Gynécologie Obstétrique & Fertilité 44 (2016) 341–344

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Original article

Methotrexate treatment for ectopic pregnancy after assisted reproductive technology: A case-control study☆

Traitement par méthotrexate des grossesses extra-utérines issues d'une assistance médicale à la procréation◇

A. Ohannessian, P. Crochet, B. Courbiere, A. Gnisci, A. Agostini *

Service de gynécologie-obstétrique, hôpital de La Conception, 147, boulevard Baille, 13005 Marseille, France

ARTICLE INFO

Article history:
Received 17 February 2016
Accepted 11 April 2016
Available online 20 May 2016

Keywords:
Ectopic pregnancy
Methotrexate
Assisted reproductive technology
In vitro fertilization

ABSTRACT

Objectives. – Ectopic pregnancy (EP) occurs in 2% to 5.6% of pregnancies achieved by assisted reproductive technology (ART). EP treatment options include medical treatment by uses of methotrexate (MTX) systemic injection. The objective of this study was to compare MTX treatment effectiveness for EP occurring spontaneously or following ART.
Methods. – A case-control study performed in the department of obstetrics and gynecology at a tertiary health care center in France. Twenty EP achieved by ART (ART group) and 60 spontaneous EP (SEP group) received MTX treatment between January 2002 and May 2012. The main outcome measures were MTX treatment failure rates, number of MTX injections administered and recovery time.
Results. – MTX treatment failure rates observed in ART and SEP groups were similar (3/20 [15%] versus 10/60 [17%]: OR = 0.88 [0.22–3.58]). Mean duration of recovery time in patients with successful MTX treatment did not differ between ART and SEP groups (33 ± 14 days versus 28 ± 13 days, $P = 0.39$). A second MTX injection was required more frequently in ART group than in SEP group (10/20 [50%] versus 10/60 [17%]: OR = 5 [1.65–15.15]).
Conclusions. – It is concluded that MTX treatment is equally effective for spontaneous EP and EP achieved by ART, two injections of MTX being more frequently required in case of ART.

Mots clés :
Grossesse extra-utérine
Methotrexate
Assistance médicale à la procréation
Fécondation in vitro

RÉSUMÉ

Objectif. – Un pourcentage de 1,4 à 1,6 des grossesses survenant à la suite d'une assistance médicale à la procréation (AMP) sont des grossesses extra-utérines (GEU). Une des options thérapeutiques est le traitement médical par injection systémique de méthotrexate (MTX). L'objectif de cette étude était de comparer l'efficacité du traitement par MTX des GEU survenant à la suite d'une AMP aux GEU survenant spontanément.
Méthodes. – Une étude cas-témoins a été réalisée dans le service de gynécologie-obstétrique du CHU La-Conception à Marseille. Vingt GEU survenant à la suite d'une AMP (groupe ART) et 60 GEU spontanées (groupe SEP) ont reçu un traitement par MTX entre janvier 2002 et mai 2012. Les principaux critères de jugement étaient le taux d'échec du traitement, le nombre d'injections de MTX administrées et le nombre de jours avant négativation des hCG.
Résultats. – Les taux d'échec étaient similaires dans le groupe ART et dans le groupe SEP : 3/20 (15 %) versus 10/60 (17 %) (OR = 0,88 [0,22–3,58]). En cas de succès, la durée avant négativation des hCG ne différait pas entre les 2 groupes : 33 ± 14 jours dans le groupe ART versus 28 ± 13 jours dans le groupe SEP

☆ See on the same subject in the same number of *Gynécologie Obstétrique et Fertilité*, the editorial signed by Henri Marret, entitled Methotrexate allowed in ectopic pregnancy, we're almost there! Gynecol Obstet Fertil 2016; 44.
◇ Voir sur le même sujet dans le même numéro de *Gynécologie Obstétrique & Fertilié*, l'éditorial signé de Henri Marret, intitulé : Le méthotrexate autorisé dans la grossesse extra-utérine : on y est presque ! [Methotrexate in ectopic pregnancy is almost allowed!]. Gynecol Obstet Fertil 2016;44. http://dx.doi.org/10.1016/j.gyobfe.2016.04.008.

* Corresponding author.
E-mail address: aubert.agostini@ap-hm.fr (A. Agostini).

http://dx.doi.org/10.1016/j.gyobfe.2016.04.004
1297-9589/

(*p* = 0,39). Le recours à une seconde injection de MTX était plus fréquent dans le groupe ART : 10/20 (50 %) versus 10/60 (17 %) (OR = 5 [1,65–15,15]).

Conclusions. – Le traitement par MTX systémique est aussi efficace pour les GEU spontanées que pour les GEU survenant à la suite d'une AMP. Le recours à deux injections de MTX est plus fréquent en cas d'AMP.

1. Introduction

Ectopic pregnancy (EP) occurs in about 1.4% to 1.6% of pregnancies achieved by assisted reproductive technology (ART) [1,2]. The risk for EP following ART varies according to ART procedure type [2]. It is increased among women with a previous EP history, in case of other tubal factors of infertility, endometriosis, and multiple embryo transfer [1–4]. EP treatment options include medical treatment by uses of methotrexate systemic injection (MTX). The reported success rates of methotrexate therapy range from 63% to 96.7% [5]. This treatment allows to avoid surgery. It is indicated for women presenting a less active EP, with few symptoms and a low hCG level (the cut-off for defining a less active pregnancy varies from 1500 to 5000 IU/L according to the authors) [6–9]. Due to the close follow-up inherent to ART procedures, EP diagnosis can be done at an early stage (using early hCG plasma levels and transvaginal ultrasound) prior to the onset of clinical signs [10]. MTX treatment is a possible option in most of these cases. This treatment that can avoid surgery is of great interest for these patients already highly medicalized. However, there are few publications studying specifically the effectiveness of the MTX treatment in case of EP occurring after ART.

The first aim of this study is to compare MTX treatment effectiveness for ectopic pregnancy occurring spontaneously or following ART. The second aim is to compare the number of MTX injections administrated and the recovery time.

2. Methods

It is a monocentric 1:3 case-control study conducted in the department of obstetrics and gynecology at a tertiary health care center in France. Women included presented with EP. In the first group, EP occurred in women treated for infertility at the hospital's ART center (ART group). These treatments were either intrauterine insemination (IUI) or in vitro fertilization (IVF). The control group was composed of women presenting spontaneous EP (SEP group).

EP diagnosis, MTX treatment and MTX monitoring were performed in the gynecological emergency unit of the department for both SEP and ART groups. The diagnostic criteria of EP and indication of MTX treatment were identical for cases and controls. Each case of the ART group was matched to three control patients based on the same hCG plasma level at day 1 (±10%). These controls were selected from the register of the gynaecological emergency unit that lists in chronological order every EP treated with MTX in the department. We have retained the first three women following the case in chronological order, with the same follow-up protocol after MTX injection [11]. EP was diagnosed in women referred for pelvic pain, vaginal bleeding, or both, who met the following criteria: positive plasma hCG (stable or rising plasma hCG level in separate measurements 48 hours apart) with an empty uterus on sonography and other sonographic signs in favour of EP: an inhomogeneous adnexal mass, an empty gestational sac with a hyperechoic ring, or an extra uterine gestational sac containing a yolk sac or fetal pole with or without cardiac activity [12,13]. The indications for MTX therapy were: absence of embryonic cardiac activity detected by transvaginal ultrasonography, hCG concentration < 5000 IU/L, ectopic pregnancy < 4 cm in size as visualized by transvaginal ultrasonography, and the ability to participate in the follow-up [14].

Contraindications for MTX treatment for EP were hepatic or renal failure, thrombopenia, anemia, or any suspicion of tubal rupture (hemodynamic instability, severe pain, or large hemoperitoneum on sonography).

Women in both groups had the same follow-up protocol after injection of MTX, as described by Stovall et al. [11]. Women received intramuscular MTX at a dose of 50 mg/m^2. The day of injection was considered day one of the protocol (D1). Plasma HCG levels were measured on days four (D4) and seven (D7). If they decreased by 15% between D4 and D7, weekly monitoring continued until they fall below 15 mIU/mL. If they failed to decline by 15% between D4 and D7 or between weekly hCG titers, the MTX injection was repeated. After the second injection, hCG titers were followed with a new day one reading. If they failed to fall appropriately after a total of three injections, treatment was considered to have failed, and surgical therapy was recommended. During this study period, women with suspicion of tubal rupture or refusal of second or third MTX injections were treated surgically.

MTX treatment failure was defined by the need for surgical treatment for suspicion of tubal rupture or the absence of an appropriate hCG decline after three injections or the woman's refusal of a second or third MTX injection. The women's characteristics studied were: age, body mass index, gestity, parity, current smoking, history of previous EP, plasma HCG level at D1. Recovery time was defined by the time until the hCG level drops below 2 IU/L after D1.

Data analysis was carried out with the Statistics Package for Social Sciences (SPSS 17.0). Qualitative data were compared by calculating the odds ratio (OR) with their 95% confidence intervals. Quantitative data were analyzed using paired sample *t*-test or Wilcoxon test, as appropriate. A *P*-value < 0.05 was considered statistically significant.

This study was approved by the Committee of Ethics for Research in Obstetrics and Gynecology (CEROG 2012-GYN-08-02). Informed consent was obtained from all participants.

3. Results

Between January 2002 and May 2012, 35 women were diagnosed with EP following treatment received at the ART center. Fifteen of those women were treated surgically in first intention. Among these 20 EP treated by MTX (57%), 17 occurred after IVF and 3 after IUI. These 20 EP (ART group) were matched to 60 spontaneous EP (group SEP) also treated with MTX in first intention. During the study period, 60% of spontaneous EP were treated with MTX in first intention.

None of the characteristics were significantly different between the two groups (Table 1). There was no difference in the smoking status of women (29% in the ART group versus 49%: OR = 0.41 [0.07–2.29]). Prior history of EP were not statistically more frequent in the ART group compared to the SEP group (6% versus 23%: OR = 0.21 [0.03–1.74]).

The treatment failure rate was not significantly different between the ART group and the SEP group (3/20 [15%] versus