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Original Research

EVALUATING THE MULTI-DOSE INTRAMUSCULAR ADMINISTRATION OF METHOTREXATE IN THE EARLY STAGE OF INTERSTITIAL ECTOPIC PREGNANCY

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ABSTRACT

Background: *Interstitial ectopic pregnancy (IEP) happens when implantation occurs in a special location, the interstitial part, of the fallopian tubes. This condition accounts for 3% of all ectopic pregnancies. When the amniotic sac just develops in the interstitial area of the uterine tube without altering the anatomy of the uterine horn, locating the gestational mass by surgery is difficult. This study aims to assess the efficacy of multi-dose intramuscular injection of MTX in the treatment of IEP in the early stages.*

Methods: *A cross-sectional study was conducted in Hanoi Obstetrics and Gynaecology Hospital from January 2018 to July 2019. The patients were selected under the sampling criteria and treated using intramuscular MTX injection with the dose of 1mg/kg/24 hours on day one. The dose in the following day depended on βhCG concentration. If βhCG concentration increases or decreases by less than 15%, the above treatment will be continued on the next day. The total number of MTX injections is 4 shots.*

Results: *26 eligible patients; successful treatment rate is 84.62%. βhCG significantly decreased after the third injection.*

Conclusion: *Multi - dose intramuscular MTX injection treatment is an effective and safe treatment option for interstitial ectopic pregnancies in early stages.*

Key words: *Interstitial ectopic pregnancy (IEP), medical treatment.*

I. INTRODUCTION

Interstitial ectopic pregnancy (IEP) occurs when the blastocyst implants in a special location, the interstitial portion of the fallopian tube. This condition is estimated for 3% of ectopic pregnancy (EP) cases [1]. This special portion of the fallopian tube, surrounded by myometrium, is a thin layer of uterine muscle, rich in nourishing blood vessels. The embryo sac usually develops easily in the early stage with relatively unclear clinical manifestations. Because of the proximity of these pregnancies to the uterus and the ovarian arteries, hemorrhage with rupture can be severe and is associated with mortality rates as high as 2.5 [2] .

In Vietnam, IEP is treated mainly by surgery, which is primarily laparoscopic. Other treatment methods such as direct injection of methotrexate (MTX) into the gestational mass or systemic MTX alone or a combination of systemic MTX with local injection or oral mifepristone administration are less commonly used in Vietnam because the advantages of the surgery method somewhat overwhelm medical treatments.

With the widespread development of high-resolution transvaginal ultrasound (TVUS) and increased awareness of Vietnamese people on reproductive health care services, less than 01% of EP cases as IEP in clinical practice is diagnosed at a very early stage when the embryo sac neither grows up yet nor inflates the uterine horn, leading to the difficulty in locating the gestational mass during laparoscopy. Furthermore, cornual resection or conservative surgical management, which requires

a bipolar knife or hemostatic suture technique, can lead to weakened uterine muscles, resulting in a uterine rupture in the successive gestation.

This study has been conducted to evaluate the efficacy of IEP treatment by using multi-dose intramuscular MTX in the early stage of IEP.

II. MATERIALS AND METHODS

All patients diagnosed with IEP indicated for medical treatment with the following characteristics: (1) In a stable clinical condition. (2) Amenorrhea followed by vaginal bleeding and ipsilateral abdominal pain. (3) Ultrasound criteria: "empty" uterine cavity and eccentrically located gestational sacs >1 cm from the most lateral edge of the uterine cavity and a thin myometrial layer (<5 mm) surrounding the chorionic sac. Early - stage of IEP was defined by gestational mass ≤ 3 cm [3], no fetal cardiac activity was observed [4]. (4) Serum βhCG < 10.000 IU/l [4].

All these patients were referred to the Gynaecology Department of Hanoi Obstetrics and Gynaecology Hospital.

Exclusion criteria: In the stage of hypovolemic shock, allergic to methotrexate and other contraindication of using methotrexate.

This cross - sectional study was conducted from 01 January 2018 to 31 July 2019 and this is a prospective study.

Treatment regimen: 01 mg/kg/24h MTX intramuscular injection is given on day one. MTX is adjusted in the following days depending on the βhCG level. If the βhCG level reduces by more than 15% then stop MTX treatment. If it decreases by less than 15%, repeat the same MTX dose. On alternate dates of MTX injections, patients are administered intravenous injection of calcium folinate 0.1 mg/kg and tested for βhCG level. The total number of MTX injections is 4 and the maximum inpatient treatment duration is 08 days. Outpatient monitoring: Patients have βhCG test and ultrasound once a week at the hospital until βhCG is less than 5 IU/l.

Evaluating treatment results based on: Medical Treatment Protocols for Ectopic Pregnancy in William Gynecology (Third Edition):

The clinical symptoms gradually decrease and then disappears.

If the βhCG level decreases by more than 15% after MTX injection, MTX injection is stopped and the patient is discharged from hospital. The outpatient monitoring is maintained until βhCG is less than 5 IU/l.

Criteria of unsuccessful treatment; then surgery is recommended: Detection of fetal cardiac activity; Detection of gestational mass rupture; After 04 doses of MTX, the βhCG level increases or decreases but less than 15%; Occurrence of serious side effects such as: severe mouth ulcers; white blood cells <3000/l; platelets <100,000/l; red blood cells <2.5 T/l); Increased liver enzymes SGOT and SGPT > 100 IU/l [5].

The cleaning data were analyzed using SPSS 16.0 and Fisher testThe study was approved by the Scientific Council of Hanoi Obstetrics and Gynaecology Hospital.

III. RESULTS

From January 2018 to July 2019, 26 eligible patients participated in this study out of the 4010 EP patients treated at Hanoi Obstetrics and Gynaeocology Hospital. The average age of the patients was: 33.19 ± 4.9 (25 - 43 years old); the age group most encountered in this study ranges from 30 - 39, accounting for 69.3%.

Clinical and subclinical characteristics of the patients

Among the 26 IEP cases of the study, pelvic pain and vaginal bleeding accounted for an equal percentage of 30.77%. No patients experienced hypovolemic shock. The average βhCG level at the time of diagnosis and before treatment was: 5344.65 ± 2900.4 (669-9650UI/l). The group of patients with βhCG levels ranging from 5,000 IU/l to 10,000 IU/l accounted for 57.69%. The gestational masses in this study were equivalent to embryo sacs of about 6 weeks old, with a mean size of 15.87 ± 6.67 (7 - 29 mm), and were completely located at the uterine horn. The mean distance from the amniotic sac to the highest point of the endometrium was 14.38 ± 2.54 (10.1 - 18.0 mm).

Treatment results

In this study, proportion of patients cured by multiple muscular injections of methotrexate was 22/26 cases, accounting for 84.62%. Three of the four unsuccessful cases were eventually treated by laparoscopic intervention: 02 cases after the first injection of MTX increased βhCG level and had fetal cardiac activity; 01 case after the 2nd injection of MTX showed signs of shock due to the rupture of gestational mass; The other one, after the 3rd injection, had a sharp rise in serum βhCG level and a severe abdominal pain presented.

βhCG follow up after MTX injection

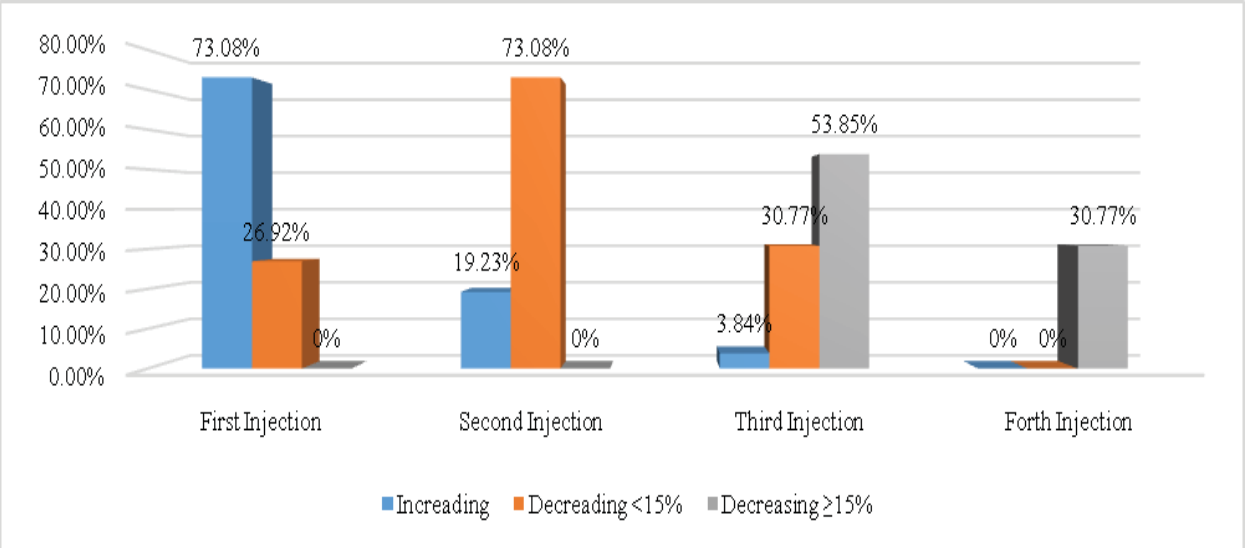

Figure 1: Changes of βhCG level after MTX injection

After the first MTX injection, most patients still witnessed an increase in the βhCG level. After the third one, βhCG level decreased by more than 15%, which happened in 53.85% of the patients. After the fourth MTX injection, all of the patients who were still on treatment experienced a fall in the βhCG level by ≥ 15%.

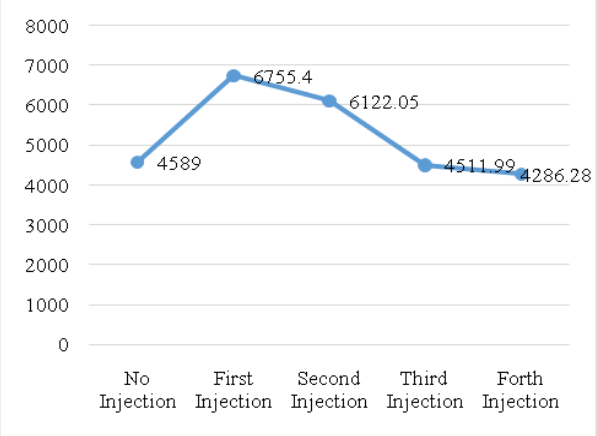

Figure 2: Changes in the mean of βhCG level after each MTX injection

The mean of βhCG level after the first injection did not decrease but increased higher than that at admission to the hospital. After the second MTX injection, the βhCG level decreased but mainly by less than 15%. After the third injection, the βhCG level significantly reduced by more than 15%, (p <0.05).

Table 1: Correlation between βhCG level and treatment outcome

Serum βhCG levels	Treatment results	n	%	p
<5000 IU/l (n = 11)	Success	11	100	p=0.063
	Failure	0	0	
5000 - 10000 IU/l (n = 15)	Success	11	73.33	
	Failure	4	26.67	

For patients with βhCG level below 5000 IU/l, the success rate of medical treatment was 100% higher than that (73.33) of patients with βhCG level from 5000 to 10000 IU/l. However, this difference was not statistically significant (p = 0.063).

Table 2: Correlation between gestational mass size and treatment outcomes

Gestational mass	Treatment results	n	%	p
< 15mm (n = 12)	Success	12	100	p=0.044
	Failure	0	0	
15 - 30mm (n = 14)	Success	10	71.43	
	Failure	4	28.57	

For patients with a gestational mass of less than 15mm, the success rate of medical treatment was 100% higher than that (71.43%) of patients with a gestational mass size of 15 - 30 IU/l (p = 0.044)

Table 3: Information on the failure cases

No	Gestational mass size (mm)	Changes in βhCG (IU/l)	Time of surgery	Reason for surgery	Method of surgery	Blood loss (ml)
P1	14 x 16	9248 -17221- 18910 - 22386	After MTX 3	βhCG increased greatly	Laparoscopic management	100
P2	19 x 21	5989 - 9652 -17497	After MTX 2	Shock	Open surgical management	1200
P3	18 x 22	9994 - 14310	After MTX 1	Fetal cardiac activity	Laparoscopic management	100
P4	25 x 33	9650 - 16060	After MTX 1	Fetal cardiac activity	Laparoscopic management	100

For 22 cases of successful treatment, no patients showed signs of vomiting and nausea or any other side effect after MTX injection. The average length of stay in the 22 successful cases was 10.82 ± 2.97 days (8 - 16 days). The duration of outpatient monitoring until βhCG became negative in the study varied from 04 to 08 weeks. The average monitoring duration was: 45.25 ± 1.6 days. No patients were required to be hospitalized again.

IV. DISCUSSION

4.1. Characteristics of the selected patients

The study findings show that most of the 26 selected patients had a gestational mass newly formed in the interstitial segment of their Fallopian tubes because the gestational mass sizes were not too large (average from 15.87 ± 6.67 mm). The majority of the patients were diagnosed early when the classic physical signs of ectopic pregnancy only accounted for a modest percentage: 30.77% for pelvic pain and vaginal bleeding. In addition, physical signs of IEP are also more blurred than those of ectopic pregnancies in normal positions. In the study of Soriano et al. (2008) investigating 27 IEP cases, signs of abdominal pain, vaginal bleeding and asymptomatic accounted for 48%, 29% and 33%, respectively [6].

The initial βhCG level in our selected patients was below 10,000 IU/l, equivalent to a newly formed embryo sac, while IEP patients appear to have higher βhCG levels. In the study conducted by Zuo X., the βhCG level was high; the average level was 14,696 ± 11,705 IU/l; all the patients in this study were operated [7]. A similar phenomenon was also demonstrated in Soriano's study; the mean value of βhCG in IEP cases was 31,199 ± 6,653 IU/l [6].

In our study, 57.69% of patients had initial βhCG level in the range of 5,000 - 10,000 IU/l, which was significantly higher than the average βhCG level in ectopic pregnancies in ordinary locations. Previously, in Vietnam, when the concentration of βhCG was greater than 5000 IU/l, medical treatment was rarely chosen for ectopic pregnancies in other locations.

4.2. The treatment efficacy

Treatment using the multi - dose MTX regimen was successful on 22 out of the 26 patients who participated in the study, accounting for 84.62%. A French study with a similar regimen had a successful treatment rate of 100%. However, this was a small study involving only 08 IEP patients [8]. A study by Korean authors on 38 IEP patients using two modes of MTX injection: direct MTX injection into the gestational masses and systemic MTX injection, reports the success rates of 87.5% and 46.7%, respectively. According to this study, the two modes of MTX administration significantly impacted the treatment outcomes with p = 0.039 [9]. However, there were only 08 cases of direct MTX injection into the gestational.

Furthermore, some out of the 08 cases with direct MTX injection into gestational masses still used systemic MTX injection. Therefore, it is difficult to confirm that MTX administration route completely determines the treatment outcomes. In addition, according to Hajenius PJ, injecting MTX into gestational masses (local methotrexate)

is rarely used for two reasons: (1) this intervention is performed under TVUS or laparoscopic guidance (2) higher success rate compared with systemic administration, but the difference was not statistically significant [10].

Studying more about the systemic administration of MTX, we find that our study had a much higher success rate of treatment (84.62%) than that of Kim MJ's systemic MTX injection (46.7%) because the newly formed gestational mass in our selected patients had an average size of 15.87 ± 6.67 mm (equivalent to 05 weeks and 06 days) and their βhCG level was less than 10,000 IU/l while the average fetal age in Kim MJ's patients was 06 weeks 03 days, and the maximum gestational age of 01 patient in Kim MJ's study was even up to 11 weeks 03 days. The outcome of systemic MTX treatment may be more related to the development of gestational masses. In our study, the treatment results with βhCG below 5,000 and the group with βhCG from 5,000 - 10,000 IU/l differ, but the difference is not statistically significant (p = 0.063). This may be because the patients with low βhCG threshold (<10,000 IU/l) are selected. Cassik P et al (2005) showed that the medical treatment was completely successful in all patients with the initial serum βhCG less than 9000 IU/l [11]. Therefore, it's important to have a study on a group of patients with higher βhCG concentrations to find the maximum βhCG threshold at which it is still possible to use medical treatment. Another factor that also determines the outcome is the gestational mass size. In this study, the treatment success rate in the group with a gestational mass of less than 15 mm was higher than that in the group with a gestational mass in the range of 15 - 30 mm with p = 0.044. Ben - David A. also had a similar comment on the size of the amniotic sac could determine the success or failure of the medical treatment with p = 0.03. The author also found that all failure cases had an amniotic sac size of more than 20 mm [12].

Therefore, the medical treatment using multi-dose intramuscular MTX injection for IEP patients should only be applied for the case in which the gestational mass is newly formed or the embryo sac is not developing too strongly. All four failure cases in our study had βhCG concentration of more than 5,000 IU/l ; three out of four cases had βhCG of more than 9,200 IU/l and amniotic sac size more than or equivalent to 15 mm.

For the 26 patients of the study, the variation of βhCG level was relatively consistent during the treatment period. After the first injection, 73.08% had increased βhCG. Although the βhCG levels of the rest were reduced, the reductions were less than 15%. This means all the patients had to continue the treatment. Two patients were operated because they had increased βhCG concentration and fetal cardiac activity appeared right after the first injection. After the second injection, 24 patients continued to have another MTX injection. The βhCG level of these patients decreased but not clearly, so they had to continue with the third MTX injection. Only after the third injection, 53.85% of patients had βhCG reducing by more than 15% and did not have to use the fourth MTX injection. Thus, to evaluate the treatment results, it is usually necessary to wait after the third injection to temporarily assess whether or not the βhCG level is significantly reduced. With such a relatively long inpatient treatment, perhaps the regimen of intramuscular MTX injection of 01 mg/kg/24 hours should be applied in public hospitals. The average inpatient treatment duration among the successful group in the study was 10.82 ± 2.97 days. This is also a limitation of this regimen.

According to a study by Tanaka K., the authors used intravenous bolus injection of 100 mg MTX for 05 minutes then infused 200 mg MTX with 500 ml of normal saline within 12 hours. The patients in this study were administered with antiemetics to prevent the side effects of MTX. They were given 15 mg folinic acid for oral administration at 30, 42, 54, and 66 hours after having MTX injection at home. With this regimen, the success rate was 93.9% (In which one patient had βhCG concentration increasing up to 106,634 IU/l and had fetal cardiac activity). With this regimen, patients only had to stay at the hospital for the first day and were on outpatient treatment the following days. This approach shortened the length of hospital stay. However, administering MTX in such a high dose resulted in adverse effects such as vomiting and nausea (3/33 patients) [1] with high potential risks of rupture when the patients are at home. The intramuscular injection of MTX combined with calcium folate for detoxification in this study is less risky and safer, as none of the patients reported experiencing nausea and vomiting.

Our study's outpatient monitoring duration for βhCG to become negative was 04 to 08 weeks. The average monitoring duration was 45.25 ± 1.6 days.

Similar to Tulandi's study, the average prolongation duration to obtain a normal serum βhCG concentration was 43 ± 6.4 days [2]. One thing to note is that a falling βhCG after methotrexate treatment does not exclude the possibility of subsequent rupture. Therefore, it is important to advise the patients not to go far from urban areas to ensure easy access to medical facilities during the monitoring period. According to Hamouda E.S (2013), the time when the interstitial gestational masses rupture is usually about 7 - 9 weeks, later than other types of ectopic pregnancies. However, in some cases, rupture happened even at 18 weeks of gestation [13].

The limitations of the study: This is a small study conducted with 26 patients only. It should be enlarged in further study to get more accurate results.

V. CONCLUSION

The results of this study suggests that, when interstitial gestational masses are newly formed with a size less than 15 mm with βhCG concentrations below 10,000 UI/l and are not too large to deform uterine horn, the medical treatment with multi-dose intramuscular MTX is an effective and safe option, which helps to avoid unnecessary surgery.

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