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Title

Methotrexate Treatment of Ectopic Pregnancy Does Not Impact Ovarian Reserve or Clinical Outcome, Regardless of the Duration of Time Since Exposure.

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Objective:
Methotrexate (MTX) is a cost-effective, minimally invasive treatment for ectopic pregnancy. Given its targeted action on rapidly dividing cells, particularly trophoblast cells at the implantation site, there is concern that this anti-metabolite could affect proliferating germinal cells in the ovary, thereby impacting folliculogenesis and ovarian reserve. While the majority of studies show MTX does not impact ovarian reserve, others suggest that its effect might be time-dependent. It is standard to have patients wait three months following MTX exposure to conceive to decrease that possibility of inducing a meiotic error during oogenesis. We sought to investigate the effect of MTX treatment and the interval of time from its administration to subsequent fertility treatment on ovarian reserve and IVF outcome.

Design:
Retrospective cohort and case-control analysis

Materials and Methods:
All patients who received MTX in a prior treatment cycle and underwent subsequent IVF ± ET from 2003 to 2016 were included. The interval of time from MTX administration to the start of their subsequent treatment cycle was calculated. Paired t-test was conducted to compare ovarian reserve markers (day 3 FSH and basal antral follicle count (BAFC)), oocyte yield, fertilization, and blastocyst count in pre- and post-MTX COH cycles. Linear and binary logistic regression were performed to analyze whether COH parameters and the odds of failed implantation and early pregnancy loss were modified by the interval from MTX administration

Results:
A total of 491 patients received MTX for treatment of an ectopic pregnancy (262 fresh IVF, 202 ovulation induction, 25 FET) and underwent subsequent COH (n=339) with fresh ET (n=279) or frozen-thawed ET (n=198). The interval from MTX administration to subsequent cycle start,

cycle characteristics and clinical outcome of COH and ET cycles are shown in Tables 1 and 2, respectively. After controlling for the increase in patient age over time, FSH, BAFC, eggs retrieved and fertilized, days of stimulation and total gonadotropin dose required and blastocyst count were not significantly different between pre- and post-MTX COH cycles. Furthermore, any subtle intercycle changes in these parameters were not correlated with the time interval from MTX treatment. PGS was performed in 51 subsequent COH cycles with a 49.2% overall aneuploidy rate. After controlling for oocyte age and cumulative MTX dose, aneuploidy rate was not correlated with interval of time since MTX. In fresh and frozen ET cycles, the odds of failed implantation (OR 1.0 [95% CI 1.0-1.001], p=0.3) and pregnancy loss (OR 1.0 [95% CI 0.9-1.0], p=0.8) were not influenced by the time interval from MTX administration.

Conclusions:

In agreement with the existing literature, these results suggest that ovarian reserve and IVF cycle outcomes are not compromised by MTX treatment of an ectopic pregnancy. The interval of time from MTX administration did not significantly influence cycle outcome or the incidence of embryonic aneuploidy. To date, this is the only study to assess embryonic aneuploidy following MTX exposure. Though the results are reassuring regarding MTX safety, large-scale, multicenter studies are required to confirm these findings.

Support:

None.

Table 1:

Subsequent ovarian stimulation – Patient Demographics and cycle characteristics.

	Controlled ovarian stimulation (n=339)
Interval since MTX (days)	359.5 +/- 378.4 (range: 64-2251)
Ovarian age	36.9 +/- 4.5
Pre-MTX D3FSH	6.7 +/- 1.2
Post-MTX D3FSH	6.4 +/- 3.9
Pre-MTX BAFC	12.3 +/- 3.5
Post-MTX BAFC	10.0 +/- 6.2
Cumulative MTX dose	108.1 +/- 40.3
Days of controlled ovarian hyperstimulation	8.9 +/- 1.4
Cumulative gonadotropin dose	3808.4 +/- 1448.3
Oocytes retrieved	12.7 +/- 7.5 (n=4292)
Mature oocytes	10.7 +/- 7.0 (n=3638)
Fertilization rate	66.6% (n=2423/3838)
Mean number of blastocysts	2.7 +/- 3.7 (n=927)
Aneuploidy rate	49.2% (n=91/185)

Table 2:
Subsequent embryo transfers – Patient demographics and cycle characteristics.

	Fresh ET (n=279)	**FET (n=152)**
Interval since MTX (days)	341.1 +/- 381.4 (range: 64-2251)	422.4 +/- 483.5 (range: 32-2585)
Patient age	36.7 +/- 4.6	34.4 +/- 4.2
Day 3 FSH	6.4 +/- 4.1	6.9 +/- 3.5
Endometrial thickness at transfer (mm)	9.6 +/- 2.3	9.3 +/- 2.3
Number of blastocysts transferred	1.8 +/- 0.9	1.7 +/- 0.9
Cumulative MTX dose	107.4 +/- 40.3	104.2 +/- 35.4
Implantation rate	45.8% (128/279)	31.7% (184/262)
Early pregnancy loss rate	25.4% (71/279)	18.4% (28/152)