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## The role of ultrasonography in methotrexate therapy for ectopic pregnancy

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### Abstract

Medical management of ectopic pregnancy with methotrexate, an antimetabolite of folic acid, is an important alternative to surgical treatment, as it ensures a similar outcome whilst being far less invasive. Ultrasound evaluation does not only facilitate an accurate diagnosis, but also helps to select patients most likely to benefit from methotrexate treatment, as opposed to those with a high likelihood of failure of medical management, who are thus eligible for primary surgical treatment. Ultrasound also allows to monitor the outcome of methotrexate therapy. This study is a review of literature regarding the management of ectopic pregnancy with methotrexate. Such ultrasound findings as the size of the ectopic mass, presence of fetal heart rate and free fluid have been confirmed as effective eligibility criteria for therapy with methotrexate. In the future, possibly also endometrial stripe thickness and the vascularity of the ectopic mass may be considered predictive of successful methotrexate therapy. The initial increase in size of the ectopic mass following methotrexate therapy confirms its effectiveness, and should not prompt concern.

## Introduction

### The history of ectopic pregnancy management

Prior to the introduction of surgical methods of managing ectopic pregnancy (EP), the mortality rate in such cases amounted to 67%. In 1884, the first series of patients treated with salpingectomy were reported, resulting with a decrease in the mortality rate to 5%<sup>(1)</sup>. Over the following years, due to the refinement of surgical techniques, development of anaesthesia, blood transfusion and antibiotic therapy, as well as the possibility of earlier diagnosis, the mortality rate continued to decline. However, for the next 100 years, surgery remained the only available treatment modality in EP<sup>(1)</sup>. The breakthrough in the treatment of EC came with the introduction of methotrexate therapy.

Methotrexate (MTX) is an antimetabolite, a folic acid antagonist<sup>(2)</sup>. The drug inhibits the activity of dihydrofolate reductase (DHFR) that catalyzes the conversion of dihydrofolic acid into the active tetrahydrofolic acid, interfering with DNA synthesis, but indirectly also RNA and protein synthe-

sis. MTX was originally used for the treatment of gestational choriocarcinoma (GC) in 1956, marking the first time a solid tumour was cured with chemotherapy. In the 1960s, MTX was introduced into the management of ectopic pregnancies, yet the application differed from the protocol used at present. The drug was administered prior to the surgical removal of the placenta from the sites of abdominal implantation in second- and third-trimester cases<sup>(3)</sup>. In 1982, Tanaka *et al.* reported a successful case of MTX therapy for EP, thus starting the era of MTX used as first-line treatment in certain cases of this gestational pathology<sup>(4)</sup>. Unfortunately, the MTX regimens employed at the time were based on the treatment of GS, with the multiple high MTX doses causing severe adverse effects. In 1989, Stoval *et al.* were the first to attempt low-dose MTX treatment for EP<sup>(5)</sup>. However, laparoscopy still being the mainstay of EP diagnosis negated the benefits of MTX therapy. In 1991, the single-dose protocol was introduced, resulting with a very high success rate, amounting to over 96%<sup>(6)</sup>. Two years later, human chorionic gonadotropin ( $\beta$ -hCG) monitoring protocol was developed, and transvaginal scan (TVS) was included into the diagnostic algorithm for EP<sup>(7)</sup>. Interestingly, diagnostic and treatment protocols introduced in the early 1990s are still used at present.

## The effectiveness of MTX therapy for EP

When introducing new, alternative treatment modalities, their effectiveness must be compared with the previously used methods. A meta-analysis comparing MTX therapy with surgery may be found in the Cochrane Database Systematic Reviews (CDSR)<sup>(8)</sup>. In the group of patients treated with MTX, adverse effects were noted more frequently, whereas the overall cost of treatment was lower. In terms of primary treatment success, tubal preservation and patency, future fertility and time to baseline  $\beta$ -hCG level, no statistically significant differences were noted between the groups treated with MTX and surgically. The authors of the meta-analysis identified no significant differences in terms of short- and long-term treatment outcome<sup>(8)</sup>. Due to the lesser invasiveness at a similar outcome, MTX therapy may be considered an important alternative to a surgical approach.

## The role of ultrasonography in MTX therapy for EP

The primary role of ultrasound evaluation in the management of ectopic pregnancy consists in its diagnostic potential. Also, US plays a significant role in two clinical settings: when deciding the patient's eligibility for MTX therapy (i.e. in predicting its effectiveness), and following MTX administration, when monitoring the outcome. It should be stressed, nonetheless, that the eligibility criteria include also biochemical tests (primarily  $\beta$ -hCG level measurements) and clinical evaluation (e.g. the patient's stable condition). US, however, plays an important role in the selection of the patients who have the greatest likelihood of benefiting from MTX therapy, as opposed to those unlikely to be efficiently treated medically, who should be referred for primary surgical treatment.

## Ultrasound predictors of eligibility for MTX therapy

The significance of ultrasound for the prediction of the effectiveness of MTX therapy is undeniable, making it an invaluable tool in referring patients for medical treatment. The literature of the subject lists various US findings rel-

evant for selecting optimum management modality in EP patients. The most important ones include the size of the ectopic mass, the presence of fetal heart rate (FHR) and/or gestational sac (GS), free fluid, endometrial stripe thickness and the vascularity of the ectopic mass.

### *The size of the ectopic mass*

One of the key EP parameters evaluated in an ultrasound examination is the largest measurement of the ectopic mass. For years the maximum ectopic mass size eligible for MTX therapy was debated, with various authors suggesting different values ranging from 3-5 cm. Currently, most authors do not recommend MTX therapy for EP >4 cm<sup>(2)</sup>. Fig. 1 shows an ectopic mass of 19 mm, meeting the eligibility criteria for MTX therapy.

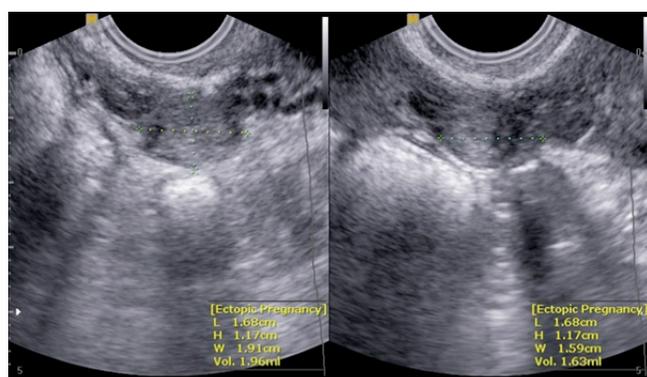
Some authors also propose measuring EP volume. Helmy *et al.* have shown that in a group of EP successfully treated with MTX, the mean baseline volume was approximately 5 ml, whereas in the group with unsuccessful MTX treatment it was approximately 15 ml, with the difference being statistically significant<sup>(9)</sup>. Currently, however, no reliable data justifying routine measurement of EP volume prior to starting MTX therapy are available, and such course of management does not seem to contribute clinically significant information in addition to measuring the maximum EP size.

### *The presence of FHR/GS*

Both the presence of FHR and GS indicate advanced stage of EP, and are thus considered predictors of a likely MTX therapy failure. The authors of a recently published literature review concluded that even though MTX therapy is contraindicated as first-line treatment for EP with detectable FHR due to a considerable risk of failure and complications, in cases where only GS is found, MTX therapy remains an option<sup>(10)</sup>.

### *The presence of free fluid*

Free fluid seen on US is considered a sign of intraperitoneal hemorrhage. Thus, it seems only reasonable not to proceed with MTX therapy in patients with sonographic free fluid, as the internal bleeding is most likely caused by tubal rupture, requiring a prompt surgical intervention. On the other hand, a small amount of free fluid is frequently found in the rectouterine pouch or the Pouch of Douglas (POD), and may be considered physiologic. Hence, upon visualizing free fluid, it is essential to estimate its amount. Free fluid extending into the upper abdomen (hemoperitoneum) is considered a contraindication for MTX therapy due to the risk of an ongoing hemorrhage (Fig. 2). Free fluid confined to the lesser pelvis is, on the other hand, considered a risk factor for an MTX therapy failure, yet it is not considered sufficient to rule out the use of MTX<sup>(10,11)</sup>.



**Fig. 1.** TVS of an ectopic mass consistent with EP of 19 mm. In terms of its size, the mass meets the eligibility criteria for MTX therapy

### Endometrial stripe thickness

The rationale for measuring endometrial stripe thickness when evaluating the patient's eligibility for MTX therapy is grounded in the assumption that it reflects the patient's  $\beta$ -hCG level. In a study evaluating the endometrial stripe thickness and  $\beta$ -hCG level in patients treated with MTX, it was observed that in the group of patients in whom MTX therapy proved effective, the mean endometrial stripe thickness was 6.4 mm, and the mean  $\beta$ -hCG level was 1936,2 mIU/ml<sup>(12)</sup>. In the group in whom MTX therapy failed, the corresponding mean values were 11.7 mm and 6831,3 mIU/ml, respectively. Another study demonstrated that in patients whose endometrial stripe thickness >12 mm, the likelihood of MTX therapy failure was significantly higher<sup>(13)</sup>. Despite these promising results, the measurement of endometrial stripe thickness is not routinely recommended prior to administering MTX therapy.

### The vascularity of the ectopic mass

The use of color Doppler allows to assess the vascularity of the ectopic mass, determining the activity of the trophoblast, and allowing to predict the likelihood of treatment success. A study by Elito *et al.* found MTX therapy to be effective in 96% of EP with a low vascular flow, whilst in EP with moderate vascularity, the effectiveness declined to 33%, and in cases with richly vascular ectopic masses, MTX therapy was ineffective<sup>(14)</sup>. It should be remembered, nonetheless, that the above-cited study is an isolated report covering a small number of patients, and the current recommendations do not include the evaluation of the ectopic mass vascularity prior to initiating MTX therapy.

### Ultrasound evaluation of MTX therapy outcome

It must be stressed that the cornerstone of monitoring MTX therapy outcome is the evaluation of changes in the  $\beta$ -hCG level. Nevertheless, the literature of the subject also offers information regarding the role of ultrasonography in evaluating the outcome. Even though the potential for predicting the effectiveness of treatment based on the evolution of the sonographic picture remains limited, its knowledge is crucial, as it can prevent unnecessary surgical interventions. In the literature, most importance has been attached to the changes in the size of the ectopic mass and its vascularity.

### Evolution of the size of the ectopic mass following MTX therapy

Shortly after ultrasound evaluation had been introduced into the diagnostic algorithm, it was noticed that an increase in the tubal size accompanying a declining  $\beta$ -hCG level was a sign of healing, and should not prompt concern<sup>(15)</sup>. Further research confirmed this observation. Gamzu *et al.* found that upon the administration of MTX, EP is observed to increase in size, which is not associated with a risk for treatment failure, and does not correlate



Fig. 2. TVS of a patient diagnosed with EP shows a large amount of free fluid. Not eligible for MTX therapy

with  $\beta$ -hCG level<sup>(16)</sup>. A recently published study suggested that the increasing EP size may even be considered a positive sign confirming the effectiveness of MTX therapy<sup>(17)</sup>.

### Evolution of the vascularity of the ectopic mass following MTX therapy

First observations of the evolution of EP vascularity following MTX therapy showed that in the majority of cases successfully managed with MTX therapy, an initial increase in the vascularity of the ectopic mass is observed and should not prompt concern<sup>(15)</sup>. Another study, however, demonstrated that increasing vascularity linked to a growing  $\beta$ -hCG level is found in cases unresponsive to MTX therapy, whereas in responsive cases the vascularity is seldom observed<sup>(17)</sup>. Thus, the significance of the changes in EP vascularity following MTX therapy has yet to be determined, with the most recent data pointing to the conclusion that a rise in the vascularity may be indicative of treatment failure.

### Conclusion

TVS plays a key role in the diagnosis of EP. Moreover, combined with  $\beta$ -hCG measurements and the clinical picture, it allows to decide the patient's eligibility for MTX therapy. Such ultrasound findings as the size of the ectopic mass, the presence of FHR and free fluid facilitate the selection of optimum treatment modality for every given patient. In the future, possibly also additional sonographic parameters, such as endometrial stripe thickness and EP vascularity may be included as the predictors of the effectiveness of MTX therapy. An increase in the size of the ectopic mass observed following MTX therapy confirms its effectiveness, thus not being a cause for concern. The prognostic value of increasing vascularity of the ectopic mass following MTX therapy remains unclear, even though the most recent data indicate its role as a predictor of therapy failure.

## Conflict of interest

The author does not state any financial or personal links to other persons or organizations that could adversely affect the content of this publication and/or claim rights thereto.

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