

## The Efficacy and Safety of Managing Interstitial Pregnancies with Transvaginal Ultrasound-Guided Local Injections of Absolute Ethanol

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### Summary

Interstitial pregnancy is a rare disease condition, but the frequency has been increasing with recent spread of assisted reproductive technology. On the other hand, development of high-sensitive hCG test drug and improvement in accuracy of transvaginal ultrasonic tomographic imaging enabled early diagnosis, and success in conservative treatment with administration of drugs including methotrexate (MTX) has been reported in some cases, but there are not a few cases in which hysterectomy is required as a result of massive hemorrhage. We have reported the efficacy and safety of local ethanol injection therapy as a treatment method that can be a substitute for local MTX injection for ectopic pregnancy so far. We encountered cases of interstitial pregnancy that was successfully treated with local ethanol injection.

**Case 1:** A 40-year-old patient. IVF-ET was performed at a hospital where the patient was previously treated. At 8 weeks and 2 days of gestation, fetal sac was observed in the left interstitial part, for which local ethanol injection therapy was provided. **Case 2:** A 38-year-old patient. IVF-ET was performed at a hospital where the patient was previously treated. At 6 weeks and 4 days of gestation, fetal sac was observed in the right interstitial part, for which local ethanol injection therapy was provided. In any of these 2 cases, hCG decreased after the local ethanol injection therapy, and menstruation was restarted 1 month after this treatment and the subsequent conditions were favorable. In addition, no adverse reaction to local ethanol injection therapy occurred.

**Keywords:** Interstitial pregnancy, local ethanol injection, Ectopic pregnancy, Fertility preservation, In Vitro Fertilization-embryo Transfer infertility (IVF-ET).

### Introduction

Interstitial pregnancy is a rare disease that accounts for 2-4% of all types of ectopic pregnancy<sup>1)</sup>, but determination of lesion in early pregnancy period is difficult, and it is not rare that massive hemorrhage in abdominal cavity leads to shock state, resulting in a condition that requires hysterectomy if rupture occurs. Previously, the mortality was 2.5%, which was higher compared to other types of ectopic pregnancy [1], and careful and prompt handling is required in making diagnosis and deciding treatment method. In recent years, development of high-sensitive hCG test drug and improvement in transvaginal ultrasonic tomography has enabled early diagnosis, which leads to increase in opportunities for initiation of treatment before appearance of clinical symptoms, and treatment methods have been diversified.

As the treatment methods, in addition to drug therapy mainly containing methotrexate (MTX) [2], surgical therapy including laparoscopic surgery has been often reported as a result of improvement in laparoscopic technology and amelioration of surgical equipment including devices [3,4]. We have reported the efficacy and safety of local ethanol injection therapy as an alternative treatment method for local MTX injection therapy for ectopic pregnancy so far [5].

We encountered cases of interstitial pregnancy that was successfully treated with local ethanol injection therapy and evaluated the efficacy and safety of that therapy.

### Case

#### Case 1

**Patient:** A 40-year-old patient with gravida 1, para 0.  
**Chief complaint:** There was no remarkable symptom.

**Medical history/family history:** There was no remarkable finding.

**History of menstruation:** The first menstruation occurred at the age of 12. The menstrual cycle was 26 days and regular.

**History of present illness:** Pregnancy was established with IVF-ET at a hospital where the patient was previously treated. Pregnancy course was monitored, but at 8 weeks and 2 days of gestation, interstitial pregnancy was suspected on ultrasonography, for which the patient was referred to our hospital for close examination and treatment.

**Physical conditions on presentation:** Blood pressure was 126/60 mmHg. Pulse was 72 beats/min. The body temperature was 37.2 degrees C.

**Blood test findings:** Hb was 12.7 g/dL. Blood hCG was 2,384 IU/L. Other findings showed no abnormality.

**Ultrasonic tomography:** Fetal sac of 20 mm in size was observed in the left interstitial part, but fetal heart rate was not confirmed (Figure 1).

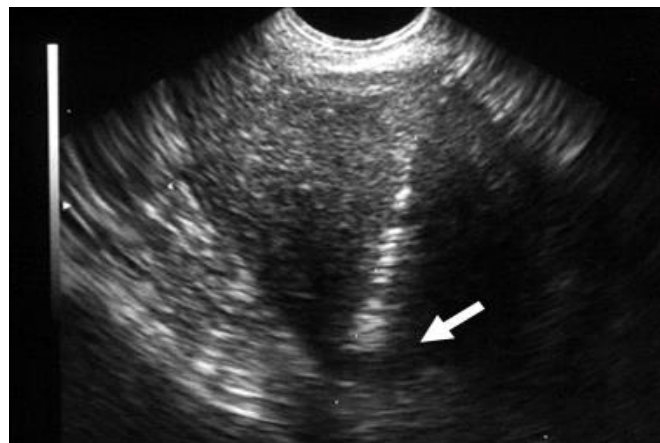


**Figure 1:** Transvaginal ultrasonic tomography.

Transvaginal ultrasonic tomography showed fetal sac of 20 mm in size in the left interstitial part that was distant from the endometrium, but fetal heart rate was not confirmed.

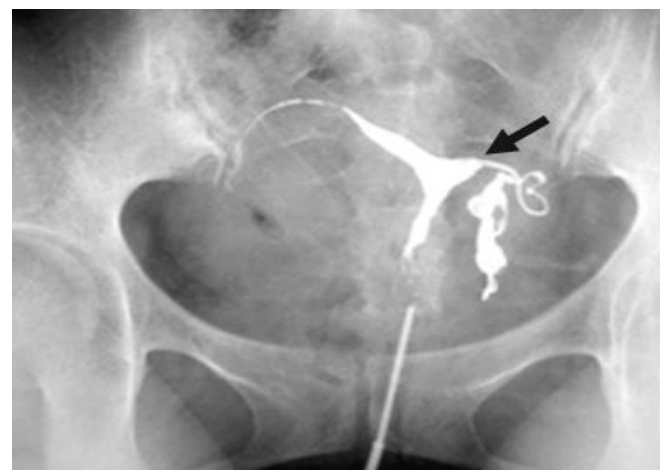
**Clinical course:** Left interstitial pregnancy was diagnosed, but the patient strongly desired fertility preservation and drug therapy. Since general conditions were stable, explanation about local ethanol injection therapy was given to the patient by word of mouth and in writing, and the informed consent for this therapy was obtained. In local ethanol injection therapy as a conservative treatment, 22-gage PTC needle was used to provide transvaginal ultrasound-guided local injection of absolute ethanol (1.5 mL) in the site of interstitial pregnancy (Figure 2). After that, blood hCG successfully decreased, but blood hCG slightly increased on the 5th day after the local ethanol injection. Therefore, additional local injection of absolute ethanol (1.0 mL) was provided. After that, blood hCG successfully decreased and the patient was discharged on the 10th day after the initial local ethanol injection. Menstruation was restarted by 1 month after the treatment, and no adverse reaction to local ethanol injection therapy was noted. In addition, uterosalpingography was

performed 2 months after the local ethanol injection, which showed no problem with fallopian tube patency.



**Figure 2:** Transvaginal ultrasonography findings at the time of local ethanol injection.

☐ The site to which local ethanol was injected. 22-gage PTC needle was used to provide transvaginal ultrasonic-guided local injection of absolute ethanol to the site of interstitial pregnancy.



**Figure 3:** Uterosalpingography (2 months after the local ethanol injection).

☐ The site to which local ethanol was injected. There was no remarkable finding on fallopian tube patency.

## Case 2

**Patient:** A 38-year-old patient with gravida 2, para 0

**Chief complaint:** Abdominal pain lower

**Medical history/Family history:** There was no remarkable finding.

**History of menstruation:** The first menstruation occurred at the age of 16. The menstruation cycle was 27 days and regular.

**History of present illness:** Pregnancy was established with IVF-ET at a hospital where the patient was previously treated. At 6 weeks and 2 days of gestation, blood hCG was 5728 IU. Fetal sac was not observed in uterus and thus

ectopic pregnancy was suspected and the patient was referred to our hospital for close examination and treatment.

**Physical conditions on presentation:** Blood pressure was 104/68 mmHg. Pulse was 72 beats/min. The body temperature was 37.1 degrees C. The abdomen was soft with mild tenderness in the lower abdominal region.

**Blood test findings:** Hb was 13.2 g/dL. Blood hCG was 11,147 IU/L. There was no finding showing abnormality.

**Transvaginal ultrasonic tomography:** Fetal sac of 25 mm in size was observed in the right interstitial part, but fetal heart rate was not confirmed (Figure 4).



**Figure 4:** Transvaginal ultrasonography findings.

Transvaginal ultrasonic tomography showed fetal sac of 25 mm in size in the right interstitial part, but fetal heart rate was not confirmed.

**Clinical course:** Right interstitial pregnancy was diagnosed, but the patient strongly desired fertility preservation and drug therapy. Since general conditions were stable, explanation about local ethanol injection therapy was given to the patient by word of mouth and in writing, and the informed consent for this therapy was obtained. As a conservative treatment, 22-gage PTC needle was used to provide transvaginal ultrasound-guided local injection of absolute ethanol (1.8 mL) in the site of interstitial pregnancy (Figure 2). After that, blood hCG successfully decreased and the patient was discharged on the 7th day after the local ethanol injection. Menstruation was restarted by 1 month after the treatment, and no adverse reaction to local ethanol injection therapy was noted.

## Discussion

Interstitial pregnancy is a rare disease condition with the frequency of occurrence of 2-5% among all types of ectopic pregnancy, but the frequency has been increasing with spread of assisted reproductive technology [1]. In interstitial pregnancy, symptoms rarely appear in early stage because fertilized egg is implanted deep in muscle layer and close to endometrium, and differentiation from normal pregnancy is commonly difficult based on image findings. Therefore, it is not rare that uterine rupture leads

to shock state, and the mortality is reported to be higher than that of other types of ectopic pregnancy, and early diagnosis and treatment is important for interstitial pregnancy because it may result in fatal condition [1]. In recent years, development of high-sensitive hCG test drug and improvement in accuracy of transvaginal ultrasonic tomography device have enabled early diagnosis so that treatment can be started before clinical symptoms appear. Fertility preservation treatment has shifted from conventional wedge resection of the uterus, and recently, cases in which fertility preservation was successfully achieved with laparoscopic surgery or treatment with drugs including MTX have been often reported. However, there are reported cases in which sudden massive hemorrhage led to serious shock state, which resulted in a condition that required hysterectomy, and treatment method for interstitial pregnancy has not been established in the current situation [6,7].

Treatment methods for this disease condition can be roughly divided into surgical treatment and conservative treatment. As surgical treatment, wedge resection of the uterus by abdominal section has been used in principle as mentioned above, but in recent years, as the technology and devices have been improved and early diagnosis has been enabled, treatment success in laparoscopic surgery has been increasingly reported [3,4]. On the other hand, conservative treatments include MTX therapy (systemic administration or local injection). If the conditions such as good general conditions, unruptured lesion, size of the lesion of smaller than 3-4 cm, and urine hCG of lower than 3000-5000 IU/L are satisfied, drug therapy can be chosen [3]. However, there is no established eligibility criteria for this therapy. In addition, since MTX is an anticancer agent, adverse reaction including bone marrow depression, hepatic function disorder, or stomatitis can develop, and treatment duration may be prolonged because it takes long time for the drug to take effect and there is a problem of occurrence of sudden massive hemorrhage that leads to serious shock state with some frequency.

We have reported the efficacy and safety of local injection of absolute ethanol as an alternative treatment method for local MTX injection for ectopic pregnancy so far. We performed local ethanol injection therapy for interstitial pregnancy as a novel treatment method that can be a substitute for laparoscopic surgery or MTX drug therapy.

Local ethanol injection therapy is a treatment method in which PTC needle is used to provide transvaginal ultrasound-guided local injection of absolute ethanol to the site where fertile ovum exists (interstitial portion of the fallopian tube), and the merits of this therapy include rapid assessment of treatment response. This is because absolute ethanol has a property to dehydrate villous tissue to denature it and thus it reduces blood hCG level in a short time. If patients' condition responds to local ethanol injection therapy, 2 hours after the therapy, blood hCG level reduces to 10-30% of the level before the therapy. Therefore, the treatment response can be assessed in a shorter time compared to conservative treatment using other drugs such as MTX. Furthermore, it is presumed that

ethanol acts on mechanism of hemostasis, and in cases of interstitial pregnancy we encountered, massive hemorrhage that is difficult to control did not occur. In addition, a probability of infection is low because of the characteristics of absolute ethanol, which is considered effective for transvaginal operations in the procedures for this therapy. In addition, since a needle with small diameter is used, reduction in hemorrhage and pain could be achieved and thus anesthesia is not required. Moreover, as drug price is lower than that of MTX, physical and medical economic burden in patients are considered to be low. In treatment with anticancer agent such as MTX, when repetitive administration is required because of poor treatment response, adverse reaction to the drug will become an issue, but local ethanol injection involves local area and thus additional local injection is feasible. Furthermore, local ethanol injection therapy is useful even in cases of simultaneous intrauterine and extrauterine pregnancy because it does not affect intrauterine fetus. In our patients who received local ethanol injection for interstitial pregnancy, no adverse reaction occurred. In addition, it is considered that conservative treatment with local ethanol injection therapy can be provided even in patients in whom MTX therapy is not indicated because of tendency to be nonresponsive to MTX therapy due to increases in the number of gestational weeks, high hCG level, or a positive fetal heart rate.

We will accumulate cases in the future to sufficiently evaluate the efficacy and safety of local ethanol injection therapy as well as management of pregnancy and delivery after fertility preservation treatment in cases of interstitial pregnancy.

## Conclusion

It is considered that local ethanol injection therapy for interstitial pregnancy can be one of safe and effective treatment methods as a novel treatment method.

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