

MOTHERISK UPDATE

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Effect of methotrexate on male fertility

ABSTRACT

QUESTION Several men with psoriatic arthritis have asked whether the methotrexate they take for rheumatoid arthritis will affect their fertility or the outcome of any of their partners' future pregnancies. What is known regarding risks to fertility and to fetuses?

ANSWER To date, there are no reports of adverse pregnancy outcomes among men exposed to methotrexate before conception. Opinions in the literature differ on the effects of methotrexate on male fertility. Several case reports and studies report no effect; others report reversible sterility. One limitation to several of these studies is the concurrent administration of other chemotherapeutic agents. Small studies reporting on methotrexate use with no other agents suggest no increased infertility. Motherisk is currently following men who are taking methotrexate alone for psoriatic arthritis to see whether it affects fertility.

RÉSUMÉ

QUESTION Plusieurs hommes souffrant de polyarthrite psoriasique ont demandé si le méthotrexate qu'ils prennent pour leur arthrite rhumatoïde affectera leur fertilité ou les issues des grossesses futures de leurs partenaires? Que sait-on des risques de cet agent sur la fertilité et les fœtus?

RÉPONSE Jusqu'à présent, il n'existe aucun rapport signalant des issues indésirables dans la grossesse des partenaires d'hommes exposés au méthotrexate avant la conception. Les avis dans les ouvrages scientifiques concernant les effets du méthotrexate sur la fertilité masculine divergent cependant. Plusieurs rapports de cas et rapports d'études ne rapportent aucun effet tandis que d'autres signalent une stérilité réversible. Une limitation dans plusieurs de ces études se situe dans l'administration concomitante d'autres agents chimiothérapeutiques. Des études de petite envergure dans lesquelles le méthotrexate était utilisé sans autre agent ne faisaient valoir aucune hausse de l'infertilité. Motherisk exerce présentement le suivi d'hommes qui prennent seulement du méthotrexate pour l'arthrite psoriasique afin de déterminer s'il affecte la fertilité.

Methotrexate, an immunosuppressive drug used to treat cancer, psoriasis, and rheumatic diseases, is a folic acid antagonist that binds to the enzyme dihydrofolate reductase. This inhibits synthesis of thymidylate, serine, and methionine, which disrupts synthesis of DNA, RNA, and protein and leads to cell death.

Concerns about methotrexate's effect on men's fertility and their partners' pregnancy outcomes arise from the mechanism of action of the drug itself. Methotrexate damages or

kills cells undergoing division, a process continually occurring during production of spermatozoa. To date, there have been no published reports of adverse pregnancy outcomes among the partners of men exposed to methotrexate before

conception. Opinions in the literature differ on the effects of methotrexate on male fertility.

A case series published in 1970¹ reported no change in sperm concentration, motility, or morphology in 11 men treated with methotrexate. Semen was analyzed both before and during long-term treatment with the medication. Grunnet et al² compared the ejaculates of 10 men using topical corticosteroids for severe psoriasis with 10 men using methotrexate therapy for the same indication. They found no adverse effects of

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methotrexate on semen quality. In fact, men treated with methotrexate were more likely than men treated with corticosteroids to have normal semen. De Luca et al³ also reported minimal to no suppression of spermatogenesis with methotrexate therapy.

Several case reports and series have documented reversible sterility in men using methotrexate.^{4,8} They reported a decrease in sperm count or quality with use of the agent. When the medication was discontinued, the sperm returned to normal levels and quality. Van Scott and Reinertson⁹ reported a decrease in sperm count 12 to 14 days after a single intravenous injection of methotrexate, but patients were not followed up to determine whether this was temporary. Shamberger et al⁸ also observed an age-dependent effect in terms of reversibility of the altered spermatozoa; men younger than 40 were more likely to experience recovery.

A study by Bacci et al¹⁰ investigated the long-term effects of combination chemotherapy for osteosarcoma. All the chemotherapy regimens contained methotrexate and other chemotherapeutic agents. Azoospermia was confirmed in 10 of the 12 men who underwent spermatography. Nine of these men, however, were administered ifosfamide and etoposide as part of their chemotherapeutic regimens. Ifosfamide

is an alkylating agent; it has been suggested that even a few doses of an alkylating agent can result in permanent azoospermia.

Siimes et al¹¹ published a case series in which 18 men received high-dose methotrexate as part of a chemotherapeutic regimen to treat osteosarcoma. Seven of the men received a regimen that contained cisplatin, and 11 one that did not contain cisplatin. The mechanism of action of cisplatin is believed also to be alkylation of DNA. The authors reported lower sperm count and testicular volume in the group who had received cisplatin compared with the group who did not. Of the 11 men not receiving cisplatin following treatment with chemotherapy for osteosarcoma, five had sperm counts in the normal range. The remainder were oligospermic, defined as sperm count lower than 20 million spermatozoa per millilitre (sp/mL).

Another study investigating the effect on the gonads of chemotherapy for childhood lymphoma¹² found that, of eight children who received methotrexate in combination with other chemotherapeutic agents, three were normospermic, two were oligospermic (100 000 to 20 million sp/mL), two had severe oligospermia (1 to 100 000 sp/mL), and one was azoospermic. One patient with severe oligospermia had received 1550 cGy of inverted-Y

radiotherapy with lead shielding his testes. Only two patients were older than 10 years.

Given the limited amount of data on use of methotrexate without concurrent medications, more studies are needed to conclusively determine what effect, if any, methotrexate has on male fertility and fetuses. ❖

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