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## **Technical Notes:**

# **Local Injection of Methotrexate Ultrasound guided-transvaginal**

### **A Franco GENT study**

Marie Allegrini<sup>1</sup>, Guillaume Legendre<sup>2</sup>, Yohann Dabi<sup>3</sup>, Thibault Thubert<sup>4</sup>, Marine Joste<sup>1</sup>, Vincent Lavoué<sup>1</sup>, Krystal Nyangoh Timoh<sup>1,5</sup>

<sup>1</sup>Department of Gynecology and Obstetrics and Human reproduction, CHU Rennes, Rennes, France

<sup>2</sup> Department of Gynecology and Obstetrics, CHU Angers, Angers, France

<sup>3</sup> Department of Obstetrics and Reproductive Medicine, Hôpital Tenon, Sorbonne University

<sup>4</sup> Department of Obstetrics and Gynecology, Nantes University Hospital, Nantes.

<sup>5</sup>University Rennes 1, France, INSERM, LTSI - UMR 1099

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## Abstract

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3 Non-tubal ectopic pregnancies can be located in the uterine portion of the tube (interstitial or cornual),  
4 in the cervix (cervical), in a caesarean scar, in the ovary, or intra-abdominally. Even though they are  
5 rare, they are associated with a high mortality. Invasive surgeries such as cornuectomy and hysterectomy  
6 were common to treat them in case of hemorrhage. Thanks to recent advances in imaging techniques,  
7 diagnosis of non-tubal ectopic pregnancy is made earlier and conservative management has been  
8 developed in order to respect fertility of patients. Beyond these treatments, systemic or local injection  
9 of Methotrexate shows very good success.  
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14 In the article, we aimed to describe the technics of vaginal injection of in situ methotrexate with  
15 ultrasound guidance.  
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17 **Key-words:** non-tubal ectopic pregnancy- surgery- fertility- methotrexate in situ injection-ultrasound-  
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## Introduction

Ectopic pregnancies (EP) represent 2% of all pregnancies [1]. The tubal ectopic pregnancy is the most common localization. Non-tubal ectopic pregnancies (NTEPs) are rarer and account for less than 10% of EPs [2]. NTEPs are associated with a higher mortality rate than tubal EPs because of delay in diagnosis and greater risk of life-threatening bleeding with need for emergency surgery such as hysterectomy[3].

Recent advances in imaging techniques facilitate an earlier diagnosis of NTEPs allowing conservative treatment to avoid invasive surgeries (cornuectomy, hysterectomy)[4]. This conservative treatment is reserved for patients who are hemodynamically stable and with few symptoms, in order to preserve subsequent fertility in young patients. To date, there is no consensus on treatment modalities for patients with NTEPs.

One of the therapeutic options, when patients are hemodynamically stable, is a treatment consisting of in situ injection of Methotrexate which can be performed either vaginally or laparoscopically.

We propose the technical description of in situ injection of methotrexate by vaginal route.

## Technical details

The patient must be informed of modalities and of the potential risk of immediate bleeding requiring emergency laparoscopy; but also, of the risk of failure that may lead to additional injections of Methotrexate or to emergency surgery.

It is also necessary to verify the absence of contraindication to the realization of this technique and of contraindication to MTX itself. Also, these following indispensable prerequisites must be seek:

- The certainty of the diagnosis: uterine vacuity, high beta HCG and ultrasound criteria for NTEP (cf table 1)
- From a clinical perspective: no suspicion of intraperitoneal hemorrhage: hemodynamically stable patient with little or no symptoms.
- From a clinical perspective
  - no intraperitoneal hemorrhage
  - vaginal access to the NTEP. This condition is mandatory before offering this technique via the vaginal route. In order for it to be fulfilled, the gestational sac of the NTEP must be located directly in contact with the endo-vaginal probe without any interposed structure (vessels, bowel)

## Local injection of methotrexate via vaginal route

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3 This procedure is usually performed in the operating room under general anesthesia or rachi- anesthesia,  
4 as for oocyte retrieval.  
5

6 The patient is settled in a gynecological position. Surgical asepsis must be performed.  
7

8 The sterile operating table is prepared (Figure 1).  
9

10 A bladder evacuation catheterization is performed at the beginning of the procedure in order to avoid  
11 bladder injury during the puncture and to bring closer the gestational sac of the NTEP towards the endo-  
12 vaginal probe.  
13

14 A pelvic ultrasound with an endo-vaginal probe with a ring or operating channel starts the procedure.  
15

16 Using the marker available on the ultrasound machine, the desired needle path is marked beforehand.  
17

18 Digestive or vascular structures interposed between the endo-vaginal probe and the gestational sac of  
19 the NTEP, that would contraindicate the procedure, are searching. Also, the presence of cardiac activity  
20 is searched if an embryo is present. However, presence of cardiac activity doesn't represent a  
21 contraindication.  
22

23 An oocyte puncture needle (17 gauge and 33 cm in length) is then introduced through the operating  
24 channel of the vaginal probe and guided by ultrasound into the gestational sac (Figure 2). Once the  
25 needle is in the gestational sac, a brief aspiration of the gestational sac fluid is performed. This aspiration  
26 confirms the correct positioning of the needle within the gestational sac, interrupts the evolution of  
27 NTEP, and limits the risk of rupture secondary to the increasing volume in the sac after methotrexate  
28 injection. Methotrexate is injected at the dose of 1mg/kg. Aso, a "whirlpool" within the gestational sac  
29 is visualized as evidence of on-site injection of the therapeutic product. Since the injection needle is  
30 often long, it is necessary to reinject the remaining product in the needle by pushing a syringe full of air.  
31 If an embryo with cardiac activity was present, the cessation of its cardiac activity is visualized, which  
32 is an important success factor (video 1).  
33

34 At the end of the procedure, a pelvic ultrasound (appearance of a medium or large intraperitoneal  
35 effusion) and inspection of the cervico-vaginal tract with the speculum (bleeding) are used to check for  
36 complications such as intraperitoneal hemorrhage.  
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38 This procedure takes an average of 10 minutes.  
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## Monitoring, follow-up and post-operative care

Monitoring of patients with NTEP must be rigorous.

This procedure can be realized in an outpatient way.

$\beta$ -hCG levels must be monitored as for classical tubal EPs. Classically, we perform BHCG levels on Day 4, Day 7 after the local injection and then every week until negativation [5]. In the event of stagnation of BHCG, a second injection of methotrexate, by the intramuscular route, may be used.

Pelvic ultrasound is performed only if symptoms such as pelvic pain or metrorrhagia are present to seek for a intraperitoneal hemorrhage.

## Discussion

The therapeutic arsenal for managing patients with NTEP includes hysterectomy, cornuectomy, systemic injection of therapeutic product, or in situ by vaginal or laparoscopic route. In the absence of a codified treatment unlike for tubal EPs, the choice of therapeutic strategy takes into account several parameters: clinician's experience, availability of the therapeutics, protocol of the center, context, patient preferences, etc.

NTEP can be located in the uterine portion of the tube (interstitial NTEP in the context of a healthy uterus or cornual NTEP in the context of history of salpingectomy/ uterine malformation), in the cervix (cervical NTEP), in a caesarean scar, in the ovary, or intra-abdominally[6]. The location of the NTEP is obviously decisive in the choice of strategy: some locations are not accessible to vaginal procedure, while others would not be easily treated by laparoscopy.

The diagnostic criteria of these NTEP must be known and constitute the foundation for adequate management of these NTEP (Table 1)[3]. With the improvement of early detection of these NTEP, the current challenge is to treat these young patients of childbearing age in a minimally invasive manner while preserving their tubal and uterine fertility

In situ injection of methotrexate has shown excellent results with a success rate of 70-100% [7-9]. Also, second injection of MTX can be proposed systematically after the local injection. To date, the in-situ injection route has not been shown to be superior to the systemic route. The advantage of the vaginal route compared with the laparoscopic route is its minimally invasive nature, the guidance provided by endo-vaginal ultrasound and the real-time confirmation of the effectiveness of the procedure by stopping the cardiac activity. It also seems possible in the future to carry out this procedure outside the operating theatre without anesthesia, as Timor Trisch points out, thus further reducing its invasive nature[6]. The ultrasound-guided vaginal route is widely used in the field of obstetrics and gynecology, particularly for oocyte punctures, but also for evacuation of tubal abscesses in the context of upper genital infections. This method is therefore simple, quick to learn and promising.

The main disadvantages of this route are:

- 1) The possibility of intraperitoneal hemorrhage. However, the rate of emergency haemorrhage secondary to this procedure is low. In a series of 64 patients, Delplanque et al observed that only one patient with NTEP required emergency laparoscopy for hemorrhage and was treated by cornuectomy after in situ injection[10]. It should be noted that in the same series, three patients had laparoscopies for hemorrhage in the follow-up after systemic injection of methotrexate.
- 2) The need for prolonged monitoring because the decrease in Beta HCG levels is often long. In the same series, Beta HCG decreased by 15% in 12 days[10].
- 3) The non-accessibility of all the locations of NTEP by the vaginal route.



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Other therapeutic agents besides methotrexate are also possible: KCL (cardiotoxic to be reserved if cardiac activity and indicated if heterotopic pregnancy), and hyperosmolar glucose serum [6]. Finally the adjunct of Mifepristone (RU 486) in addition to Mtx in situ in case of elevated progesterone (level >10 ng/ml) must be discussed as suggest by the study of Rozenberg et al [11].

This minimally invasive approach preserves the integrity of the genital tract necessary for subsequent fertility of patients by avoiding surgical treatment such as cornuectomy or hysterectomy.

The injection of methotrexate in situ is a simple and rapid procedure that can be used to treat NTEP.

Table 1

**Ultrasound-based criteria for non-tubal ectopic pregnancies** (by Dolinko et al, [3])

Type of Ectopic Pregnancy	Ultrasound Criteria
Abdominal Pregnancy	<ul style="list-style-type: none"> <li>- Absent intra uterine gestation</li> <li>- Absent of dilated tube and complex adnexal mas</li> <li>- Gestational sac, trophoblastic mass, placenta, and/or fetus seen separate from the uterus, tubes, and ovaries</li> <li>- Gestational cavity surrounded by loops of bowel and separated by peritoneum</li> <li>- Significant mobility/fluctuation of the sac with pressure of transvaginal probe toward the posterior cul-de-sac</li> </ul>
Intraligamentous Pregnancy	<ul style="list-style-type: none"> <li>- Absent intra uterine gestation</li> <li>- Gestational sac and/or fetus seen outside and adjacent to the lower part of the side of the uterus</li> </ul>
Cervical Pregnancy	<ul style="list-style-type: none"> <li>- Absent intra uterine gestation</li> <li>- Barrel-shaped cervix</li> <li>- Gestational sac or trophoblastic mass below the level of internal cervical os</li> <li>- Negative “sliding organ sign*”</li> <li>- Peritrophoblastic circulation using color Doppler</li> </ul>
Cesarean Scar Pregnancy	<ul style="list-style-type: none"> <li>- Absent intra uterine gestation</li> <li>- Gestational sac located anteriorly at the level of the internal os covering the visible or presumed site of the previous lower uterine segment cesarean section scar</li> <li>- Peritrophoblastic circulation using color Doppler</li> <li>- Negative “sliding organ sign*”</li> </ul>
Interstitial Pregnancy	<ul style="list-style-type: none"> <li>- Absent intra uterine gestation</li> <li>- Eccentrically located gestational sac &gt;1cm from endometrial stripe with continuous rim of myometrium measuring &lt;5-8mm</li> <li>- Interstitial line sign</li> </ul>

Cornual Pregnancy	<ul style="list-style-type: none"> <li>- Pregnancy occurring in the horn of an anomalous uterus (e.g. bicornuate or unicornuate uterus)</li> </ul>
Ovarian Pregnancy	<ul style="list-style-type: none"> <li>- Empty uterine cavity</li> <li>- Cystic structure with wide echogenic ring on or within ovary</li> <li>- Embryo or yolk sac within the cyst is diagnostic</li> <li>- Negative “sliding organ sign”</li> </ul>
Heterotopic Pregnancy	<ul style="list-style-type: none"> <li>- Both intrauterine pregnancy and a tubal or non-tubal</li> </ul>

Legends:

Figure 1:

Operative table showing the indispensable instruments required: the needle, urinary catheter, syringe, the probe protection, the speculum.

Figure 2:

Sonographic image of an interstitial NTEP during a local injection of methotrexate via vaginal route.

White arrowheads show the needle.

Video:

The movie shows the puncture of the gestational sac fluid. Methotrexate is injected at the dose of 1mg/kg. A "whirlpool" within the gestational sac is visualized as evidence of on-site injection of the therapeutic product.

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**Video**

video NTEP Mtx in situ .mp4

