

The ultrasonographic 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 56 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 (TVUS), 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 cm². **RESULTS:** Ectopic tubal mass was identified on TVUS in 45 (80%) women with a mean size of 4 ± 0.5 cm². Following the first week of MTX injection, the mean size of the ectopic mass significantly increased to 6 ± 0.8 cm² ($P = 0.02$). 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 27 women following a mean of 42 ± 2.4 days (range 7–63 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 ultrasonography

Introduction

The incidence of extrauterine pregnancy (EUP) has increased in recent times to a rate of ~2% of all pregnancies. Concomitant with this increase, however, has been a significant decrease in lethality, partly due to increased awareness and early as well as accurate diagnosis (Pisarska and Carson, 1999).

The diagnosis of ectopic pregnancy is currently made by integration of the clinical presentation, sensitive hCG pregnancy tests (in urine and serum) and high-resolution transvaginal ultrasonography (TVUS). The use of TVUS allows both the exclusion of an intrauterine sac and visualization of a suspected adnexal mass even as small as 10 mm (Pisarska and Carson, 1999). The likelihood of detecting an adnexal mass by TVUS in cases with suspected EUP depends partly on the hCG concentration, and is estimated to be ~80% (Sadek and Schiotz, 1995).

The evolution of a reliable, non-surgical diagnostic approach subsequently facilitated the use of medical/conservative management of EUP. 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 (Buster and Pisarska, 1999; Lipscomb *et al.*, 1999).

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 of EUP 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 EUP who were admitted to the gynaecology department at the Lis Maternity Hospital from January 2000 to May 2001 were recruited into the study. The main indication for admission was that of our general practice to admit any suspected

case of EUP for baseline evaluation. Women with suspected EUP were evaluated by TVUS and serial hCG concentrations (Immulite® 2000; DPC®, Los Angeles, CA, USA) 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.

Eligibility for MTX treatment was described previously (Lipscomb *et al.*, 1999). The study women received i.m. MTX (Abitrexate, Teva, Israel) at a dose of 50 mg per m² of body surface area. The day on which MTX was injected was considered as day zero. Patients were discharged for outpatient surveillance on either the same or the following day. 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. All the women who met these criteria for MTX treatment provided their informed consent for the treatment protocol.

Transvaginal ultrasonography was performed by two gynaecological ultrasonographers, each with at least 10 years experience, using Sonoline Elegra (Siemens Medical System, Munich, Germany) with a vaginal probe of 5–9 MHz. The size of the mass was calculated by multiplying its two greatest dimensions (measured in cm). The mass included a haematoma that could not be separated from the ectopic mass in 20 ultrasound evaluations. The tube was measured separately in all the other evaluations. Serial TVUS was performed weekly until the hCG concentration was ≤200 mIU/ml or the size of the ectopic mass declined to 1 cm². In cases with residual mass, the TVUS was repeated after a period of 3–5 weeks.

Statistical analysis

Results are given as mean (± SEM). According to power analysis, a total of 50 cases is the minimum required for correlation coefficient = 0.3 to reach significance (alpha = 0.05 and 80% power). All the variables were analysed for the normality of their distribution by the one-sample Kolmogorov–Smirnov test procedure. A significant difference was defined using the two-sided paired *t*-test. Correlations were calculated using the Pearson's correlation test. All statistics were performed using SPSS for windows version 8.0 (SPSS Inc, Chicago, IL, USA).

Results

A total of 56 women fulfilled the inclusion criteria. The mean (± SEM) age and gestational age of the study group was 34 ± 0.5 years and 42 ± 3.5 days respectively. The mean initial hCG concentration was 2167 ± 220 mIU/ml. Only five cases in the study group had an hCG value <1000 mIU/ml (range 490–894). In no case was the hCG seen to be declining, thus, the chance of missed abortion was low. The hCG concentration declined to 1654 ± 228, 881 ± 167 and 498 ± 114 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 ± 0.5 cm². Most of the masses (38 cases, 84%) 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 ± 0.8 cm², $P = 0.02$) 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 ($r = -0.001$, -0.2 and -0.2 respectively). 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 42 ± 2.4 days (range 7–63 days). The other 12 still had a residual mass with a mean size of 11 ± 3.8 cm² (range 2.1–39 cm²) at the time of hCG normalization. Complete resolution of the tubal mass in the last 12 women took a further 44 ± 4.3 days (range 28–63 days).

Discussion

The present study is the largest prospective report of ultrasonographic documentation of tubal pregnancy treated with MTX. The indications and actual success of MTX treatment of EUP is still controversial (Lipscomb *et al.*, 1999; Hajenius *et al.*, 2000; Mol *et al.*, 2000; Shalev and Ben-Shlomo, 2001). 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. This suggests that the residual mass is not an active trophoblastic tissue in most cases.

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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