Evaluation of Tubal Pregnancy After Treatment With Methotrexate by Ultrasound Elastography

Meng Xie, MD, PhD, Xuyin Zhang, MD, PhD, Wenping Wang, MD, PhD, Keqin Hua, MD, PhD

Objectives—The purpose of this study was to evaluate the application of ultrasound elastography in the assessment of methotrexate (MTX) treatment for tubal pregnancy and the association with the elasticity score and human chorionic gonadotropin (hCG) concentration.

Methods—A total of 73 cases of unruptured tubal pregnancy were diagnosed and treated systemically with MTX. The sonographic characters of conventional transvaginal sonography and elastography and serum hCG concentrations before and after MTX therapy were retrospectively reviewed and analyzed.

Results—The mean elasticity score was statistically significantly lower for the ectopic tubal masses of the success group (mean $\pm$ SD, 2.58 $\pm$ 0.68) than for the failure group (3.33 $\pm$ 0.47) on day 7 ($P < .001$) and similar on day 0. The median elasticity score for the success group on day 7 was 3, and for the failure group, it was 4. When elasticity scores of 3 and 2 were used for the criterion of successful MTX treatment, the elastography had 94.5% sensitivity, 61.1% specificity, 88.1% positive predictive value, and 78.6% negative predictive value. Elastography of the ectopic masses and subsequent hCG concentration at 1 week after the MTX injection in the success group had a strong relationship.

Conclusions—Our results suggest that transvaginal elastography was a useful tool in the evaluation of tubal pregnancy after pharmacologic management.

Key Words—elastography; gynecology; methotrexate; tubal pregnancy

An ectopic pregnancy is the implantation of an embryo outside the endometrial cavity. The incidence of ectopic pregnancy is 2% to 3%. Most ectopic pregnancies are tubal pregnancies. According to a recent guideline, transvaginal sonography provides a diagnostic tool for tubal ectopic pregnancy. It appeared that a heterogeneous or noncystic adnexal mass with an empty uterine cavity was the typical and common finding in tubal pregnancy cases.

Surgical, pharmacologic, and expectant treatment are the 3 main options for the therapy of tubal pregnancy. Methotrexate (MTX) at a dose of 50 mg/m² has been widely used as a single dose because of its effect on patients with unruptured tubal ectopic pregnancy. It was reported that success rates for single-dose MTX for tubal ectopic pregnancy ranged from 65% to 95%, and 3% to 27% of the patients required a second dose.

However, it has been difficult to evaluate the effect of MTX except for the human chorionic gonadotropin (hCG) concentration. Ultrasound elastography, which was proposed by Ophir et al in...
1991, is a relatively new sonographic procedure for color reconstruction of tissue elasticity. It has been confirmed as a promising diagnostic instrument to discriminate different tissue stiffness by measuring the degree of strain-related distortion under the action of an external force. It appeared that different degrees of elasticity were indicated by different colors: blue for hard, red for soft, and green for medium. Elastography appeared to be useful in the differential diagnosis of breast cancer, thyroid cancer, prostate cancer, and liver cirrhosis, in spite of the fact that it is not yet used in routine clinical practice. The clinical value and clinical application of elastography in differentiating between different lesions in terms of stiffness versus softness have been investigated in recent years. It was reported that combining elastography with sonography improved the sensitivity in detection of acute appendicitis and could also be used to triage the severity of inflammation in such patients. Kapoor et al reported that combining elastography with transrectal sonography significantly improved the ability to detect prostate carcinoma in patients with raised prostate-specific antigen levels.

In recent years, we investigated the function of elastography in gynecology. We successfully applied elastography in the discrimination of high- and low-grade serous ovarian cancer, the diagnosis of the extent of the large-scar endometriosis, evaluation of neoadjuvant chemotherapy in patients with high-grade serous ovarian carcinoma, and the levator ani with no defect on elastography in women with pelvic organ prolapse.

However, to our knowledge, little research has been devoted to evaluating the effect of MTX in the treatment of tubal pregnancy by elastography. In this study, we aimed to assess the application of elastography in the assessment of MTX treatment for tubal pregnancy and the association with the elasticity score and hCG concentration.

Materials and Methods

This work was a retrospective study. The study design and protocol were approved by our Institutional Review Board, and all patients gave written informed consent after the nature of the procedure was explained fully. Between January 2016 and October 2016, patients with a diagnosis of tubal pregnancy who desired medical therapy at the Department of Gynecology in our hospital were retrospectively analyzed.

All procedures were performed by a single radiologist with 10 years of experience in transvaginal sonography who had specialized in elastography for the last 3 years. All patients underwent imaging with a MyLab 60 ultrasound system (Esaote SpA, Genoa, Italy) using a transvaginal 7-MHz transducer. First, conventional transvaginal sonography (with a vaginal probe of 7 MHz) was performed.

Tubal pregnancy was diagnosed and patients were included on the basis of the following conditions. No intrauterine gestational sac was identified. An adnexal mass moving separately from the ovary was visualized. The adnexal mass was less than 3 cm. An abnormal rise in the serum hCG concentration was detected and was less than 5000 mIU/mL. The patients were hemodynamically stable.

The transvaginal transducer was placed in the posterior fornix. The adnexal mass was located and assessed for its size and overall sonographic appearance. In the scanning plane with conventional sonography, transvaginal elastography was performed immediately after the conventional grayscale sonogram was obtained. After that, the grayscale sonogram and real-time elastogram were shown in the dual mode concurrently. The transducer was focused on the target lesion with light compression, as the pressure index showed a value of 4. After 10 seconds, the region of acquisition in the elastogram was set to contain sufficient surrounding mass tissues when the image was stable. Superimposed over the sonogram, the tissue elasticity information was shown in color: blue indicating hard tissue, green indicating medium tissue stiffness, and red indicating soft tissue.

A pretreatment laboratory examination included a blood count and kidney and liver function tests. The patients received intravenous MTX at a dose of 50 mg/m² of body surface area. The day on which MTX was administered was regarded as day 0. Patients were discharged on day 1. For outpatient surveillance, serum hCG measurements were evaluated weekly until the concentration was undetectable. If the difference between hCG levels on days 0 and 7 was greater than 15%, the therapy was considered successful. If the difference was less than 15%, the therapy was considered a failure. A second dose of MTX was administrated for therapy failure. Surgical intervention was performed for the patients who refused MTX therapy again and a tubal rupture suspected by unstable hemodynamics, a falling
hemoglobin level, or acute severe abdominal pain during the follow-up. Transvaginal elastography was performed, and the serum hCG concentration was evaluated on day 7. The toxicity of MTX therapy was recorded.

An independent observer (W.W.) was invited to access the elasticity scores. Due to the lack of generally accepted criteria for scoring elastograms of tubal pregnancy in the published literature and as new research, for ease of image analysis, the elasticity images were evaluated by using a 4-point scoring system, which was used in the study of neck masses. Although the colors indicating tissue elasticity in various studies were different, the principle of showing tissue stiffness was consistent. Our previous studies demonstrated it was effective and convenient.

SPSS version 11.0 for Windows software package (IBM Corporation, Armonk, NY) was used for statistical data analysis. Data were expressed as mean ± standard deviation. A Mann-Whitney U test was performed to determine whether the elasticity scores were different before and after treatment with MTX. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated. The correlations between the elasticity scores and concurrent hCG concentrations were observed, and a Pearson correlation coefficient was calculated.

Results

Seventy-three patients with tubal pregnancy fulfilled the inclusion criteria, and 58 cases were excluded. The mean age and gestational age of the study group were 33.3 ± 8.1 years and 48.5 ± 7.2 days, respectively. The mean initial hCG concentration was 2532.8 ± 753.7 mIU/mL. Ectopic tubal masses had a mean size of 2.3 ± 1.2 cm³, as identified by conventional transvaginal sonography. The correlation between the ectopic tubal mass size and initial hCG level was $r = -0.25$ ($P = .02$).

After the MTX treatment, the success group included 55 cases, and the failure group included 18 cases. All of the failure cases refused a second dose of MTX, and surgery was performed. The hCG concentration decreased substantially on day 7 in the success group versus the failure group. No significant differences was observed between the mean sizes of the ectopic tubal masses and the pretreatment sizes in both groups (Table 1). No significant correlations were observed between the sizes of the ectopic masses and subsequent hCG concentrations on day 7 after MTX treatment in the success and failure groups ($r = -0.28$ and $-0.32$; $P = .08$ and .04, respectively). Twenty-eight cases (38.3%) had mouth ulcers, and the others did not have any apparent adverse reactions.

The mean elasticity score was statistically significantly lower for the ectopic tubal masses of the success group than the failure group on day 7 and similar on day 0 (Figures 1 and 2). The median score for the success group on day 7 was 3, and for the failure group, it was 4. The distributions of elasticity scores for the success and failure groups are shown in Table 2. Of the 55 patients in the success group on day 7, 94.5% had a score of 2 or 3; 3.6% had a score of 1; and 1.8% had a score of 4. Of the 18 patients in the failure group on day 7, 38.9% had a score of 2 or 3. There were also 5.6% cases that was scored as 1 and 55.5% that were scored as 4 (Table 2).

When elasticity scores of 3 and 2 were used for the criterion of successful MTX treatment, elastography had 94.5% (95% confidence interval [CI], 81.2%–99.1%) sensitivity, 61.1% (95% CI, 50.8%–72.6%) specificity, 88.1% (95% CI, 73.4%–94.4%) positive predictive value, and 78.6% (95% CI, 65.5%–89.7%) negative predictive value. The correlation between elastography of the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Success (n = 55)</th>
<th>Failure (n = 18)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>30.6 ± 10.6</td>
<td>34.5 ± 12.8</td>
<td>.78</td>
</tr>
<tr>
<td>Patients’ body mass index, kg/m²</td>
<td>22.7 ± 2.8</td>
<td>21.4 ± 4.7</td>
<td>.89</td>
</tr>
<tr>
<td>Gestational age, d</td>
<td>52.5 ± 10.6</td>
<td>47.9 ± 15.5</td>
<td>.64</td>
</tr>
<tr>
<td>hCG on day 0 before MTX, IU/L</td>
<td>2788.8 ± 985.3</td>
<td>2412.1 ± 834.2</td>
<td>.74</td>
</tr>
<tr>
<td>hCG on day 7, IU/L</td>
<td>1572.2 ± 154.7</td>
<td>2368.1 ± 843.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ectopic pregnancy mass size on day 0, cm³</td>
<td>2.2 ± 1.2</td>
<td>2.5 ± 1.6</td>
<td>.64</td>
</tr>
<tr>
<td>Ectopic pregnancy mass size on day 7, cm³</td>
<td>2.1 ± 1.8</td>
<td>2.0 ± 1.5</td>
<td>.88</td>
</tr>
<tr>
<td>Elasticity score on day 0</td>
<td>3.75 ± 0.43</td>
<td>3.56 ± 0.58</td>
<td>.73</td>
</tr>
<tr>
<td>Elasticity score on day 7</td>
<td>2.58 ± 0.68</td>
<td>3.33 ± 0.47</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
ectopic masses and subsequent hCG concentrations at 1 week after the MTX injections in the success group was $r = 0.68 \ (P = .02)$.

Discussion

In this study, we revealed that elastography played an important role in the evaluation of MTX therapy in the tubal pregnancy. The variation of the mass size and its relationship with the hCG concentration could not indicate the success of the MTX therapy. However, the elasticity score of the mass decreased after MTX therapy, and it had a distinguished correlation with a descending hCG concentration.

Systemic MTX at a dose of 50 mg/m$^2$ is the most commonly used drug for the pharmacologic treatment of tubal ectopic pregnancy. It was reported that randomized controlled trials comparing laparoscopic surgery with MTX showed MTX to be equally successful to surgery in some cases of tubal pregnancy.$^{16}$ The hCG level was attempted to predict the success or failure of MTX treatment. It was reported that hCG levels decreased between days 0 and 4 in 40.0% of cases, and these cases all had successful treatment; hCG levels increased in

Figure 1. A, Conventional sonogram and elastogram from a patient in the success group, which appeared predominantly blue and was clearly distinguishable on day 0, with an elasticity score of 4. B, Same patient who received MTX treatment. The conventional sonogram and elastogram on day 7 appeared predominantly green, with an elasticity score of 3.

Figure 2. A, Conventional sonogram and elastogram from a patient in the failure group, which appeared predominantly blue and was clearly distinguishable on day 0, with an elasticity score of 4. B, Same patient who received MTX treatment. The conventional sonogram and elastogram on day 7 appeared predominantly blue, with an elasticity score of 4.
60.0% of cases, and 61.8% of these cases had successful treatment. Skubisz et al suggested that the first verification of the treatment response was acquired no sooner than day 7. The serum hCG level decreased between days 0 and 4 after MTX treatment in 33 patients, and the ectopic pregnancy was cured in 88% of these cases without additional treatment. A positive predictive value of 97% between days 1 and 4 during MTX treatment was detected in a study of 129 consecutive patients.

It must be pointed out that rupture of a tubal ectopic pregnancy was an emergent status, and emergency surgery had to be performed. Therefore, prevention of the situation was very important. There have been many trials designed to predict successful treatment with MTX by sonography. Desai et al reported that nonresponders to MTX treatment among patients with tubal pregnancy showed increased vascularity on serial examinations. There was also a trend for nonresponders with increased vascularity to be associated with a greater increase in hCG levels and responders with decreased vascularity to be associated with a greater decrease in hCG levels. However, the time of follow-up in that study was different, which was 3 to 16 days.

Endometrial sonographic features were another index to predict the success of treatment with MTX injection. Lim et al reported 4 types of endometrial patterns in patients with ectopic pregnancy: trilaminar, homogeneous, heterogeneous, and pseudosac. Predictive rates of successful MTX treatment were different for each group. The failure rate of MTX treatment was increased when a pseudogestational sac or heterogeneous pattern was detected in tubal pregnancy. However, sonography for categorization depended on subjective analysis by radiologists in the study.

The size of the tubal pregnancy detected by sonography was another marker evaluated to identify the effect of MTX therapy. However, both responders (57%) and nonresponders (61%) with tubal pregnancy showed an increase in size after MTX treatment. The initial size of a tubal pregnancy was found not to be associated with the success of MTX treatment; MTX treatment in tubal pregnancy was followed by an initial enlargement in the size of the ectopic mass. Certainly, such augmentation of the ectopic mass should not be erroneously identified as a higher risk of treatment failure. Brown et al also suggested that enlargement of the adnexal mass during therapy did not necessarily predict treatment failure. It was reported that the mass of an ectopic pregnancy may remain after the hCG result is negative. Therefore, a persistent mass should not be considered a treatment failure.

In this study, no significant difference was observed between the size of the ectopic tubal mass after and before treatment. No significant correlations were observed between the size of the ectopic mass and subsequent hCG concentration at 1 week after the MTX injection in the success and failure groups. We considered this finding to be due to the administration route of MTX. In our study, patients received MTX intravenously, which was different from intramuscular injection in other published studies.

Table 2. Elasticity Scores in Success and Failure Group on Days 0 and 7 (n = 73)

<table>
<thead>
<tr>
<th>Score</th>
<th>Success (n = 55)</th>
<th>Failure (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 7</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>55</td>
</tr>
</tbody>
</table>

In conclusion, it was indicated that transvaginal elastography was a useful tool in the evaluation of tubal pregnancy after pharmacologic management. It detected the stiffness variation of tubal pregnancy tissues as a pathologic process, instead of the size and vascularity. Perhaps transvaginal elastography can play a greater role in the detection of early ectopic pregnancy, and we will investigate this possibility in the future.
References


