Ovarian reserve and subsequent assisted reproduction outcomes after methotrexate therapy for ectopic pregnancy or pregnancy of unknown location

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Objective: To assess ovarian reserve after methotrexate treatment for ectopic pregnancy or pregnancy of unknown location after assisted reproductive technology (ART).
Design: Retrospective cohort study.
Setting: Large ART practice.
Patient(s): Women receiving methotrexate or surgery after ART.
Intervention(s): None.
Main Outcome Measure(s): Follicle-stimulating hormone (FSH), antral follicle count (AFC), and oocyte yield compared between women treated with methotrexate or surgery, with secondary outcomes of clinical pregnancy and live birth.
Result(s): There were 153 patients in the methotrexate group and 36 patients in the surgery group. Neither group demonstrated differences in ovarian reserve or oocyte yield in a comparison of the before and after treatment values. The change in ovarian reserve and oocyte yield after treatment were similar between the two groups. The number of doses of methotrexate was not correlated with changes in ovarian reserve, indicating no dose-dependent effect. Time between treatment and repeat ART was not correlated with outcomes. Live birth in subsequent cycles was similar in the two groups.
Conclusion(s): Ovarian reserve and subsequent ART cycle outcomes were reassuring after methotrexate or surgical management of ectopic pregnancy. No adverse impact of methotrexate was detected in this large fertility cohort as has been previously described elsewhere. (Fertil Steril® 2014;101:413–9. ©2014 by American Society for Reproductive Medicine.)
Key Words: ART, ectopic, methotrexate, ovarian stimulation, pregnancy of unknown location, salpingectomy

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Methotrexate is a chemotherapeutic agent commonly used in the treatment of ectopic pregnancy and pregnancies of unknown location. Methotrexate acts as a dihydrofolate reductase inhibitor and targets rapidly proliferating cells (1, 2), raising the concern that methotrexate treatment might adversely affect ovarian follicles and result in diminished future fertility (3, 4). Adverse effects on ovarian

follicles and fertility have been clearly demonstrated with other chemotherapeutic agents (5, 6). Despite this potential concern, several studies have shown that methotrexate treatment of naturally occurring ectopic pregnancies does not adversely affect ovarian reserve or future spontaneous fertility (7–9). These reassuring data have come from studies of patients who naturally conceived an ectopic pregnancy, were treated with methotrexate, and had subsequent spontaneous fertility. However, it is biologically plausible that the ovaries of patients undergoing assisted reproductive technology (ART) are at an increased risk of ovarian damage from chemotherapy (10).

Ectopic pregnancy is more common with infertility patients (11) and accounts for 4.9% of maternal deaths in developed countries (12). Ovarian stimulation for ART results in increased size and blood flow to the ovaries (13, 14). Angiogenic factors, such as vascular endothelial growth factor, are highly secreted in the stimulated ovary (15, 16). The altered ovarian physiology from exogenous gonadotropin stimulation could result in increased uptake and exposure to chemotherapeutic agents (10). Additionally, infertile patients are often older and demonstrate lower ovarian reserve than spontaneously fertile patients (17). It is biologically plausible the patients requiring ART may have ovaries and follicles that are more susceptible to the damaging effects of chemotherapy when compared with spontaneously fertile women. If there was an adverse effect of methotrexate on later fertility potential, this would be of particular concern to ART patients as they are already being treated for fertility problems and would want to avoid treatment that might further interfere with their attempts to conceive.

The current published data comparing methotrexate treatment with surgical treatment of abnormal pregnancies after ART are limited to small cohort studies of fewer than 100 patients (18, 19). Although some studies have documented no adverse effect on ovarian reserve from methotrexate (4, 18–20), this finding is not always consistent. McLaren et al. (3) demonstrated a decrease in oocyte yield in patients who underwent repeat ovarian stimulation and ART within 180 days of methotrexate treatment but in not those who had repeat ART 180 days after methotrexate. This finding indicates a potential time-dependent negative effect of methotrexate on folliculogenesis. Additionally, the current literature evaluating methotrexate after ART cycles is limited to studies assessing single-dose regimens (3, 4, 19, 20). To our knowledge, the effect of multidose methotrexate on ovarian reserve after ART cycles has not been evaluated. Our study compared the ovarian reserve and subsequent oocyte yield in ART patients treated with surgery or methotrexate for ectopic pregnancy or pregnancy of unknown location in a larger cohort of patients. The secondary objective was to assess the effect of multidose methotrexate on ovarian reserve.

MATERIAL AND METHODS

Study Design

This was a retrospective cohort study of all fresh autologous ART patients treated for ectopic pregnancy or pregnancy of unknown location at Shady Grove Fertility Reproductive Science Center from 2004 to 2010. The retrospective review and analysis of data collected during routine clinical care was approved by the institutional review board.

Patients

The charts of all patients who underwent fresh autologous ART were screened, and any patients treated with methotrexate or surgery for a diagnosis of ectopic pregnancy were included in the study. Pregnancies of unknown location without evidence of an intrauterine gestation were included as ectopic pregnancies. Pregnancy of unknown location included patients with multiple plateaued quantitative values of human chorionic gonadotropin (hCG) (values not increasing over 50% in 48 hours) or with hCG values $>$2,000 and no ultrasonographic evidence of intrauterine gestation.

Outcomes

The primary study outcomes were basal antral follicle count (AFC), basal serum follicle-stimulating hormone (FSH) levels, and oocyte yield from ART. Secondary outcomes were subsequent clinical pregnancy and subsequent live birth. Clinical pregnancy was defined as a transvaginal ultrasound with confirmed fetal cardiac activity. Live birth was defined as a living infant born after 23 weeks' gestation. Additional data were collected on variables that might affect response to methotrexate, including multiple doses of methotrexate, patient age, diminished ovarian reserve, and time between treatment and repeat ART cycles.

Statistical Analysis

Normally distributed data were expressed as mean with standard deviation. Nonparametric data were expressed as median and range. Chi-square or Fisher's exact test were used to compare dichotomous outcomes. Student's *t*-test or Mann-Whitney *U* test were used to compare baseline demographics and AFC, FSH, and oocyte yield between the groups. Paired Student's *t*-test or Wilcoxon rank sum test was used to compare ovarian reserve yield in patients before and after treatment within each group. Student's *t*-test or Mann-Whitney *U* test was used to compare changes in oocyte yield from pretreatment to posttreatment values between the treatment groups. Analysis of covariance (ANCOVA) was used to compare changes in ovarian reserve between the groups while controlling for patient age and the time duration between treatment and repeat ART cycles. Analysis of variance (ANOVA) was used to compare changes in ovarian reserve in patients receiving one, two, or three treatment courses of methotrexate and changes in ovarian reserve between patient age groups. Univariate regression was used to examine dose effects of the number of methotrexate courses needed on ovarian reserve. Less than efficiency curves were used to examine the effect of time after methotrexate treatment and oocyte yield. The statistical analysis was performed using SPSS software (IBM). $P<.05$ was considered statistically significant.