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Review

Overview and guidelines of off-label use of methotrexate in ectopic pregnancy: report by CNGOF

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ABSTRACT

Our objective is to describe off-label use of methotrexate in ectopic pregnancy treatment using evidence based medicine. The patient group includes all women with a pregnancy outside the usual endometrium, or of unknown location.

Method used was a Medline search on ectopic pregnancy managed using methotrexate treatment; evidence synthesis was done based on this current literature analysis.

Level of evidence (LE) were given according to the centre for evidence base medicine rules. Grade was proposed for guidelines but no recommendation was possible as misoprostol is off label use for all the indications studied.

In the absence of any contraindication, the protocol recommended for medical treatment of ectopic pregnancy is a single intramuscular injection of methotrexate (MTX) at a dosage of 1 mg/kg or 50 mg/m^2 (Grade A). It can be repeated once at the same dose should the hCG concentration not fall sufficiently. Pretreatment laboratory results must include a complete blood count and kidney and liver function tests (in accordance with its marketing authorization).

MTX is an alternative to conservative treatment such as laparoscopic salpingotomy for uncomplicated tubal pregnancy (Grade A) with pretreatment hCG levels $\leq$ 5000 IU/l (Grade B). Expectant management is preferred for hCG levels $<$ 1000 IU/l or in the process of spontaneous decreasing (Grade B).

Intramuscular MTX is also recommended after the failure of surgical salpingotomy (Grade C) or immediately after surgery, if monitoring is not possible. Except in special circumstances, a local insitu ultrasound-guided MTX injection is not recommended for unruptured tubal pregnancies (Grade B).

In situ MTX is an option for treating cervical, interstitial, or cesarean-scar pregnancies (Grade C).

In pregnancies of unknown location persisting more than 10 days in an asymptomatic woman who has an hCG level > 2000 IU/l, routine MTX treatment is an option.

MTX is not indicated for combination with treatments such as mifepristone or potassium.

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Contents

Introduction

In the context of vigilance increased towards the off label prescription, it was useful and urgent that the CNGOF (French college of gynaecology and obstetrics) produces a synthesis of the scientific data on methotrexate (MTX) use in ectopic pregnancy treatment. This text is the summary of large reviews on each subject published in the French journal of gynaecology and obstetrics [1]; full references could be found in the original texts, only a main selection was presented in this paper. Level of evidence (LE) were given according to the centre for evidence base medicine rules [2]. No recommendation was possible as MTX is off label use for all the indications studied. In red are proposed the CNGOF conclusions.

Before any recommendations about the prescription of MTX for the medical treatment of ectopic pregnancy, we note three essential rules that must be complied with before any treatment:

- The diagnosis of ectopic pregnancy must be confirmed by specific algorithms that are not considered in these guidelines. The use of selection criteria is recommended (Grade B) [3].
- Gynecological contraindications must be ascertained by the application of clinical and ultrasound criteria to eliminate/minimize complications.
- The doctor must inform the woman of the diagnosis, its potential consequences and the different treatments available. To the extent possible, the treatment should be chosen in a shared decision-making process.

Dosage for off-label use in ectopic pregnancies [4–9]

The multidose protocol currently used, especially in the United States, involves 4 doses of MTX (1 mg/kg, IM) on D1, D3, D5 and D7, with 0.1 mg/kg of folinic acid IM on D2, D4, D6 and D8. The single-dose protocol is used more often in France, but no validated pharmacological data currently justify a conclusion about the dosage (1 mg/kg or 50 mg/m^2) to be preferred for treatment of ectopic pregnancy. The dosage of 1 mg/kg has the advantage of being easier to determine in everyday practice. The meta-analysis by Barnhart et al. compared single- and multi-dose protocols: The use of single dose was associated with a significantly greater chance of failed medical management than the use of the multidose in both crude (odds ratio [OR] 1.71; 1.04, 2.82) and adjusted analyses (OR 4.74; 1.77, 12.62) and showed that the single-dose version was associated with fewer adverse effects (LE1, odds ratio 0.44 [0.31–0.63]). In such a single-dose protocol, folic acid supplementation is not currently recommended but it should be envisioned if a second dose turns out to be needed several days later. So there are no validated pharmacological findings that could currently justify a conclusion about the best protocol or whether one or repeated injections should be used in ectopic pregnancy.

MTX is teratogenic and known to carry a risk of fetal malformations. Malformations and miscarriages have been reported after administration of MTX for suspected ectopic pregnancy. A three-month waiting period before conception is advisable after a MTX injection.

At this day, and in the absence of any contraindication, a single IM injection of MTX at a dosage of 1 mg/kg or 50 mg/m^2 is the protocol with the best risk to benefit ratio for the medical treatment of ectopic pregnancy. It can be repeated several days later at the same dose. Pretreatment laboratory results must include a complete blood count and kidney and liver function tests (in accordance with its marketing authorization). This testing must be performed before any MTX injection.

Use of MTX in women with tubal pregnancies

Surgical treatment vs. *MTX [10–14]*

A meta-analysis shows that MTX at a single dose of 1 mg/kg is less effective than laparoscopic salpingotomy in the treatment of ectopic pregnancy to normalize the hCG level: OR = 0.38 [0.20–0.71]. Initial use of a multidose regimen does not change the result (LE1). The interpretation of this result nonetheless must be qualified according to the principal endpoint chosen: failure of a dose, or indication for surgery; that is, the meta-analysis found that only 22.5% of the medical treatments resulted in a normalized HCG level after a single dose, but only 5.8% ultimately required surgery;