



Case Report

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Combination of Methotrexate and Kcl Injection for Bilateral Tubal Ectopic Pregnancy

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Abstract

This is a case report conducted in National Guard Hospital, Riyadh, Saudi Arabia, presenting 27 years old primigravida, who had an induced pregnancy by Clomiphene, presenting at 6 weeks + 4 days of gestation by her last menstrual period. The patient complained of a 14-day history of brownish vaginal discharge and left lower abdominal pain. Trans-vaginal ultrasound assessment revealed bilateral tubal ectopic pregnancy with a viable fetus in the right adnexa. Ultrasound-guided Potassium Chloride injection was performed on the viable gestational sac. Further management was in the form of a three-dose Methotrexate regimen. Hysterosalpingography performed three months following the first Methotrexate dose showed bilateral patent tubes. The patient conceived spontaneously after 4 months of treatment and delivered vaginally at 39 weeks.

Introduction

Ectopic pregnancy, the implantation of a fertilized ovum in a place other than the endometrium of the uterus, is a leading cause of maternal death [1,2]. The rarest form of ectopic pregnancy is bilateral tubal ectopic pregnancy (BTP), with an incidence of 1 per 725 to 1 per 1580 of all ectopic pregnancies [3]. The incidence in live births is equal to 1/200,000 live births [4]. Given the similar presentation of BTP and unilateral tubal ectopic pregnancy the diagnosis is rarely made preoperatively [5]. The incidence of BTP is increasing given the growing use of assisted reproductive techniques [3].

Tanaka et al initially described the use of Methotrexate as a treatment for un-ruptured ectopic pregnancy, and since then, it has been a well-established conservative method for the management of such cases [6,7]. Methotrexate as a treatment for ectopic pregnancy compared to surgical treatment is cost-effective and has

a similar success rate [8]. Factors associated with lower rates of success and therefore regarded as relative contraindications for the use of Methotrexate in the treatment of ectopic pregnancy include fetal cardiac activity, Beta hCG levels greater than 5000 mIU/ml, and an ectopic mass sized greater than 4 cm [9].

We present a case report of a simultaneous, bilateral tubal ectopic pregnancy with a viable fetus in the right adnexa, treated medically with a combination of ultrasound-guided trans-vaginal Potassium Chloride injection and systemic Methotrexate. To the researcher's knowledge, there is no published data of a similar case report.

Case presentation

This is a case of a 27-year-old female, married for 1year, primigravida, at 6 weeks + 4 days of gestation by her last menstrual



period. Her pregnancy was induced by Clomiphene. She had a negative past medical and past surgical history. The patient denied any history of pelvic inflammatory disease, chronic pelvic pain, or use of hormonal contraception.

She presented to the emergency room with a 14-day history of per vaginal brownish discharge and left lower abdominal pain. Upon examination she was well and not in pain. Her vital signs were Blood pressure (117/56 mmhg), heart rate (100 beat/min), respiratory rate (19 breath/min), temperature (36.8 degrees Celsius). Her abdomen was soft and non-tender. On digital vaginal

examination the external OS was closed and there was no bleeding. During this visit, the Beta hCG level was 6423.5 mIU/ml. Her laboratory investigations (complete blood count, liver function test, and kidney function test) were all normal. An official gynecological Trans-vaginal ultrasound was performed as well. The ultrasound showed; an empty uterus, right adnexal extra-uterine gestational sac (measuring 19x13x19 mm) with a single viable fetus, left adnexal heterogenous mass (measuring 12x13x12 mm) with anechoic center and minimal blood flow (Figure 1). Based on this, the diagnosis of a bilateral tubal ectopic pregnancy was confirmed, with a viable fetus in the right tube.

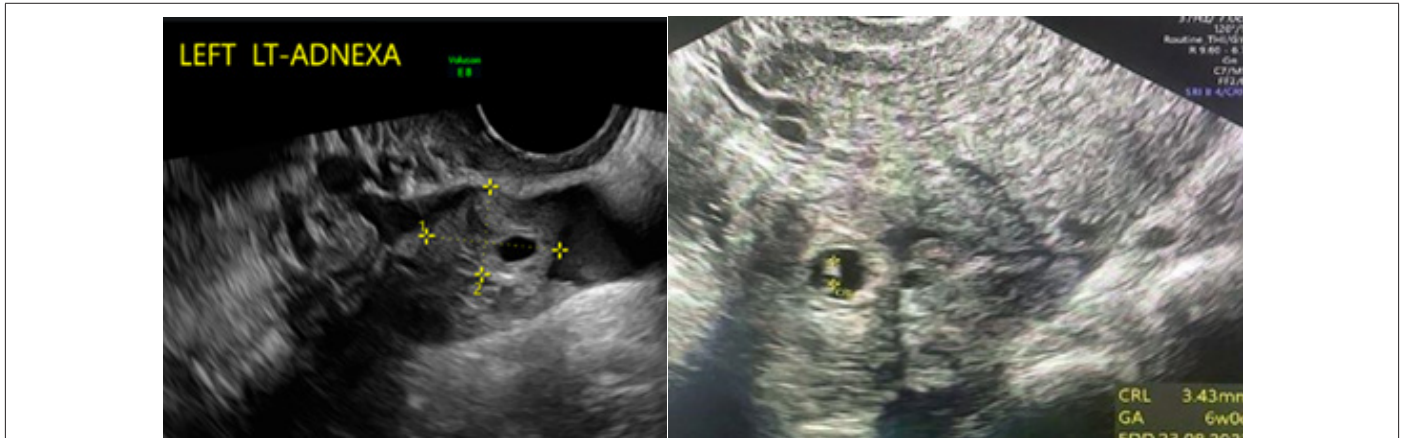


Figure 1: Transvaginal ultrasound showing bilateral tubal ectopic pregnancy.

Based on her diagnoses, the patient was counseled regarding the management options (surgical VS medical), explaining the process, risks, and benefits of each. As the patient had a strong desire to preserve her tubes for future pregnancies, she opted for the medical management option in the form of Potassium Chloride injection to the viable fetus followed by systemic Methotrexate as in-patient management. Therefore, the risk of failed medical management and the need for surgery with salpingectomy in case of rupture ectopic pregnancy was explained.

The patient was then admitted to the ward and was kept fasting (NPO). She was then shifted to the radiology department and underwent the procedure of trans-vaginal ultrasound-guided Potassium Chloride injection (2 ml of KCL) into the viable fetus (on the right fallopian tube). The procedure was straightforward with no complications. The patient was then transferred to the wards for observation. On the same day she received the systemic Methotrexate injection (88 mg, intramuscularly). Two days following the Potassium Chloride injection and Methotrexate administration, the patient was seen and examined, she was vitally stable, had no complaints, thus, she was discharged with a scheduled readmission after two days for a second Methotrexate dose.

Four days following the Methotrexate injection, the patient was admitted for the second dose. Her Beta hCG level was: 3363.0 mIU/ml and laboratory investigations were normal. Therefore, the second dose of Methotrexate was given. She was kept overnight for observation. On the next day, she was clinically stable. Therefore, she was discharged with a plan of repeating Beta HCG on the 7th day following the first Methotrexate administration.

Upon her visit, on the 7th day post Methotrexate administration, the Beta hCG level was 2884.7 mIU/ml. As this drop was less than 15.0% compared with day 4 (3363.0 mIU/ml), the patient was re-admitted for a third dose of Methotrexate. Although the patient was clinically stable and had no pain, she complained of mild brownish vaginal discharge. The third methotrexate dose was administered, and the patient was subsequently discharged with the plan of repeating Beta HCG on day 11 from the first Methotrexate dose.

On day 11 of Methotrexate injection, she had no complaints apart from minimal vaginal bleeding. She was clinically stable. Her Beta hCG level dropped to 1520.0 mIU/ml. She was discharged with a planned review within a week.

Our patient was reviewed weekly for three consecutive weeks. During her reviews, her Beta HCG levels showed a progressive decrease, 377, 21 reaching 2.4 mIU/ml by the third week. Although she had minimal vaginal bleeding during the first two visits, by the third visits she had no complaints. She started on oral contraceptive pills (Marvelon) and a Hysterosalpingography was scheduled for her after three months.

During the follow up period, the patient was counseled regarding the red flags symptoms that require a visit to the emergency department, in case of experiencing symptoms related to rupture of ectopic pregnancy (ex. severe abdominal pain, per vaginal bleeding, and pain radiating to shoulders).

Three months later, a Hysterosalpingography (HSG) was performed as scheduled and yielded; a normal endometrial cavity, patent fallopian tubes, and a mild left hydrosalpinx (Figures 2,3).

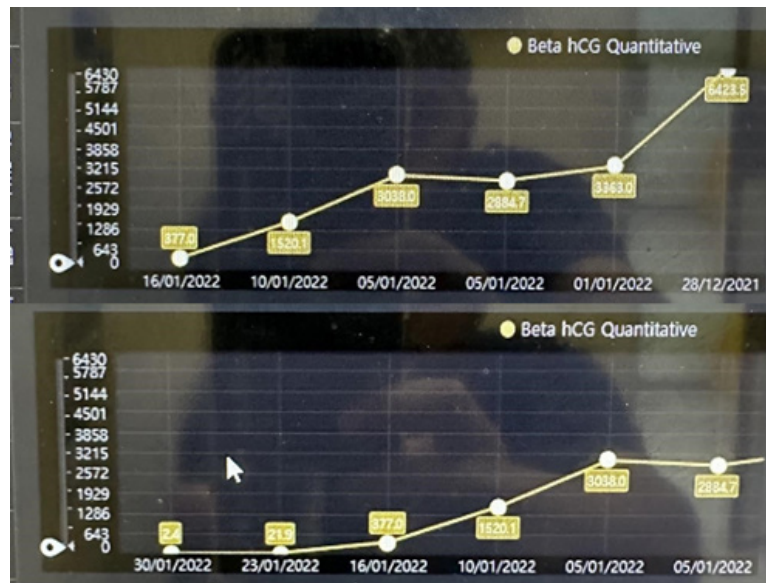


Figure 2: Patient's Bhcg trend following ultrasound guided KCL injection and methotrexate injection. 28/12/2021 is the day of the procedure and the first methotrexate dose.



Figure 3: Hysterosalpingography highlighting left hydrosalpinx.

In regard to her condition, the patient was counseled about the increased risk for future ectopic pregnancies and the importance of prompt assessment with close monitoring in case of amenorrhea, and to seek urgent medical assessment if she develops any symptoms of abdominal pain or vaginal bleeding.

After 4 months of the previous mentioned event, the patient was presented to our hospital with amenorrhea of 6 weeks, BHCG of 4575 mIU/ml, and a pelvic ultrasound which showed a viable intrauterine pregnancy corresponding to the gestational age. Moreover, she had uneventful antenatal visits, with regular follow ups, and delivered vaginally at term.

Discussion

We presented a case of simultaneous bilateral tubal ectopic pregnancy with a single viable fetus, which was treated via ultrasound-guided Potassium Chloride injection and 2 doses Methotrexate injections.

There are multiple theories regarding the mechanism of Bilateral Tubal Ectopic Pregnancy (BTP). One hypothesis is the migration of trophoblastic cells trans-peritoneally [10]. An additional theory is based on multiple ovulatory processes, with one oocyte being fertilized and subsequently implanting in sites

of tubal damage [11]. Lastly, Superfetation, the fertilization and development of an additional oocyte in a pregnant woman, has been proposed as mechanism for BTP [10,12].

BTP is most commonly diagnosed intraoperatively [5]. Measurement of Beta hCG was shown to be ineffective in diagnosing BTP [13,14]. Clinically, BTP and unilateral tubal ectopic presentation share the same clinical picture [15]. Nevertheless, in this study, the diagnosis of BTP was made preoperatively. An initial private clinic TVUS revealed only unilateral tubal ectopic pregnancy, but after conducting an additional TVUS in our institute, an additional gestational sac was revealed in the contralateral adnexa. This highlights the importance of thorough ultrasound assessment in ectopic pregnancy even if an extrauterine gestational sac was found, especially in high-risk patients (ex. post ovulation induction).

Assisted reproductive technology increases the risk of ectopic pregnancy including BTP [3,16]. In this case report, the patient's pregnancy was induced by Clomiphene. Clomiphene is classified as a selective estrogen receptor modulator, inhibiting the hypothalamic negative feedback exerted by circulating estrogen, therefore increasing the secretion of gonadotropin-releasing hormone, ultimately resulting in higher levels of follicle stimulating hormone and luteinizing hormone [16]. Clomiphene can cause poly-ovulation which could explain its role in the development of BTP [3].

Although fetal cardiac activity and Beta hCG levels greater than 5000 mIU/ml are associated with lower Methotrexate success rates and regarded as relative contraindications to its use in ectopic pregnancy [9], in this case report it was used successfully. Ultrasound-guided trans-vaginal injection of Potassium Chloride (KCL) was firstly done to induce fetal asystole, postulating that this would increase the effectiveness of Methotrexate treatment. This technique was first described by *Aboulghar, et al.* [17] and *Verma & Jacques* [18], where live tubal pregnancies were treated successfully through KCL injection in the ectopic pregnancy and a single dose of systemic Methotrexate. In a more recent study, *Dadhwal, et al.* reported successful management of live tubal ectopic pregnancy by

ultrasound-guided Potassium Chloride injection and Methotrexate [19].

Given the high pre-treatment Beta hCG level (6423.5 mIU/ml), two doses of Methotrexate were administered in this study. In a systemic review, a single dose of Methotrexate treatment had a 3.7% failure rate among patients with a Beta hCG level less than 5000 mIU/ml compared to 14.3% failure rate among patients with a Beta hCG level greater than 5000 mIU/ml [20]. Furthermore, *Alleyassin et al* found that multiple doses of Methotrexate are more effective among patients with high Beta hCG levels (greater than 5000 mIU/ml) [8]. In 2022, *Obaid et al* reported the successful management of a live tubal ectopic pregnancy with high Beta hCG titers by a two-dose Methotrexate regimen [21].

Given the absence of a current treatment guideline for the management of BTP, methods of treatment adopted by previous case reports of BTP vary. *Benz, et al.* and *Hoffman, et al.* both reported a case of BTP discovered incidentally during a laparoscopy for unilateral tubal ectopic pregnancy [5,22]. In concordance with our study, *Benz, et al.'s* patient was on Clomiphene [5]. She was treated by unilateral salpingectomy and salpingotomy for the contralateral ectopic pregnancy [5], while bilateral salpingotomy was performed in *Hoffman et al* report [22]. *Nyakura et al* reported a case of ultrasound-diagnosed unilateral ruptured ectopic pregnancy [23]. At laparotomy, ruptured BTP was noted, and bilateral salpingectomy was performed. [23].

Similar to our study, *Niviti et al* described an ultrasound-based diagnosis of BTP, however in their case, the BTP was ruptured, and therefore bilateral salpingectomy was carried out via laparotomy [24]. In a recent case report (2022), *Masten et al* reported a case report of a lady that underwent laparoscopy secondary to ruptured ectopic pregnancy [25]. The patient underwent salpingectomy for the ruptured ectopic pregnancy, however, upon inspection a contralateral un-ruptured ectopic pregnancy was revealed and was expelled through mobilization of the fallopian tube [25]. To add, two doses of Methotrexate were then administered [25] (Figures 4,5).

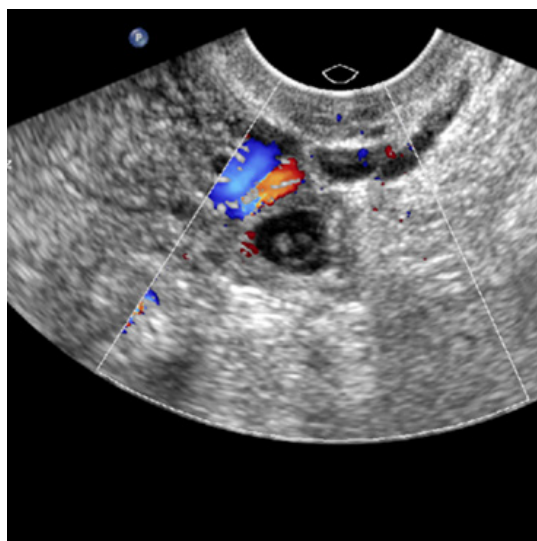


Figure 4: Before KCL injection.

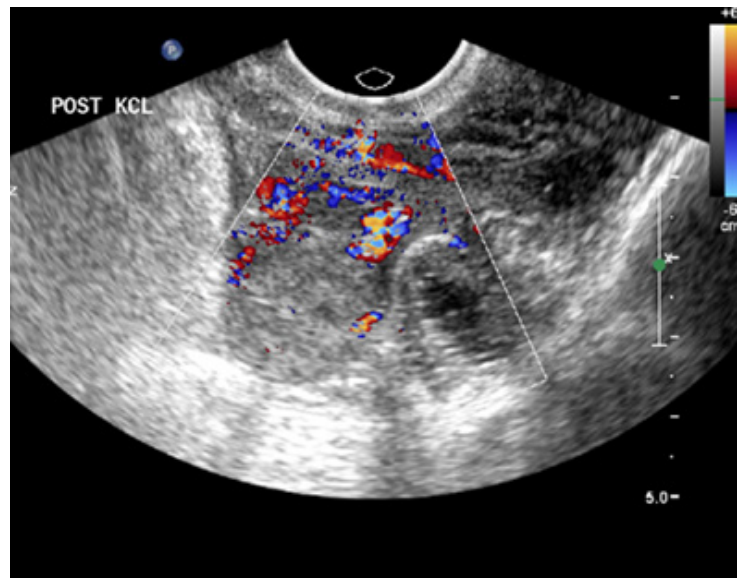


Figure 5: After KCL injection.

This study adds to the growing pool of knowledge demonstrating the effectiveness of the combination of ultrasound-guided Potassium Chloride injection and Methotrexate as a conservative form of management for bilateral tubal ectopic pregnancy with a viable fetus. To the researcher knowledge, this represents the first case report of a medically managed BTP with a single viable fetus.

Conclusion

Methotrexate injection combined with Potassium Chloride is an effective treatment option to avoid surgical intervention, particularly when a medically based treatment VS surgery has a higher chance of future conception if the patient wants to preserve fertility. In cases of medical management, frequent and close monitoring is mandatory to assess the patient's progression and detect treatment-related or ectopic pregnancy-related complications. Many cases will need to be conducted to establish a criterion and build a protocol to choose nonsurgical intervention as a treatment of bilateral tubal ectopic pregnancy.

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