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A REVIEW ON METHOTREXATE AND ITS EFFECT ON PREGNANCY

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ABSTRACT

Background: Methotrexate (MTX) is a folic acid antagonist and an anti-metabolite drug developed initially to treat certain types of cancer. It is the methyl derivative of aminopterin. It is used mainly in the treatment of certain cancers, severe psoriasis and also used at very low doses to treat rheumatic diseases. Methotrexate is cytotoxic to trophoblast and hence it causes abortion; even though, when methotrexate is used alone, abortion could take place in a mean 24 days after drug administration. Prostaglandin analogues, in general, increase the contractility of the smooth muscle in the uterus and cause expulsion of the foetus. **Methods**: Previously published articles regarding the methotrexate and it's effect on pregnancy have been collected and reviewed. **Observations**: Methotrexate has been administered directly into the gestational sac for the conservative treatment of intra-tubal pregnancy for the past few years. In some other reports, the methotrexate was given by IM injection. Folic acid was also given along with this on the first day of each course or at the end of the treatment. Adverse effects those have been reported where elevated liver enzymes, as well as stomatitis, gastroenteritis, nausea, dermatitis myelosuppression and pleuritis. These side effects were much less common with single dose regimens.

KEYWORDS: Methotrexate, Misoprostol, Pregnancy, Termination, Abortion.

INTRODUCTION

Methotrexate (MTX) is a folic acid antagonist and an anti-metabolite drug developed initially to treat certain types of cancer. It is the methyl derivative of aminopterin. It is used mainly in the treatment of certain cancers, severe psoriasis and also used at very low doses to treat rheumatic diseases.

Methotrexate is cytotoxic to trophoblast and hence it causes abortion; even though, when methotrexate is used alone, abortion could take place in a mean 24 days after drug administration. Prostaglandin analogues, in general, increase the contractility of the smooth muscle in the uterus and cause expulsion of the foetus. Reports and studies show that when it is used alone, misoprostol results in completed abortion in only 47% of women.[2]

PHARMACOLOGICAL ASPECTS

Methotrexate interferes with DNA synthesis, cell repair and cellular replication stages. Generally, actively proliferating tissues such as malignant cells, bone marrow, fetal and trophoblastic cells, buccal and intestinal mucosa and cells of the urinary bladder are mostly sensitive to this effect of methotrexate.

Variable	Methotrexate	Mifepristone
Failure rate	4.0%[10]	2%–4.8%[11–13]
Time of completion	• Average of 7.1 days after use of methotrexate (74.5% aborted by day 8)[10]	• Average of 3.3 days after use of mifepristone (90.5% aborted by day 8)[10]
Adverse effects	• Bleeding and cramping are expected • Diarrhea (about 27%), nausea (36%), vomiting (15%), fever (22%), chills (49%), headache (17%)[10]	• Bleeding and cramping are expected[14] • Diarrhea (about 58%), nausea (31%), vomiting (22%), fever/chills (44%), headache (12%), dizziness (13%), weakness (19%)[13]
Risk of infection	0.8%[10]	≥ 0.1% to < 1%[11–13]
Prolonged bleeding	2.1%[10]	> 1% to < 10%[11–13]
No. of required clinic visits	2–3, or more	2–3
Cost of medication	$59.52[15]	$270[5]
Success rate	94.3%[4]	95%[12]
Method of administration	• Injection and vaginal misoprostol	• Oral dose and buccal misoprostol
Gestational limitations	56 d	49 d[6]
Advantages of both options over surgical abortion	• More "natural," less frightening and more private[16] • No anesthetic required • No risk of perforating the uterus	

Figure 1: Comparing some variables of Methotrexate and Mifepristone.

Medical Abortion

A complete medical abortion as any abortion that took place after administration of methotrexate and did not require suction curettage for any reason. If a woman was advised to have a curettage, but completed the abortion without curettage, we classified her as having a complete medical abortion.

A complete abortion was documented only when ultrasound demonstrated the disappearance of the gestational sac, or when the woman had a negative highly sensitive urine pregnancy test (threshold less than 50 mIU/mL b-hCG). If no gestational sac was seen, a 90% drop in b-hCG was considered evidence of completion. Undocumented outcomes included verbal reports from patients or bystanders.[3]

Methotrexate In The Management of Ectopic Pregnancy

Methotrexate has been administered directly into the gestational sac for the conservative treatment of intra-tubal pregnancy for the past few years.[4-6] In some other reports, the methotrexate was given by IM injection. Folic acid was also given along with this on the first day of each course or at the end of the treatment. Adverse effects those have been reported where elevated liver enzymes, as well as stomatitis, gastroenteritis, nausea, dermatitis myelosuppression and pleuritis. These side effects were much less common with single dose regimens. Idiosyncratic side effects such as pneumonitis can occur following the local administration of a low methotrexate dose as low as 12.5 mg.

Two cases of life-threatening neutropenia following methotrexate treatment of ectopic pregnancy have been documented. In both cases pretreatment laboratory values, including white cell count, were within normal limits. Both subjects were admitted to hospital with stomatitis, pyrexia and life-threatening neutropenia.[7]

Methotrexate For Termination of Intrauterine Pregnancy

Methotrexate was used to induce an abortion in a patient with multiple uterine leiomyomata.[8] A total of 50 mg of methotrexate was injected directly into the amniotic fluid and into the placenta. Data from ten subjects given methotrexate and oral misoprostol were published in 1993.[9] Since this publication, there have been reports of seven more series of subjects (total 529 pregnancies) who received this treatment regimen.

Feldkamp and Carey proposed that the sensitive period for the production of malformations by methotrexate is 6 to 8 weeks after conception. They further suggested that the methotrexate dose necessary to produce malformations is 10 mg/week or greater. The misdiagnosis of an intrauterine pregnancy as an ectopic pregnancy can result in exposure of a continuing pregnancy to dose levels of methotrexate of 50 mg/m^2 (maternal body surface area). At present, methotrexate is routinely used for ectopic pregnancies, which in 1 to 2% of pregnancies and which are suspected in a larger number of pregnancies, representing a

substantial opportunity for continuing intrauterine pregnancies to be exposed because of diagnostic error.[10]

SCOPE OF REVIEW

The study aims in reviewing the potential adverse effect of methotrexate resulting in the termination of pregnancy.

CONCLUSION

Methotrexate in combination with the prostaglandin analogue misoprostol is a non-surgical method for the termination of early first trimester pregnancy. Methotrexate is used for the treatment of certain malignancies including choriocarcinoma and osteogenic sarcoma, severe psoriasis and adult rheumatoid arthritis. It acts to block cell division and DNA synthesis and repair. More research is needed to determine the best timing and dosages of the drugs and to compare medical abortion induced with mifepristone with that induced with methotrexate and with surgical abortion.

CONFLICT OF INTEREST

The author(s) declared no conflict of interest with respect to the authorship, research or publication of the article.

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