, 95% CI 0.65, 1.68), stillbirth (OR 0.85, 95% CI 0.11, 6.45) or preterm birth (OR 0.95, 95% CI 0.59, 1.53) were observed following paternal methotrexate exposure.

Figure 3: Analysis of major congenital malformations with adjusted ORs

[redacted]

Source: Figure 1-C of Uysal et al 2025 [43]

The authors conclude these findings indicate that paternal methotrexate exposure does not significantly increase the risk of major congenital malformations, stillbirth, or preterm birth. In addition, it was not associated with a consistent pattern of malformations.

Comments:

There were no significant increases in the risk of major congenital malformations, stillbirth or preterm birth following paternal methotrexate exposure.

4.1.9 Summary of findings

A summary of findings from review articles described within section 4.1 is presented in Table 13.

Table 13: Summary of findings from review articles

Study	Number of studies	Number exposed to MTX	Exposure period	Findings
Rademaker 2017 (expert opinion)	n/a	n/a	n/a	Although MTX is a potential teratogen post-conception, there is little evidence for this pre-conception.
Gutierrez & Hwang 2017 (expert opinion)	n/a	n/a	n/a	Recommendation to stop MTX 3 months before conception should be based on a discussion between prescribers and patients.
Grosen 2017	Total 53 studies: 13 MTX	284 pregnancies	During or 3 months before conception	Given the limited data, a conservative approach would be to advise withdrawal of MTX 70 days before conception
Garritsen 2017	Total 26 studies: 13 MTX	279 pregnancies		No increase in adverse pregnancy or fetal outcomes
Bo Jensen 2019	Total 36 studies: All MTX 5 studies in meta-analysis	265 fathers 1,004,834 controls		Major malformation OR 1.02 (95% CI 0.48-2.20) All malformations OR 1.02 (95% CI 0.62-1.66)
Mouyis 2019	Total 84 studies: 4 MTX cohort studies of fertility outcomes 13 MTX cohort studies of pregnancy outcomes	1511 pregnancies		Low-dose methotrexate may be compatible with paternal exposure
Perez-Garcia 2020	Total 161 studies: 50 pregnancy outcomes (12 MTX) 130 sexual health outcomes (6 MTX)	3 in case reports 51 in case series 831 pregnancies in cohort studies	Varied from 3-6 months prior or at the time of conception	Safety of immunosuppressive medicines in males wishing to father children is inconclusive
Uysal 2025	Total 7 cohort studies: All MTX	487 infants No. of infants in control group varied depending on the analysis		Major congenital malformations aOR 1.05 (95% CI 0.65, 1.68) Stillbirth OR 0.85 (95% CI 0.11, 6.45) Preterm birth OR 0.95 (95% CI 0.59, 1.53)

MTX = methotrexate

4.2 Cohort/registry studies

4.2.1 Wallenius et al 2015 – Norwegian data linkage study [38]

Title: No excess risks in offspring with paternal preconception exposure to disease-modifying antirheumatic drugs

The objective was to examine pregnancy outcomes in partners of male patients with inflammatory joint disease who were or were not exposed to disease-modifying antirheumatic drugs (DMARDs) before conception compared with outcomes in reference subjects from the general population.

Data linkage from a longitudinal observational study of patients with inflammatory joint disease (the Norwegian DMARD registry study) and the medical birth registry of Norway enabled a comparison of pregnancy outcomes. Outcomes of pregnancies in which the father was exposed to DMARDs within 12 weeks of conception and those in which the father was never exposed to DMARDs were analysed separately and compared with outcomes in reference subjects. Potential associations between DMARD exposure and adverse pregnancy outcomes were assessed by logistic regression analysis.

A total of 1796 men with inflammatory joint disease were associated with 2777 births. In 110 of these births, the father had been exposed to DMARDs within 12 weeks before conception, and in 230 births the father had never been exposed to DMARDs before conception. The DMARDs (monotherapy or combination) to which the fathers were exposed most frequently within 12 weeks of conception were methotrexate (n=49), sulfasalazine (n=17) and TNF inhibitors (n=57).

No differences were observed in the logistic regression analyses of birth outcomes between patients and reference subjects (Table 14). The relative risks (RRs) of serious malformation were not different between groups (for DMARD-exposed births RR 1.22, 95% CI 0.45, 3.31; for never DMARD-exposed births RR 0.70, 95% CI 0.26, 1.86). Malformations were registered in 4 of the 110 preconception DMARD-exposed births: 1 newborn with ventricular septum defect (methotrexate exposure), 1 newborn with pes equinovarus (combined methotrexate and TNF inhibitor exposure), and 2 newborns with unspecified abdominal atresia (TNF inhibitor exposures).

Table 14: Pregnancy outcomes in partners of male patients with inflammatory joint disease according to DMARD exposure within 12 weeks before conception

Source: Table 3 of Wallenius et al 2015 [38]

When examined in multiple linear regression analyses with explanatory variables, mean differences in birth weights were not different in the DMARD-exposed group (25.1 g, 95% CI -68.9, 119.2) and the never DMARD-exposed group (-3.6 g, 95% CI -14.5, 7.3).

The authors conclude preconception paternal exposure to DMARDs was not associated with an increase in adverse pregnancy outcomes. Importantly, no increased risk of congenital malformations was observed.

Comments:

Of the 2777 births, only 110 were associated with paternal DMARD exposure within 3 months of conception. The authors state a number of births were excluded from analysis because they occurred before paternal onset of rheumatic disease.

4.2.2 Eck et al 2017 – Danish registry study [12]

Title: Risk of adverse pregnancy outcome after paternal exposure to methotrexate within 90 days before pregnancy

The authors conducted a nationwide register study to investigate the association between paternal exposure to methotrexate within the 90-day period before pregnancy and congenital malformations and stillbirth in offspring.

The cohort consisted of all live births in Denmark between 1997 and 2011 identified from the Medical Birth Registry, allowing 1-year follow-up for diagnosis of neonatal malformations. Methotrexate-exposed fathers were identified from the National Prescription Registry – in the study period, 72% of methotrexate use was dispensed in pharmacies and the users are therefore identifiable. From the National Hospital Registry, the authors identified paternity, live births, and stillbirths as well as discharge diagnoses on congenital malformations.

Exposure was defined as paternal dispensing of a methotrexate prescription for systemic use within 90 days before pregnancy. Primary outcome was any major congenital malformations diagnosed within the first year after birth according to the European Surveillance of Congenital Malformations classification system. Secondary outcomes were subgroupings of major congenital malformations, minor malformations as well as risk of stillbirth after paternal methotrexate exposure.

A total of 849,676 live births with known paternity were identified. There were 127 live births of methotrexate-exposed fathers. Exposed fathers were more likely to be older compared to unexposed fathers (mean 35.6 years vs. 32.8 years). Women having a child with a man exposed to methotrexate within 90 days before pregnancy were also more likely to be older (mean 31.7 years vs. 30.1 years) and were more likely to have given birth previously. Fathers exposed to methotrexate were more likely to be exposed to other medicines such as antirheumatics, antipsoriatics, corticosteroids, folic acid, and intestinal anti-inflammatory agents.

Results on congenital malformations are summarised in Table 15. Of the 127 live births to methotrexate-exposed fathers, four (3.2%) had major malformations compared with 28,814 (3.4%) in the unexposed. The odds ratio for major congenital malformation among exposed fathers compared to unexposed was 0.93 (95% CI 0.34-2.51) and when adjusted for year of birth, maternal age, educational length, household income, and parity, the adjusted OR was 1.01 (95% CI 0.37-2.74).

To analyse the association with minor congenital malformations, a combined model of both minor and major malformations was included. Five children (3.9%) with fathers exposed to methotrexate were born with either a major or a minor congenital malformation compared with 42,245 (5%) among children to unexposed fathers resulting in an adjusted OR of 0.86 (95% CI 0.35-2.10).

Due to the small number of congenital malformations in the exposed group, only those of the heart could be analysed. There was no significant difference in the number of major malformations of the heart in the exposed and unexposed groups (unadjusted OR 2.66, 95% CI 0.85-8.30; adjusted OR 2.79, 95% CI 0.89-8.78).

There were no stillbirths in the methotrexate-exposed group compared with 2541 (0.3%) in the unexposed group and no increased risk of preterm birth (adjusted OR 1.31, 95% CI 0.66-2.59) among the children from exposed fathers.

The authors conclude no association between paternal exposure to methotrexate within 90 days before pregnancy and congenital malformations, stillbirths, or preterm birth was seen. Available data suggest pre-pregnancy paternal methotrexate exposure should not be of major concern. Multinational recommendations should be changed accordingly.

Table 15: Paternal exposure to methotrexate within 90 days before pregnancy and risk of congenital malformations

Source: Table 3 of Eck et al 2017 [12]

Comments:

The registries do not have records of the father for miscarriages or induced abortions. Therefore, terminated pregnancies due to a fetal malformation were not included in the exposed and unexposed groups and would result in an underestimation of congenital malformations in both study groups.

There is also no information on doses used, though it is possible that low-doses were predominantly used.

4.2.3 Winter et al 2017 – Danish registry study [14]

Title: Birth outcomes after preconception paternal exposure to methotrexate: A nationwide cohort study

This study, using the National Danish Registries, aimed to examine the association between paternal methotrexate use 3 months before conception and adverse birth outcomes.

The study included all live born singleton children in Denmark from 1 January 1997 through 2013. Children fathered by men treated with methotrexate within 3 months before conception constituted the exposed cohort (n=193) and children fathered by men not treated with methotrexate constituted the unexposed cohort (n=1,013,801). Birth outcomes included congenital anomalies (within the first year of life), preterm birth and small for gestational age (SGA).

The three most common reasons for methotrexate prescriptions among fathers were a history of rheumatologic disease (63.7%), dermatologic conditions (32.6%) and unknown reason (17.1%). There were 14 men (7.3%) with inflammatory bowel disease who took methotrexate within 3 months of conceiving a child. The proportion of exposed fathers who had a prescription for methotrexate within 0-30 days before conception was 71/193 (36.8%), and within 0-60 days before conception was 124/193 (64.2%). Children in the exposed cohort had a median birth weight of 3510 g and were born at a median gestational age of 39.7 weeks.

Results are summarised in Table 16. The adjusted OR for preterm birth was 1.38 (95% CI 0.68-2.81) when adjusted for maternal age, paternal age, parity and maternal smoking status. Of the 13 preterm infants, 11 (84.6%) were moderate to late preterm with gestational age 32-37 weeks. The adjusted risk for congenital anomalies was 1.10 (95% CI 0.57-2.13), and for SGA was 0.98 (95% CI 0.39-2.50).

Table 16: Crude and adjusted odds ratios for birth outcomes in children fathered by men treated with methotrexate within 3 months of conception

Source: Table 2 of Winter et al 2017 [14]

Ten children in the exposed group had congenital anomalies and the types of anomalies were:

- Face/skull: 2 children (one had plagiocephaly and one had a malformation of the face/neck).
- Cardiac: 2 children (one with stenosis of the pulmonary artery and one with an unspecified cardiac congenital anomaly).
- Other: 1 child each for syndactyly, hypospadias, talipes equinovarus, Hirschsprung's disease.

The authors conclude these results on the effect of paternal use of methotrexate within 3 months before conception on birth outcomes of congenital anomalies, preterm birth and SGA and overall reassuring.

Comments:
This Danish registry study has a similar design to the Eck et al 2017 study. The strengths and limitations of these studies are therefore similar.

4.2.4 Friedman et al 2017 – Danish registry study [32]

Title: Paternal use of azathioprine/6-mercaptopurine or methotrexate within 3 months before conception and long-term health outcomes in the offspring

The authors had 2 goals to investigate the paternal use of AZA/6-MP or methotrexate within 3 months before conception: examine the long-term risk of malignancy in children, and to further explore the specific effect on the risk of developmental disorders in the offspring.

This study included all children born in Denmark from 1 January 1997 through 2013. Individual based data on children and their fathers were linked from nationwide Danish registries.

The exposed cohort were children fathered by men who used AZA/6-MP (n=735) or methotrexate (n=209) within 3 months before conception. The unexposed cohort were children fathered by men who did not use AZA/6-MP or methotrexate (n=1,056,524). The outcomes included were malignancies, autism spectrum disorders (ASD)/schizophrenia/psychosis, and attention deficient hyperactivity disorder (ADHD).

The majority of fathers on AZA/6-MP were treated for IBD (n=556, 75.6%). Paternal diseases in the methotrexate cohort included IBD (n=18, 8.6%), rheumatologic diseases (n=126, 60.3%), connective tissue disease (n=11, 5.3%) and psoriasis (n=73, 34.9%).

In the AZA/6-MP exposure group, there was one child with leukaemia (0.15%), one with ASD/schizophrenia (0.14%) and 3 with ADHD (0.41%). In the methotrexate exposure group, there were 3 with ADHD (1.4%). In the unexposed group, there were 1710 malignancies (0.16%), 2107 with ASD/schizophrenia (0.2%), and 2799 with ADHD (0.26%). Median follow up times were 6.7 years (IQR 3.6-11.3) and 9.9 years (IQR 5.7-14.3), respectively. There were 25% of exposed children with a follow up period longer than 11.3 years.

Regression models could not be applied due to the low number of cases among the exposed. Proportions of fathers from the exposed cohort who were also treated with AZA/6-MP or methotrexate in the time window of 90-180 days before conception were 540/735 (73.47%) and 81/209 (38.76%), respectively. In the sub-analysis

where the exposure window was changed to 30-120 days before conception, results did not change and the same number of cases were found among the exposed.

The authors conclude there was no negative impact of paternal preconception use of AZA/6-MP or methotrexate on selected childhood health outcomes.

Comments:

This Danish registry study used the same cohort of fathers in the Winter et al 2017 study, but included all children rather than only singletons.

Regression modelling could not be done because of the low number of cases in the exposed groups.

4.2.5 Egeberg et al 2017 – Danish registry study [30]

Title: Birth outcomes in children fathered by men treated with immunosuppressant drugs before conception – A Danish population-based cohort study

In a letter to the editor, the authors report on the risk of adverse birth outcomes in a nationwide cohort of the Danish population.

The study comprised Danish children born between 1 January 2004 and 31 December 2010 with available information on the biological father by linking databases. Study outcomes were any type of congenital abnormality, low birth weight (<2500 g), and premature birth (birth before 37 weeks). Additional analyses were performed for congenital malformations, deformations, and chromosomal abnormalities in the years after birth.

A total of 417,634 children were included, of which 31,238 (7.5%) were born with congenital abnormalities, 22,089 (5.3%) had low birth weight and 18,972 (4.5%) were born preterm. A total of 2123 father had claimed prescriptions for immunosuppressants before conception: azathioprine (n=1246), cyclosporin (n=247), methotrexate (n=864), mycophenolate mofetil (n=37). There were 163, 117 and 107 cases of congenital abnormalities, low birth weight, and preterm birth, respectively, among children fathered by men treated with immunosuppressants before conception.

Of 864 methotrexate-treated fathers, there were 72 cases of congenital abnormalities (adjusted OR 1.12, 95% CI 0.87-1.43) and 40 children had low birth weight (adjusted OR 0.86, 95% CI 0.62-1.19) (Table 17). Similarly, 39 children were born preterm (adjusted OR 1.02, 95% CI 0.74-1.42).

The authors conclude the study does not provide any evidence for an increased risk of congenital abnormalities, low birth weight, or preterm birth in the offspring. This may help physicians in clinical decision making and counselling of men with chronic inflammatory disorders who plan to start a family.

Table 17: Odds ratios with 95% confidence intervals for birth outcomes

Source: Supplementary Table S1 of Egeberg et al 2017 [30]

4.2.6 Meserve et al 2021 – US cohort study using claims data [25]

Title: Paternal exposure to immunosuppressive and/or biologic agents and birth outcome in patients with immune-mediated inflammatory diseases

The authors conducted a retrospective cohort study to inform the safety of exposure to immunosuppressive and/or biologic agents around conception in expectant fathers with immune-mediated inflammatory diseases (IMIDs) on birth outcomes.

Using a de-identified administrative claims database (Optum Labs Data Warehouse) 7,453 expectant fathers aged 20-55 years with IMIDs (inflammatory bowel diseases, rheumatoid arthritis, psoriasis/psoriatic arthritis, ankylosing spondylitis) linked to newborns with periconception medicine exposure between 38-60 weeks prior to newborn delivery date (34-58 weeks prior for pre-term newborns) and neonatal follow-up for 3 months after delivery date were identified.

Through logistic regression adjusting for paternal age and race (and in a subset for maternal age, race, presence of IMIDs and non-singleton births), the risk of major congenital malformations (primary outcome) and preterm birth and low birthweight in fathers exposed to thiopurines (n=461), methotrexate (n=171), TNFα antagonists (n=1082) or non-TNF-targeting biologic agents (n=132) were compared with fathers not exposed to any of these medicines (n=5607).

Compared to unexposed fathers (3.4% prevalence of major congenital malformations), exposure to thiopurines (RR 1.12, 95% CI 0.66-1.76), methotrexate (RR 0.67, 95% CI 0.21-1.55), TNFα antagonists (RR 1.14, 95% CI 0.81-1.57) and non-TNF-targeting biologic agents (RR 1.75, 95% CI 0.80-3.24) was not associated with increased risk of major congenital malformations (Table 18). No association was observed between paternal medicine exposure and risk of preterm birth or low birth weight. Results were stable on sub-analyses of linked father-mother-newborn triads.

Table 18: Risk of major congenital malformations by paternal medicine exposure status

Source: Table 2 of Meserve et al 2021 [25]

The authors conclude in this large cohort study of 7,453 expectant fathers with IMIDs, exposure to immunosuppressive or biologic agents around conception was not associated with increased risk of adverse birth outcomes.

4.2.7 Zarén et al 2023 – Swedish registry study [44]

Title: Methotrexate use among men – association with fertility and the perinatal health of their children: A Swedish nationwide register study

The objective was to study the effect of methotrexate on male fertility and subsequent effects on their children.

This nationwide multi-register cohort study included all children born alive in Sweden between 2006 and 2014 and their fathers. Three cohorts were defined: children to fathers with periconceptional methotrexate exposure (exposed cohort), children whose fathers stopped methotrexate ≥2 years before conception (previously exposed cohort), and children to fathers with no methotrexate exposure (control cohort).

Periconceptional exposure was defined as fathers having at least one dispensed methotrexate prescription from pharmacies 0-3 months before conception along with at least one more dispensed methotrexate prescription 0-12 months before conception. For the previously exposed cohort, the father had no dispensed methotrexate prescriptions in the 2 years before conception, but at least two dispensed prescriptions before that.

The main outcome measures were congenital anomalies, preterm birth, being small for gestational age (SGA), and need for intracytoplasmic sperm injection (ICSI) to achieve pregnancy. Outcomes were analysed using logistic regression.

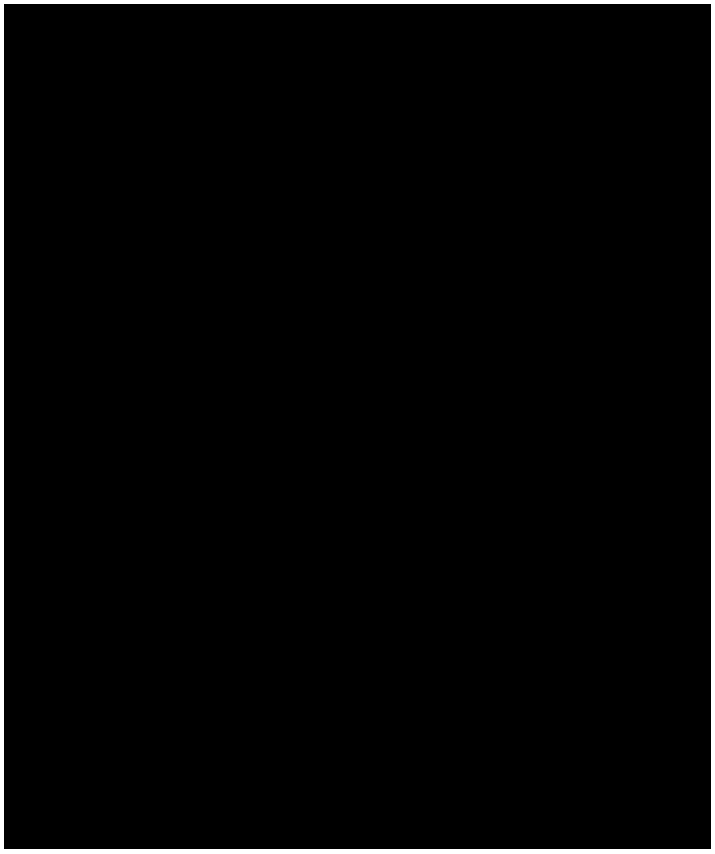
A total of 223 children were identified for the exposed cohort, along with 356 children in the previously exposed cohort and 809,706 controls.

In children in the exposed cohort, the adjusted odds ratios were (Table 19):

- Major congenital anomalies: OR 1.1 (95% CI 0.4-2.4)
- Any congenital anomalies: OR 1.4 (95% CI 0.7-2.3)
- Preterm birth: OR 1.0 (95% CI 0.5-1.8)
- SGA: OR 1.0 (95% CI 0.4-2.2)
- Conception by use of ICSI: OR 4.6 (95% CI 2.5-7.7).

The authors conclude this study suggests paternal periconceptional methotrexate use does not increase the risk of congenital anomalies, preterm birth or SGA in the offspring but may temporarily reduce fertility.

Table 19: Perinatal health of children according to paternal methotrexate exposure



Source: Table 2 of Zarén et al 2023 [44]

4.2.8 Shao et al 2025 – Taiwanese registry study [45]

Title: Effects of paternal preconception exposure to conventional and biologic DMARDs on newborn outcomes

This study examined the impact of paternal exposure to disease-modifying antirheumatic drugs (DMARDs) on birth outcomes of offspring, specifically small for gestational age (SGA), preterm labour, and congenital abnormalities. The DMARDs included conventional synthetic (csDMARDs), biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs).

A population-based birth cohort was constructed with fathers diagnosed with autoimmune rheumatic diseases from 2004 to 2020 using data from a maternal and child health database, the birth registry, and national health insurance data. Paternal preconception exposure was fathers who were prescribed immunosuppressants or biologics between 38 and 60 weeks before the newborn's delivery date. Inverse probability of treatment-weighted (IPTW) logistic regression models were used to assess the effects of variables on associations of interest considering other covariates.

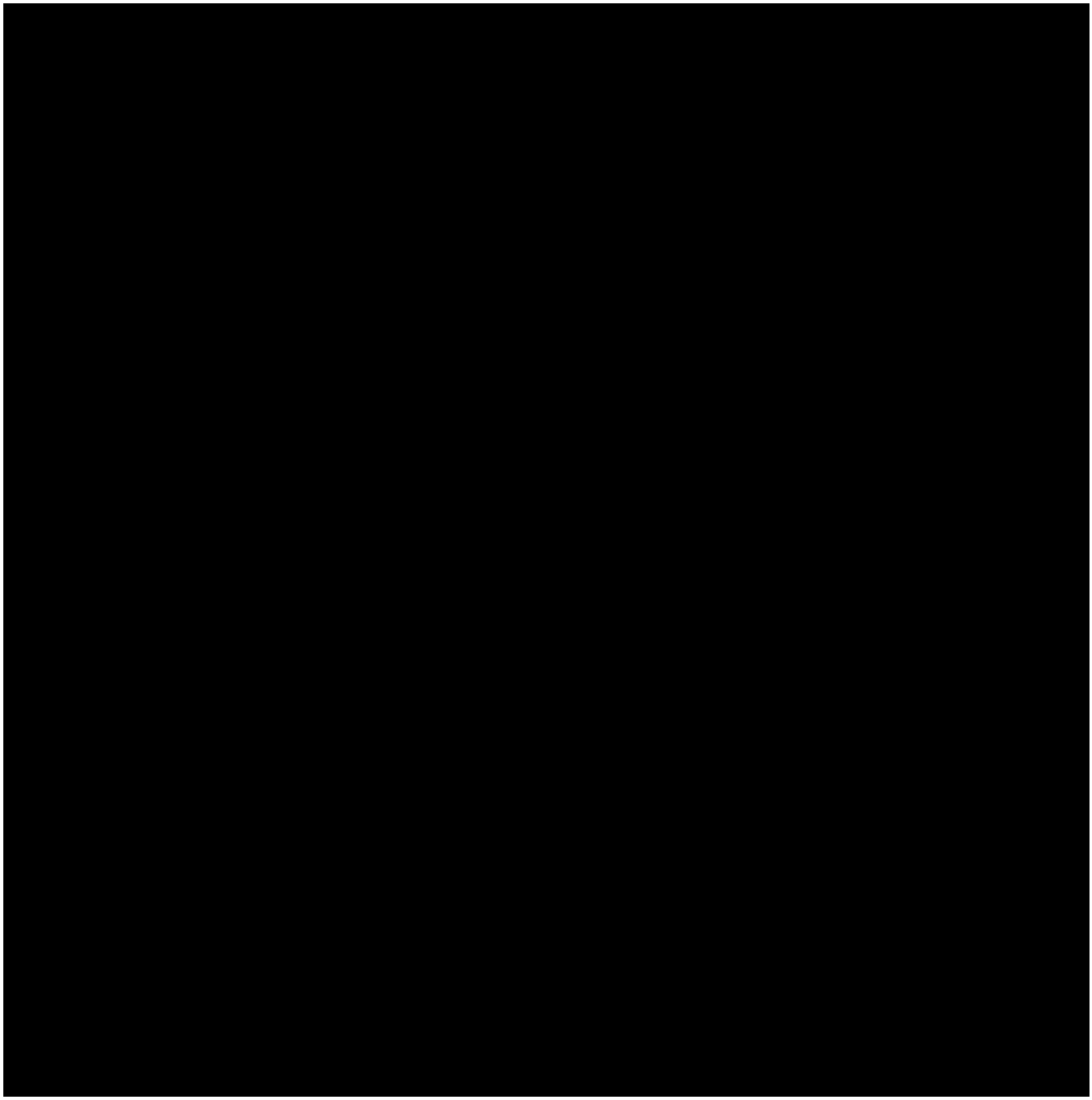
The study analysed 42,493 births to fathers with autoimmune conditions of which 14.3% of fathers were exposed to immunosuppressants or biologics during the preconception period. IPTW logistic regression analysis showed medicine-specific risks for preterm birth, birth defects, or very small for gestational age (VSGA).

Among fathers in the exposed group, 59.11% were diagnosed with rheumatoid arthritis or juvenile idiopathic arthritis (RA/JIA), and 59.32% were diagnosed with ankylosing spondylitis (AS). In contrast, only 27.05% and 23.13% of the non-exposed group were diagnosed with RA/JIA or AS, respectively. Among fathers in the exposed group, sulfasalazine (61.9%) was the most widely used medicine followed by hydroxychloroquine (18.71%) and methotrexate (17.15%).

Overall, babies born to fathers in the exposed group were significantly more likely to have a shorter gestational age, lower birth weight, and a higher likelihood of preterm birth (<37 weeks) compared to those in the unexposed group. However, no significant differences were observed in the sex ratio, rates of SGA or VSGA, APGAR scores, or rates of birth defects between the exposed and unexposed groups.

Results are summarised in Table 20. Methotrexate showed no adverse effect on birth outcomes (birth defects, VSGA, preterm birth). However, certain medicines such as ciclosporin was associated with an increased risk of VSGA and preterm birth by 45% (95% CI 1.19-1.76) and 51% (95% CI 1.35-1.70), respectively.

Table 20: Risk of birth defects, VSGA, and preterm birth with paternal exposure to DMARDs during preconception



Source: Table 3 of Shao et al 2025 [45]

The authors conclude while paternal use of methotrexate was not associated with adverse birth outcomes, exposure to other immunosuppressants or biologics may be linked to possible adverse birth outcomes despite small event numbers.

4.2.9 Summary of findings

A summary of findings from cohort/registry studies described within section 4.2 is presented in Table 21.

Table 21: Summary of findings from cohort/registry studies

Study (country)	Therapeutic area	Population size	Exposure period	Findings
Wallenius 2015 (Norway)	Inflammatory joint disease	1796 men with inflammatory joint disease (2777 births): 110 births exposed to DMARDs (49 MTX) 230 births never exposed to DMARDs	DMARDs within 12 weeks of conception	Serious malformations vs. reference subjects: DMARD-exposed births RR 1.22 (95% CI 0.45, 3.31) Never DMARD-exposed births RR 0.70 (95% CI 0.26, 1.86)
Eck 2017 (Denmark)		849,676 live births: 127 MTX fathers	90 days before pregnancy	Major congenital malformation MTX exposed vs. unexposed aOR 1.01 (95% CI 0.37-2.74)
Winter 2017 (Denmark)	Rheumatologic disease 63.7% Dermatologic conditions 32.6% Unknown reason 17.1% IBD 7.3%	193 MTX exposed 1,013,801 unexposed	3 months before conception	Congenital anomalies MTX exposed vs. unexposed aOR 1.10 (95% CI 0.57-2.13)
Friedman 2017 (Denmark)	For MTX: Rheumatologic disease 60.3% Psoriasis 34.9% IBD 8.6% Connective tissue disease 5.3%	209 MTX exposed 635 AZA/6-MP exposed 1,056,524 unexposed to AZA/6-MP or MTX	3 months before conception	For ADHD: 3 (1.4%) in MTX exposed 3 (0.41%) in AZA/6-MP exposed 2799 (0.26%) in unexposed
Egeberg 2017 (Denmark)		417,634 children: 2123 exposed to immunosuppressants (864 MTX)	3 months before conception	Congenital abnormalities in MTX exposed vs. unexposed aOR 1.12 (95% CI 0.87-1.43)
Zarén 2023 (Sweden)		223 MTX exposed 356 previous MTX exposure (≥2 years before conception) 809,706 no MTX exposure (controls)	0-3 months before conception	Major congenital anomalies in MTX exposed vs. controls OR 1.1 (95% CI 0.4-2.4)
Meserve 2021 (United States)	Immune-mediated inflammatory diseases	171 MTX exposed 5607 unexposed	38-60 weeks prior to delivery	Major congenital malformations in MTX exposed vs. unexposed RR 0.67 (95% CI 0.21-1.55)
Shao 2025 (Taiwan)	Autoimmune rheumatic diseases	42,493 births: 14.3% exposed to immunosuppressants or biologics (17.15% MTX)	38-60 weeks prior to delivery	Birth defects in MTX exposed vs. unexposed OR 0.88 (95% CI 0.78-0.99)

MTX = methotrexate; DMARDs = disease-modifying antirheumatic drugs; ADHD = attention deficit hyperactivity disorder; AZA/6-MP = azathioprine/mercaptopurine; IBD = inflammatory bowel disease

4.3 Teratology information service studies

4.3.1 Beghin et al 2011 – French teratology information service study [37]

Title: Paternal exposure to methotrexate and pregnancy outcomes

Using prospective data from the authors' teratology information service based in Paris, France, outcomes of paternal methotrexate exposure at the time of conception or up to 3 months before conception were analysed.

From 1997 to 2009, there were 42 pregnancy outcomes involving 40 men treated with methotrexate at the time of conception (Table 22). Of these, 23 men were treated for an inflammatory disease (54.8%), 9 for psoriasis (21.4%) and 8 for a malignant disease (19%). Weekly doses were available for 34 cases and varied between 7.5 mg and 30 mg (median 15 mg/week, 2 pregnancies at a dose of 30 mg/week). Doses were generally ≤15 mg/week and higher doses were not restricted to malignant diseases.

The pregnancies resulted in 36 live births, 3 spontaneous abortions, and 3 voluntary abortions. No congenital malformations were observed.

Table 22: Outcomes of pregnancies in which fathers were treated with methotrexate

Source: Table 1 of Beghin et al [37]

The authors conclude based on their results and case reports in the literature, paternal methotrexate exposure at the time of conception does not seem to raise any major concern for offspring.

4.3.2 Weber-Schoendorfer et al 2014 – German teratology information service study [13]

Title: No evidence for an increased risk of adverse pregnancy outcome after paternal low-dose methotrexate: an observational cohort study

The authors performed a prospective observational cohort study. Pregnancies were identified through the authors' teratology information service in Berlin, Germany. The study group consisted of pregnant women whose partners had been treated with low-dose methotrexate (≤30 mg/week) for rheumatic or inflammatory diseases at conception (week 2 + 0 after last menstrual period (LMP)) or within 3 months prior to conception. The comparison group consisted of pregnancies not exposed to methotrexate nor other teratogens. Outcomes evaluated were major birth defects, spontaneous abortion, elective termination of pregnancy, gestational age at delivery, and birth weight.

Follow-up of pregnancy outcome after paternal low-dose methotrexate exposure was initiated in 147 cases and completed in 134 (91%). After exclusions based on the study protocol, a total of 113 pregnancies with paternal low-dose methotrexate treatment were compared with 412 non-exposed pregnancies. Of the 113

exposed pregnancies, 19 had paternal methotrexate exposure during the pre-conception window only, and 94 pregnancies had treatment up until conception or longer.

The most frequent indication for paternal methotrexate was rheumatoid arthritis in 50% (57/113), followed by psoriasis or psoriatic arthritis (33/113). The median methotrexate dose was 15 mg/week (IQR 10-20, range 0.6-30) for all fathers. The median duration of methotrexate administration after LMP in the post-conception exposed cases was 10 weeks (IQR 6-37.7, range 2-41). In the cases with the last dose before conception, 50% of the fathers stopped methotrexate by 2 weeks prior to LMP (IQR -7.5 to 0, range -10 to 1.4). Concomitant medicines included glucocorticoids (n=20), biologics (n=15), NSAIDs/COX-2 inhibitors (n=12), leflunomide (n=11) and miscellaneous (each maximum n=2).

A summary of pregnancy outcomes in the exposed and non-exposed pregnancies are shown in Table 23. The cumulative incidence of spontaneous abortion in the exposed cohort (21.4%) did not differ significantly from the comparison cohort (22.4%) yielding an HR of 1.19 (95% CI 0.65, 2.17). The cumulative incidence of elective termination was 13.4% in the exposed and 8.5% in the unexposed, but the difference was not significant (HR 1.69, 95% CI 0.81, 3.51). Gestational age at delivery and birth weights did not differ significantly between groups.

Table 23: Pregnancy outcome by cohort[a]

Source: Table 2 of Weber-Schoendorfer et al 2013 [13]

Rates of birth defects are shown in Table 24. The rate did not differ significantly between groups for all birth defects (OR 0.97, 95% CI 0.40, 2.4), for major birth defects (OR 1.02, 95% CI 0.16, 6.57) and for de novo chromosomal aberrations (OR 2.06, 95% CI 0.27, 15.8). The observed birth defects were not at all indicative of methotrexate embryopathy.

Table 24: Rates of birth defects

Source: Table 4 of Weber-Schoendorfer et al 2013 [13]

The authors conclude these findings do not support the need for a 3-month methotrexate-free interval until conception. In the case of unavoidable paternal methotrexate treatment, it seems reasonable not to postpone family planning.

Comments:
The sample size in this study was only able to detect a ≥3-fold increase in the risk of major birth defects given a baseline risk of 3% and power of ~80%. Therefore, any finding less than a 3-fold risk could be due to chance.

4.3.3 Summary of findings

A summary of findings from teratology information service studies described within section 4.3 are presented in Table 25.

Table 25: Summary of findings from teratology information service studies

Study (country)	Therapeutic area	Population size (MTX dose)	Exposure period	Findings
Beghin 2011 (France)	23 (54.8%) inflammatory disease 9 (21.4%) psoriasis 8 (19%) malignant disease	42 pregnancy outcomes in 40 MTX exposed men (median dose 15 mg/week, range 7.5 to 30 mg/week)	Up to 3 months before conception	No congenital malformations
Weber-Schoendorfer 2013 (Germany)	Rheumatic or inflammatory diseases: 57 (50%) rheumatoid arthritis 33 psoriasis or psoriatic arthritis	113 pregnancies exposed to MTX (dose ≤30 mg/week) 412 unexposed pregnancies	At conception or within 3 months prior to conception	MTX exposed vs. unexposed: All birth defects OR 1.02 (95% CI 0.4, 2.5) Major birth defects OR 1.02 (95% CI 0.16, 6.57)

MTX = methotrexate

4.4 Effects on sperm/fertility

4.4.1 Zakhem et al 2019 – Dermatologic medicines and effects on fertility [46]

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

The objective was to assess whether systemic dermatologic medicines can cause infertility and teratogenicity when taken by men.

A systematic review of the literature (Pubmed, Embase, Cochrane central register of controlled trials), and reviews of the FDA adverse events reporting system (FAERS) and prescribing information were performed to identify the effects of categories D and X dermatologic medicines on male fertility and teratogenicity.

A total of 13 medicines met inclusion criteria (Table 26). Of 1032 studies identified, 19 were included after a systematic review of the literature. Studies evaluating medicine effects with paternal exposure were identified for 10 of the 13 evaluated medicines. Of the 10 medicines, evidence of a negative effect on male fertility was identified for 6 medicines (colchicine, cyclophosphamide, doxycycline, finasteride, tetracycline, thalidomide) and evidence against negative effects on fertility was identified for the remaining 4 medicines.

For methotrexate (Table 27), there was one study suggesting its antiproliferative effects do not affect spermatogenesis [47]. In this study, semen parameters of 10 men treated with methotrexate for severe psoriasis were compared with those of 10 men using topical steroids. The authors found the methotrexate

group was significantly more likely to have normal parameters. However, interpretation of these results may be complicated by high rates of abnormal semen parameters among the 2 groups.

No studies addressing teratogenicity after paternal exposure to methotrexate were found.

Table 26: FDA pregnancy category D and X medicines meeting inclusion criteria

Source: Table II of Zakhem et al 2019 [46]

Table 27: Summary of methotrexate with evidence against possible teratogenic effects of negative effects on fertility

Source: Portion of Table IV of Zakhem et al 2019 [46]

4.4.2 Jensen et al 2021 – Systematic review of spermatotoxic and genotoxic effects [48]

Title: A systematic overview of the spermatotoxic and genotoxic effects of methotrexate, ganciclovir and mycophenolate mofetil

This overview focuses on the antimetabolites methotrexate and mycophenolate mofetil (MMF), and the acyclic nucleoside ganciclovir (GCV) because of the discrepancy between existing aggregated information and clinical significance.

A systematic literature search of Medline and Embase databases was done using a combination of relevant terms to search for studies on spermatotoxic or genotoxic changes related to treatment with methotrexate, GCV or MMF. The search was restricted to English language, in vivo animal studies (mammalian species) and clinical human studies)

A total of 102 studies were identified (25 human studies, 77 animal studies).

There were five human studies that investigated the spermatotoxic effects of methotrexate. Immunosuppressive doses were administered in four of these studies and showed transient effects on sperm quality parameters which returned to reference values within 3 months.

There were nine human studies that investigated the genotoxic effects of methotrexate, of which eight studies investigated immunosuppressive dose ranges. No studies investigated the sperm DNA damaging effect of

methotrexate, but in other organs the genotoxic effects reported differed with some studies reporting a genotoxic effect and others not.

In animal studies, immunosuppressive and cytotoxic doses of methotrexate adversely affect sperm quality parameters and show widespread genotoxic damages in various organs. Cytotoxic doses transiently change the DNA material in all cell stages of spermatogenesis in rodents.

The authors conclude data from human and animal studies indicate transient spermatotoxic and genotoxic potentials of immunosuppressive and cytotoxic doses of methotrexate.

4.4.3 Grosen et al 2022 – US semen study [23]

Title: Low-dose methotrexate therapy does not affect semen parameters and sperm DNA

The authors evaluated sperm DNA integrity and basic semen parameters according to the WHO recommendations for evaluation in male patients with inflammatory diseases treated with methotrexate.

Adult male patients between the ages of 18 and 45 years diagnosed with either Crohn's disease, ulcerative colitis, rheumatoid arthritis, or psoriatic arthritis were recruited from outpatient clinics between May 2016 and June 2017. In a cross-sectional design, semen parameters from patients on methotrexate maintenance therapy were compared with those from a group of healthy volunteers. In a paired design, semen samples from patients both on and off methotrexate treatment were evaluated. Patients were on maintenance methotrexate therapy for a minimum of 4 months.

Patients who initiated methotrexate therapy delivered a sample before initiation and a follow-up sample after at least 4 months of clinical remission and maintenance therapy to ensure drug exposure during 1 spermatogenic cycle. For those who stopped methotrexate, samples on and off treatment were collected while the patients were in clinical remission during at least 4 months. Further, therapy duration was at least 4 months before sampling, and patients were off methotrexate for at least 4 months before follow-up sampling. Concomitant treatment with non-phthalate-containing 5-aminosalicylic acids and steroids was permitted. Anti-TNF alpha inhibitors (infliximab, adalimumab) and anti-integrins (vedolizumab) do not have a negative influence on semen parameters so concomitant treatment with these medicines was also allowed.

Sperm DNA fragmentation index (DFI), concentration, motility, and morphology were evaluated. Blood sex hormones and methotrexate levels were measured in blood and semen. To detect a 9% difference in DFI with a power of 80% and a significance level of 5% in an unpaired design, a total sample size of 10 patients with IBD on methotrexate and 40 controls was calculated to be sufficient.

The final cohort consisted of 14 patients, of whom 12 had inflammatory bowel disease, and 2 had inflammatory joint disease. The control group consisted of 40 healthy volunteers. Median oral methotrexate dose was 12.5 mg/week (range 7.5-25 mg). The 14 patients had been treated for a median of 13 months (range 5-77 months) before providing a sample on therapy.

DFI in methotrexate-treated patients was comparable with that in healthy volunteers (11.5 vs. 15) and DFI did not change significantly on and off methotrexate in the paired samples (12 vs. 14) (Table 28). Sperm concentration, motility and morphology did not differ between men treated with methotrexate and healthy volunteers. Sperm progressive motility increased off therapy compared with on therapy (65% vs 45%) but all fluctuations in progressive motility were within the WHO reference interval. All methotrexate polyglutamates1-5 were detected in blood, but only methotrexate polyglutamate1 in semen. Serum testosterone was unaffected by methotrexate.

The authors conclude patients treated with low-dose methotrexate have sperm quality comparable with that of healthy volunteers, and methotrexate treatment does not increase sperm DNA fragmentation. This study does not support cryopreservation of semen before treatment initiation nor at the 3-month methotrexate-free interval prior to conception.

Table 28: Differences in semen parameters between patients receiving maintenance methotrexate treatment and healthy volunteers, and a subgroup of patients on and off methotrexate maintenance treatment

Source: Portions of table 1 of Grosen et al 2022 [23]

4.4.4 Perez-Garcia et al 2023 – Dutch cohort study on testicular toxicity [24]

Title: Is methotrexate safe for men with an immune-mediated inflammatory disease and an active desire to become a father? Results of a prospective cohort study (iFAME-MTX)

The authors prospectively evaluated the testicular toxicity profile of methotrexate focusing on several markers of male fertility, including semen parameters and sperm DNA fragmentation index (sDFI). As a secondary outcome, whether MTX-polyglutamates can be detected in spermatozoa and seminal plasma and the enzymatic activity in spermatozoa of folypolyglutamate synthetase (FPGS) were evaluated.

This was a prospective cohort study conducted in Rotterdam, The Netherlands. Participants were aged 18-55 years and were proven fertile (history of a partner's positive pregnancy test). Three groups of men were included in the study. First, men diagnosed with an immune-mediated inflammatory disease based on the expert opinion of their rheumatologist or dermatologist who were not exposed to methotrexate in the last year and were going to start methotrexate were included in the MTX-starters group. Second, to evaluate the effect of chronic methotrexate exposure, men who were exposed to methotrexate (≥15 mg/week for ≥1 year) were included in the MTX-chronic group (descriptive purposes only). Third, healthy men were included as healthy controls. Participants in the first group were instructed to produce 2 semen samples (a pre-exposure and a post-exposure sample after 13 weeks) and participants in the second and third group to produce 1 sample.

A total of 20 MTX-starters and 25 controls were included. The pre-exposure and post-exposure semen parameters of MTX-starters were not statistically significantly different (Table 29). Compared with healthy controls, the conventional semen parameters and the sDFI of MTX-starters were not statistically significantly different. These data were corroborated by the marginal accumulation of MTX-PGs in spermatozoa, consistent with the very low FPGS enzymatic activity associated with the expression of an alternative FPGS splice-variant.

The authors conclude treatment with methotrexate is not associated with testicular toxicity, consistent with the very low concentration of intracellular MTX-PG. Therefore, treatment with methotrexate can be safely started or continued in men who wish to become a father.

Table 29: Conventional semen parameters and sperm morphology

Source: Table 2 of Perez-Garcia et al 2023 [24]

4.4.5 Summary of findings

A summary of findings from studies on methotrexate's effects on sperm/fertility described within section 4.4 is presented in Table 30.

Table 30: Summary of findings from studies on methotrexate's effects on sperm/fertility

Study	Number of studies	Population size	Findings
Zakhem 2019	Total 19 studies: 1 MTX	Severe psoriasis: 10 MTX-exposed men 10 topical steroid-exposed men	Antiproliferative effects do not affect spermatogenesis. Avoid pregnancy for minimum of 3 months after therapy.
Jensen 2021	Total 102 studies: 5 human studies on MTX spermatotoxic effects 9 human studies on MTX genotoxic effects		Transient spermatotoxic and genotoxic potential with immunosuppressive and cytotoxic MTX doses
Grosen 2022	n/a	14 MTX patients (median oral dose 12.5 mg/week, range 7.5-25 mg/week): 12 IBD 2 inflammatory joint disease. 40 healthy volunteers	DNA fragmentation index in MTX-treated patients comparable with healthy volunteers (11.5 vs. 15)
Perez-Garcia 2023	n/a	MTX starters: 20 Controls: 25	DNA fragmentation index in MTX starters not statistically significantly different compared to controls

5 DISCUSSION AND CONCLUSIONS

Low-dose methotrexate has a clear place in the management of severe autoimmune conditions such as psoriasis and rheumatoid arthritis. Manufacturers currently recommend that males should use effective contraception or avoid conception during treatment with methotrexate and for at least 3 months after stopping treatment.

The recommended contraception duration of 3 months (or 90 days) is due to the 60-75 days for sperm production plus another 10-14 days for transport of sperm to the testicles. Regulatory guidelines for genotoxic medicines from the EMA and US FDA also include an additional five half-lives after the last dose to account for potential genotoxic metabolites.

Data from observational studies, including those conducted using Scandinavian registries and datasets, indicate there is no statistically significant difference in the rate of major congenital anomalies reported in babies with paternal low-dose methotrexate exposure within 3 months of conception compared to babies with no paternal methotrexate exposure. This is largely confirmed in systematic reviews and meta-analyses, with some recommending that the contraception/conception advice should be based on a discussion between prescribers and patients. The patient's disease state and other treatment options should also be considered.

However, the numbers of patients included in these studies are low and only large increases in risk, for example a three-fold increase could be reliably detected.

6 ADVICE SOUGHT

The Committee is asked to advise:

- If the current advice in the methotrexate data sheets for male patients to use effective contraception during treatment and for a minimum of three months after stopping treatment is sufficient. The Committee may wish to consider whether there are differences in the risk of paternal exposure for low-dose vs. high-dose methotrexate, and whether additional context for advice in the data sheets is needed (eg, data from observational studies).

7 ANNEXES

1. Specialist correspondence

8 REFERENCES

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