

# Sonographic appearance of tubal pregnancy in patients treated with methotrexate

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**BACKGROUND:** The aim of the present study was to evaluate the effect of methotrexate (MTX) treatment on the ultrasonographic appearance of extrauterine pregnancy (EUP) and, particularly, to test the hypothesis that the ultrasonographic appearance is not predictive of treatment success.

**METHODS:** A prospective cohort study. The study group included 51 women with tubal EUP who received a single-dose protocol of MTX. EUP was diagnosed whenever an intrauterine gestational sac was not identified by transvaginal ultrasonography , accompanied by an abnormal rise or plateau in hCG concentration. Serial TVUS was performed weekly until hCG normalization or the size of the ectopic mass declined to 1 cm<sup>2</sup>.

**RESULTS:** Ectopic tubal mass was identified on TVUS in 42 (78%) women with a mean size of 4 +/- 0.5 cm<sup>2</sup>. Following the first week of MTX injection, the mean size of the ectopic mass significantly increased to 6 +/- 0.8 cm<sup>2</sup> ( $P = 0.02$ ). The initial size of the ectopic mass was not related to the success of the treatment nor to serum hCG levels. Ultrasonographic resolution of the ectopic mass was documented in 25 women following a mean of 42 +/- 2 days (range 6–60 days)

**CONCLUSIONS:** The initial size of a tubal pregnancy is not related to the success of MTX treatment. MTX treatment in tubal pregnancy is followed by an initial increase in the size of the ectopic mass. Accordingly, such enlargement of the ectopic mass should not be considered as a higher risk for failure of treatment.

**Key words:** extra-uterine pregnancy/methotrexate/transvaginal ultrasonograph

## INTRODUCTION

The incidence of ectopic pregnancy has increased in recent times at about 3% of total pregnancy, simultaneously there is a decrease in mortality due to ectopic gestation complication possibly due to increased awareness & early detection of ectopic sac.

The diagnosis of ectopic is made by integration of clinical presentation, serial beta HCG & TVS , TVS scan can detect as early as 10mm

Tanaka *et al.* published the first case report of successful medical treatment of tubal pregnancy with methotrexate (MTX), which has gained considerable popularity and is considered highly effective (Tanaka *et al.*, 1982). The follow-up of women treated by MTX includes primarily serial hCG measurements, whereas repeated TVUS is done only according to clinical indications

The ultrasonographic appearance of a tubal EUP mass treated with MTX was reported only once in a small cohort. Brown *et al.* described the ultrasonographic appearance of 18 pregnancies treated with a multi-dose MTX protocol and found that the serial TVUS did not alter the management of most patients (Brown *et al.*, 1991). The aims of the present study were to define the effect of single-dose MTX treatment on its

ultrasonographic appearance and, particularly, to test the hypothesis that the ultrasonographic appearance is not predictive of the success of the treatment

## MATERIALS AND METHODS

Women with suspected tubal Ectopic from January 2019 to May 2020 were recruited into the study. The main indication for admission was that of our general practice to admit any suspected for baseline evaluation. Women with suspected EUP were evaluated by TVUS and serial hCG concentrations for at least 3 consecutive days.

A viable EUP was diagnosed when no intrauterine gestational sac was identified by TVUS, accompanied by an abnormal rise of serum hCG concentration ( 50% rise in 2 days) or plateau ( 15% decline within 3 days). EUP was diagnosed as ‘missed’ in cases in which hCG concentrations declined (by at least 15% within 3 days), and these were excluded. Accordingly, MTX treatment was initiated only after 3–5 days of serial serum hCG evaluations. Cases with embryonic cardiac activity, unstable haemodynamics or serum hCG levels 10 000 IU/l were also excluded. Conversely, neither the size of the ectopic mass nor free fluid outside the pelvic cavity, as determined by TVUS, were contraindications for MTX treatment.

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In the study women received i.m. MTX at a dose of 50 mg per m<sup>2</sup> of body surface area. The day on which MTX was injected was considered as day zero.

Serum hCG measurements were performed weekly until the concentration reached 25 mIU/ml. Failure of hCG levels to fall by at least 15% during any successive week resulted in repeated administration of MTX. Surgical intervention was performed for a tubal rupture suspected by unstable haemodynamics, falling haemoglobin or acute severe abdominal pain. Success of treatment and its timing were defined as the time of achievement of an hCG concentration of 25 mIU/ml without surgical intervention.

Serial TVS was performed weekly until hCG concentration was 200 mIU/ml or the size of the ectopic mass declined to 1 cm<sup>2</sup>. In cases with residual mass, the TVUS was repeated after a period of 3–5 weeks.

A total of 54 women fulfilled the inclusion criteria. The mean ( SEM) age and gestational age of the study group was 33+-5 years and 42 +-5 days respectively. The mean initial hCG concentration was 2100 mIU/ml. Only six cases in the study group had an hCG value 1000 mIU/ml. In no case was the hCG seen to be declining, thus, the chance of missed abortion was low. The hCG concentration declined to 1540, 160 and 480 mIU/ml, 1, 2 and 3 weeks following the MTX injection respectively.

Ectopic tubal mass was identified on TVUS in 45 (80%) of women and had a mean size of 4 cm<sup>2</sup>. Most of the masses 80% in this series were primarily solid.

The correlation between ectopic size and initial hCG level was  $r = -0.17$  (not significant by the Pearson test). Free fluids were identified in the pouch of Douglas in 38 women (68%). Eight of the eleven cases without identifiable ectopic mass had free fluids in the pouch of Douglas as the only sign of EUP

Following the first week of MTX injection, the mean size of the ectopic mass increased significantly (to 6 cm<sup>2</sup>,  $P < 0.02$ ) and free fluid was identified in 40 women (71%). An increase in the ectopic mass was observed in 25 women (55%), mostly (23 women) in the first week (92%). No

Significant correlations were observed between the size of the ectopic mass and subsequent hCG concentration at 1, 2 or 3 weeks following the MTX injection

The initial and subsequent increase in the size of the ectopic mass was not related to the success of the treatment.

Ectopic mass was identified by sonography before initiation of MTX in all six cases in which MTX failed and surgery was performed. Ultrasonographic resolution of the ectopic mass was documented in all of the remaining 39 women. The resolution of the mass was observed in 27 women (69%) before or with normalization of hCG, following a mean of 40 days (range 7–63 days). The other 11 still had a residual mass with a mean size of 11 cm<sup>2</sup> (range 2.1–39 cm<sup>2</sup>) at the time of hCG normalization. Complete resolution of the tubal mass in the last 12 women took a further 40 days (range 28–63 days).

## Discussion

The present study is prospective report of ultrasonographic documentation of tubal pregnancy treated with MTX.

The indications and actual success of MTX treatment of EUP is still controversial. The present study aimed to assess the role of TVUS in the indications for receiving MTX as well as the indications for surgical intervention and monitoring of the treatment.

The role of TVUS in the management of cases with suspected EUP includes the capability to exclude the presence of an intrauterine gestational sac and, at the same time, to identify an adnexal mass, as well as to determine the eligibility for conservative management, mostly MTX treatment. According to the findings of the present study, the rate of detection of tubal mass in cases with ectopic pregnancy was 80%, which concurs with previous reports (Fleischer *et al.*, 1990; Sadek and Schiotz, 1995). One can argue that the ectopic mass in the 11 cases in which the ectopic pregnancy was not identified by TVUS could be in the cervix, ovary or elsewhere. In any event, however, these were not the focus of our study.

The conclusions of the present study are that a weekly TVUS follow-up of the size of the ectopic mass or the amount of free fluids has limited, if any, diagnostic value following MTX treatment of EUP. Failure of MTX treatment and the decision to intervene surgically were based on clinical signs of acute severe abdominal pain or haemodynamic imbalance and not on TVUS results. These conclusions should be viewed with respect to the specific protocol of the present study (i.e., inclusion criteria, single dose MTX, weekly TVUS) and the possibility that a different set of cases or a different protocol of TVUS monitoring would give different results cannot be ruled out.

Previous reports (Ory *et al.*, 1986), and guidelines (American College of Obstetricians and Gynaecologists, 1999) have

suggested that certain ultrasonographic features should contraindicate treatment with MTX, e.g. the presence of free fluids or of an EUP mass 3–4 cm (at its greater dimension), as well as fetal heart rate (Ory *et al.*, 1986; American College of Obstetricians and Gynaecologists, 1999). According to our results, however, the size of the EUP mass was not different in the failed cases nor did it correlate with the level of hCG concentration. This is in accordance with a previous study (Lipscomb *et al.*, 1999) who reported that only the initial serum hCG concentration determines the success rate, whereas neither of the sonographic parameters has a significant value (Buster and Pisarska, 1999; Lipscomb *et al.*, 1999). Although failure still occurs more often when fetal heartbeat is identified

(Lipscomb *et al.*, 1999), such cases are usually accompanied with high hCG concentrations

Furthermore, according to our results, the size of the ectopic mass increases in most cases during TVUS follow-up. This

increase concurs with a previous report (Brown *et al.*, 1991) in a small cohort. Thus, the decision for surgical intervention

due to enlargement of the mass above certain limits is not justified.

Interestingly, we observed a few cases in which there was a change in the sonographic features of the tubal mass from primarily solid into a semi-solid mass containing more sonolucent areas. A possible explanation is the presence of blood clots and haematoma around the mass that cannot be easily separated from the main mass.

The present data support previous reports regarding the association between ectopic mass and hCG normalization

(Brown *et al.*, 1991; Lipscomb *et al.*, 1999). The resolution of the ectopic mass lagged far behind the hCG resolution in at least 12 cases. For example, the ectopic mass resolved in four women only 9 weeks after the hCG was 200 mIU/ml.

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The main lessons that can be learned from the present study are that the initial size of tubal pregnancy is not related to the success of single-dose MTX treatment and that MTX treatment in tubal pregnancy is followed by an initial increase in the size of the ectopic mass.

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