Does methotrexate treatment for ectopic pregnancy influence the patient's performance during a subsequent in vitro fertilization/embryo transfer cycle?

In a study on the influence of methotrexate (MTX) treatment on ovarian stimulation characteristics during the subsequent IVF cycle, 14 patients admitted to our department with the diagnosis of ectopic pregnancy and successfully treated with MTX were evaluated. No differences were observed in ovarian stimulation characteristics between the IVF cycle that had resulted in the ectopic pregnancy and the IVF cycle that followed MTX treatment. Treating ectopic pregnancy with MTX has no influence on patients' performance in the following IVF cycle. (Fertil Steril® 2007;88:1685–6. ©2007 by American Society for Reproductive Medicine.)

The first in vitro fertilization (IVF) pregnancy reported was an ectopic pregnancy (EP) (1). Since then, considerable progress has been made in the diagnosis and management of EP, leading to earlier interventions and conservative treatment that preserves the patient's fertility and reduces morbidity (2, 3). Methotrexate (MTX), the most widely used drug for the medical management of EP, is a chemotherapeutic agent that is considered to be equivalent in efficacy to conservative treatment with laparoscopy (4). Chemotherapy and radiotherapy have deleterious effects on ovarian function and are known to hasten oocyte depletion with truncated fecundity and premature menopause; yet, surprisingly, the reproductive outcome after MTX treatment for EP has been scarcely studied (2, 3, 5). We found no information in the literature regarding the influence of MTX treatment on ovarian stimulation during a subsequent IVF cycle attempt, which could be considered the most reliable sign of a decreased ovarian reserve (6).

In our present study, to aid both fertility specialists and their patients in the decision-making process, we evaluated the influence of MTX treatment on ovarian stimulation characteristics during the subsequent IVF cycle.

The study population consisted of all patients admitted to our department during a 5-year period with the diagnosis of EP who were successfully treated with methotrexate (MTX). Moreover, we included only patients whose EP had resulted from IVF treatment, who then underwent a subsequent IVF cycle following MTX therapy. The ovarian stimulation characteristics, number of oocytes retrieved, and number of embryos transferred were assessed and compared for the patient's IVF cycle with EP versus the subsequent cycle after MTX treatment.

Statistical analysis was performed with paired-Student's *t*-test and chi-square, as appropriate. Results are presented as mean ± standard deviation. $P<.05$ was considered statistically significant.

Fourteen patients with a mean age of 34 ± 5.2 years (range: 26 to 43 years) were evaluated. Only one patient required multiple-dose MTX treatment; all of the others were treated with the single-dose MTX protocol. The mean interval between the IVF cycle resulting in EP and the subsequent IVF cycle after MTX therapy was 5.7 ± 2.3 months (range: 3.5 to 12 months).

The clinical characteristics of their IVF cycles before and after MTX treatment are shown in Table 1. All patients except one underwent the same controlled ovarian hyperstimulation protocol before and after MTX treatment, with an equivalent initial dose of gonadotropin. There were no differences between the cycles in the length of ovarian stimulation, number of gonadotropin ampules used, peak estradiol (E_2) and progesterone levels, number of oocytes retrieved, or fertilization rate (see Table 1). Furthermore, although no difference was observed in the number of embryos transferred, no patient conceived in the IVF cycle that followed MTX treatment.

We observed no influence of MTX treatment on the patients' performance during their immediate subsequent IVF cycle. These results are in agreement with those of Shamberger et al. (7) who demonstrated no deleterious effect of high-dose MTX with and without vincristine on ovarian function in a small group of cancer patients (n = 7), as assessed by levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol and progesterone.

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TABLE 1

Comparison of in vitro fertilization cycles before and after treatment with methotrexate (MTX).

Clinical characteristic	Before MTX treatment	After MTX treatment	*P* value
Day-3 FSH levels (IU/L)	6.7 ± 1.9	6.1 ± 3.1	.48
Length of stimulation (days)	10.0 ± 1.8	10 ± 1.9	1.00
No. of gonadotropin ampules used	44.9 ± 28.7	49.7 ± 25.6	.47
Peak E_2 levels on day of hCG administration (pg/mL)	1850 ± 1084	2027 ± 1108	.56
Progesterone levels on day of hCG administration (ng/mL)	1.4 ± 1.4	0.9 ± 0.6	.41
No. of oocytes retrieved	9.1 ± 4.6	10 ± 5.5	.45
Fertilization rate	72 ± 53	69 ± 56	.97

Orvieto. IVF cycle following MTX therapy. Fertil Steril 2007.

We could not extrapolate from our data or other published data what our patients' performance might be during IVF cycles more remote from the MTX treatment, or what degree ovarian reserve deterioration might have occurred. However, the observed ability of MTX to hasten menopause by 3 years (8) and the observation that none of our patients conceived in the IVF cycle following MTX treatment should alert physicians that postponing IVF treatment for later periods is not advisable.

The main limitation of our study is that the sample size (14 patients) may have been too small statistically. To demonstrate a difference of 30% in the number of oocytes retrieved at a power of 80% and an alpha value of 5% using the uncorrected chi-squared test, 33 study participants would be needed.

We observed no influence of MTX treatment on the patients' performance in their immediate subsequent IVF cycle. Further studies are needed to elucidate the influence of MTX treatment on immediate and late ovarian reserve to aid both fertility specialists in counseling and their patients in this decision-making process.

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