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Case Report

Spontaneous Conception Following Treatment of Tubal Pregnancy with Methotrexate: A Case Report and Review of Literature

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Abstract

Ectopic pregnancy, defined as a fertilized ovum that implants outside of the uterine cavity, the commonest site being the uterine tube, occurs in about 2.0% of reported pregnancies. It's a major life-threatening pregnancy complications and a leading cause of first trimester pregnancy-related deaths.

Due to increased awareness, advances in diagnostic technologies and improved access to health care, more cases of ectopic pregnancies are being diagnosed early, high resolution transvaginal ultrasound combined with quantitative sensitive β-hCG being a useful tool in this regard. Early diagnosis has made it possible for a wider choice of therapeutic options. There is a growing trend towards non-invasive or conservative management approaches for unruptured ectopic pregnancy, to reduce related costs, morbidity and mortality and preserve fertility. This may include medical management, for which systemic methotrexate, is an acceptable option with good success rates, preservation of future fertility, it's cost-effective and with no long term negative impact on the patient's wellbeing.

While this has been used widely in the developed regions of the world, its use in developing regions including sub-Saharan Africa, has remained quite low or none, for various reasons. As a result thereof, related publications from the region are non-existent.

A 32 year old nulliparous lady, currently pregnant, following natural conception after successful treatment with methotrexate, in East Africa, is presented with review of literature.

Keywords: *Tubal Pregnancy; Methotrexate; Ectopic Pregnancy; β-hCG*

Introduction

Ectopic pregnancy occurs when a fertilized ovum implants outside of the uterine cavity, with the uterine tube accounting for 95 - 98% of them [1,2] and the rest occurring in the uterine cervix, the ovary, and abdominal cavity [2,3]. Location of a small proportion of ectopic pregnancies is unknown and these are referred to as "pregnancy of unknown location (PUL)" [4].

The incidence of ectopic pregnancy is reported to have increased globally over the recent past chiefly due to advances in technologies and risk factors thereto. It varies from one region to another and even within regions and countries, due to differences in the prevalence of its risk factors, the degree of awareness, access to health care and diagnostic capabilities [5,6]. Gamzu., *et al*. (2002) reported an incidence of 2.0% of diagnosed pregnancies in the USA [7]. The actual incidence in Africa and other developing regions of the world might be much higher than this due to challenges in making accurate diagnosis and the fact that some ectopic pregnancies resolve spontaneously without any intervention and may therefore not be documented, as well as poor documentation.

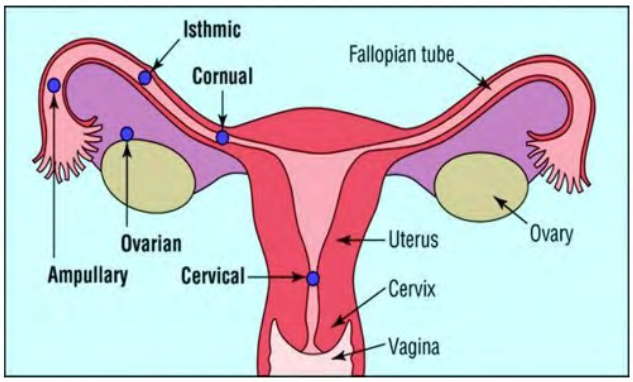

Figure 1: *Ectopic locations in the uterine tube.*

One of the major complications of ectopic pregnancy especially tubal, is rupture usually between 6 - 8 weeks gestation. The resultant hemorrhage being the main cause of maternal deaths, estimated to account for about 73% of first trimester deaths [8]. Ectopic pregnancy contributes to 10 - 15% of all MDs [9,10] and Leke RJ., *et al*. (2004) reported that mortality from EP in developing countries was 10% in women diagnosed with EP, due to late diagnosis [11].

Improved diagnosis and management of ectopic pregnancies in recent decades have seen a significant reduction in related morbidity and mortality. McGurk., *et al*. (2019) reported that the mortality has dropped to as low as 0.35% and 0.5% in the UK and USA respectively [12]. The correct situation in sub-Saharan Africa is not as clear for various reasons [13]. With improved diagnostic capabilities, especially high-resolution transvaginal vaginal ultrasonography which has high sensitivity and specificity, combined with highly sensitive quantitative serum β-hCG, it is possible to make an early an accurate diagnosis thus enabling the attending physicians to have a wide choice of therapeutic options [14]. These include expectant and medical approaches for small and un-ruptured ectopic with low β-hCG levels, or surgical i.e. salpingostomy or salpingectomy, through either laparoscopic or open laparotomy for the others or failed expectantly and medically treated ones [15-17]. Medical approach with either single- or multiple doses of methotrexate, a folic acid antagonistic, has been used on patients who have small un-ruptured adnexal masses (< 4 cm), with no foetus or cardiac activity and no co-existing intrauterine pregnancy; low β-HcG levels (1500 - 5000 mIU/ml); who are haemodynamically stable; desire to preserve their fertility and have no contraindications to the use of methotrexate [10,18,19].

Preservation of fertility is one of the main concerns among women diagnosed with ectopic pregnancy is one of their major concerns. It is also one of guiding principles in the choice of therapeutic option for ectopic pregnancy. Whereas the best approach in preserving spontaneous fertility is yet to be determined [20], medical treatment with methotrexate, especially the single-dose protocol, has been shown to particularly not affect future fertility as it does not impair ovarian reserve and preserves tubal patency and function [21-23]. Its success rate in maintaining tubal patency and for subsequent spontaneous fertility reported to be 67 - 80% [24-26], has been said to be comparable to those of conservative surgical approach i.e. salpingostomy [27].

This paper presents a 32 year old nulliparous, married African woman successfully managed medically with the use of two single-doses of methotrexate, 75 mg IM, by the author in his private clinic in Nairobi Kenya. She conceived spontaneously exactly a year after the treatment and the pregnancy is going on well so far.

Case Presentation

KCW, a 32 year old lady, para 0+0, was planning her wedding, and intended to delay pregnancy for at least six months, when together with her fiancé then, now her husband, came to see me for contraceptive advice in December 2020. After physical examination and counselling they opted for the combined oral pills (microgynon) which was duly prescribed. I saw her again 14 months later, February 2022, with a 5-weeks amenorrhoea and early symptoms of pregnancy, i.e. nausea, breast discomfort and sensitive nipples. A home urine pregnancy test was positive. On physical examination she was not pale, her body-weight was 67 kg and the blood pressure was 112/77 mmHg, with a regular pulse rate of 76/min. A transvaginal ultrasonography showed a thickened endometrial stripe measuring 18 mm, but no evidence of intrauterine or ectopic pregnancy and no free fluid in the cul-de-sac. She was give given an appointment for review and repeat sonography after two weeks as is our usual practice.

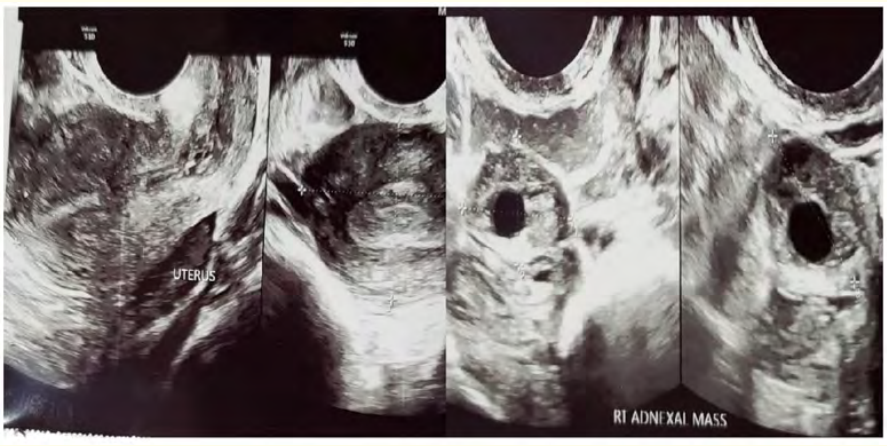

Figure 2: *Showing the ectopic pregnancy.*

Note the empty uterine cavity on the left side and the ectopic with an empty gestational sac on the right.

At this review, the symptoms of pregnancy had increased, but still no vomiting, no abdominal pains or vaginal bleeding. A repeat transvaginal ultrasonography showed a right adnexal mass, measuring 2.5 cm, with no live foetus, no free fluid in the cul-de-sac and no intrauterine pregnancy. She was not pale clinically, had normal vital signs and no abdominal tenderness. She did not have previous history of any major illnesses or allergies. The couple was appraised of the findings and diagnosis, as well as potential complications and were counselled on the various modes of treatment. They were given the pros and cons of each treatment approach and criteria for the expectant and medical approaches. The couple was concerned about future fertility and risk of recurrence. After counselling they opted for the medical option. The serum β-HcG level was 7092 mIU/ml, liver and renal function tests and haemogram were within normal limits. She was given methotrexate 75 mg IM, and discharged home with clear instructions of what to observe for and to contact the gynaecologist in case of any unusual symptoms.

When reviewed four days later she had not experienced any serious symptoms, only mild muscle pains in both legs the first two days, which had subsided spontaneously. She was haemodynamically stable, no abdominal pains or tenderness. The serum β-hCG level was 9652 mIU/ml and a pelvic sonographic examination showed the same findings as before. She was reassured and advised to continue monitoring. A review on day 7 from initiation of treatment, showed normal vital signs, no abdominal tenderness or vaginal bleeding. The serum β-hCG level was 4594 mIU/ml, the liver and renal function tests, haemogram and urinalysis were all normal. An ultrasound showed

the same-sized adnexal mass and minimal fluid in the cul-de-sac. They were reassured that she was responding well to the treatment, but they expressed concern that the mass was still the same, wanted a more rapid resolution thereof, and wanted a second dose, which was given. She was followed up on a weekly basis and the serum β-hCG level continued to drop. It was 1775 mIU/ml a week later and 553.86 mIU/ml two weeks later. Pelvic ultrasound showed the same-sized mass but no increased vascularity as before. Her last visit was on 12/05/2022, two months after the initial treatment. The β-hCG levels were down to normal < 5 mIU/ml, a pelvic ultrasound showed the same adnexal mass and an endometrial stripe measuring 9.5 mm in thickness. At this stage she was considered to have recovered and was discharged from the clinic to be seen in case of any issues or if she conceived.

She presented exactly 12 months later, in early May 2023, with a history of amenorrhea for 5 weeks, and a transvaginal ultrasonography showed an intrauterine gestational sac, equivalent to a 5 week and three days pregnancy, no foetal pole, no adnexal mass and no fluid in the cul-de-sac. She was reviewed and had a pelvic sonographic examination two weeks later, which confirmed a live intrauterine pregnancy of 7 weeks. She was put on supportive antenatal supplements and appointed to be seen biweekly till 14 weeks gestation. So far the pregnancy is progressing well.

Discussion

Management of ectopic pregnancy has improved significantly in the recent past, thanks to advances in diagnostic technologies, which have made early and accurate diagnosis possible. High resolution transvaginal ultrasound (TVUS), with an accuracy of 90% [8], a sensitivity of 87 - 99.0% and specificity of 94 - 99.9% [4]. A low discrimination level of β-hCG (1500 mIU/ml), is a very useful tool for early diagnosis of ectopic pregnancy [28]. This has made possible the use of non-invasive therapeutic options [21,29]. The presented patient had the diagnosis made at a fairly early stage. The presence of an adnexal mass, which had not been there two weeks before, an empty uterine cavity with a positive pregnancy test and amenorrhea of 7 weeks, early symptoms and signs of pregnancy, were sufficient to make the diagnosis in her case.

Systemic methotrexate (MTX), the most commonly used medical treatment option, involves either a single-dose or multiple-dose protocol [30,31]. The choice of a medical approach using single dose methotrexate, 50 mg/m^2, for her treatment was considered appropriate as she fulfilled the requisite criteria. The adnexal mass was small (< 4.0 cm), there was no foetal pole, the uterine cavity was empty, nol fluid in the cul-de-sac, β-hCG of 7092 mIU/ml, and she was haemodynamically stable. The relevant laboratory tests, i.e. liver and kidney function and haemogram were within normal limits. She did not have history of any serious illnesses priorly and no allergies. She desired to preserve her fertility and conceive as soon as possible as they did not have a child, and was prepared and ready to follow all given follow-up instructions.

With proper selection of qualifying candidates for systemic methotrexate either single- or multiple dose protocol, success rates of up to 95% have been reported [4,10,19,26]. Some of the predictors of success include size of the adnexal mass (< 4.0 cm); absence of foetus or foetal cardiac activity, or no gestation sac seen in the mass, low β-hCG levels (< 5000 mIU/ml) [17,31,32]. A small rise in the β-hCG levels of 11 - 20% in the last 48 hours before treatment has been reported to be associated with higher success rates [17] and so too is a drop in β-hCG levels between day 0 and day 4 as opposed to a rise [10,33,34]. We don't know if there was a rise in our patient before treatment as we only did one test just before initiating treatment. Despite a rise of β-hCG between day 1 and day 4 her treatment was successful. Kirk., *et al*. (2006) opined that variation in the success rates may be due to different inclusion criteria with patients who might have healed spontaneously being included [35]. Secondly some studies have used higher cut-off levels of β-hCG with good success rates [10,28,36]. Some authors opine that as long as the patient fulfills the other criteria, the β-hCG level is not an important criterion [10,19].

A rise in the β-hCG levels between days 1 and 4 has been shown to be associated with a lower success rate compared with a drop (42 - 66% vs 85 - 100% respectively [10,33,37]. This is said to be due to effects of methotrexate action on the rapidly divining trophoblastic

cells [19,33] and is therefore not a predictor of treatment failure [33,38]. Many authors state that it's the day 7 β-hCG levels that should be used as a predictor of success instead of day 4 [39]. There was a rise in the β-hCG levels from 7092 mIU/ml to 9682 mIU/ml in our patient between day 1 and day 4, and it did not appear to influence the outcome.

Day	Therapy
1	Serum β-hCG, U&E, LFTs, FBC, blood group, 50 mg/m^2 intramuscular methotrexate
4	Serum β-hCG
7	Serum β-hCG • If β-hCG decrease less than 15% days 4–7, for repeat TVS & methotrexate 50 mg/m^2 if still fulfils criteria for medical management. • If β-hCG decrease greater than 15% days 4–7, for repeat β-hCG weekly until levels less than 15 iu/l.

Table 1: *Single-dose methotrexate protocol.*

A second dose was given as the couple was very anxious and worried that the resolution was not fast enough especially the mass size, despite assurances that she was doing very well as the levels of β-hCG was dropping as expected. Some studies have shown better and faster resolution among patients who received the second single-dose [31,34]. The single-dose protocol has advantages, including the non-necessity of a rescue regimen, a lower incidence of adverse effects and better compliance [40] but is associated with a higher treatment failure rate than the fixed multi-dose protocol [30]. In an attempt to combine the efficacy and convenience of the fixed multi-dose and single-dose protocols a new regimen, called the 'two- dose' protocol was introduced by Barnhart., *et al*. in 2007 [41]. It has been reported that the two-dose protocol minimizes the number of injections and surveillance visits. After the second dose our patient did very well, the β-hCG levels was down to normal by the seventh week from initiation of treatment. The timeframe to resolution ranges from 3 - 7 weeks from initiation of therapy [41].

Preservation of fertility without an increase in the recurrence rates, is one of the major concerns for both patients and the physicians. Although it's been reported that the best therapeutic option is yet to be determined, systemic single-dose methotrexate has been widely used and has a fairly good fertility preservation rates among other benefits such as cost reduction, avoidance of surgically related morbidity [26,41]. Single-dose systemic methotrexate does not impair ovarian reserve and appears to preserve tubal patency and function, as on top of its action on the trophoblasts cells it also helps in the repair of the placenta bed, i.e. tubal epithelium thus restoring tubal integrity [21,22,24]. Tubal obstruction following ectopic pregnancy is related to the degree of trophoblastic tissue invasion of the tube which is reflected in the level of β-hCG, a level of > 5000 mIU/ml, being directly related to tubal obstruction [21,43]. Multiple-dose protocol has been shown to have negative impact both on the placental bed and initial tubal epithelial repair compromising tubal integrity [4,38]. Tubal patency in single-dose treated women is better than in the multiple dose group (83.9 vs. 56.7% respectively), and drug-related tubal epithelial damage might explain the high bilateral tubal obstruction in the multiple dose treated group compared to the single-dose group, 13.3% vs 6.5% respectively [44].

Approximately 30 percent of women treated for ectopic pregnancy have difficulty conceiving thereafter [45]. The rate of spontaneous conception following single-dose methotrexate 50 mg/m^2 is between 67 - 80.7% [19,28,46] and a recurrence rate of 25.5% vs 18.5% in the single and multiple dose respectively [28]. Conception rate is said to be lower in those aged > 35 years, have a history of infertility or

tubal disease [28]. The presented patient conceived naturally within 12 months of completing treatment of ectopic pregnancy and the pregnancy is progressing quite well so far. She is still young < 35 years, had no obvious risk factors for ectopic pregnancy and no history of infertility, we don't know the integrity of the affected tube either now or prior to the ectopic pregnancy. What we are sure of is that at least one tube is patent and it looks like it is the contralateral one as she seemed to have ovulated on that side according to the ultrasound done in the early stages of the current pregnancy. We cannot rule out a risk of recurrence in the future.

She is the first of the two patients I have successfully managed to diagnose before rupture and who fulfilled the criteria for non-surgical intervention i.e. medical option, over a period of 15 months. I am waiting to see if the second one will conceive, how soon and its outcome.

Conclusion

Single-dose methotrexate therapeutic approach for ectopic pregnancy has increased globally especially in the developed countries. It's a cost-effective, safe option for properly selected patients, has good success rates and good fertility preservation rates and no long-term effects on the woman's well-being and quality of life. It'd therefore considered a viable treatment option for those who fulfill the requisite criteria. It is safe and effective for asymptomatic, hemodynamically stable patients with ectopic pregnancies who are interested in conservative treatment, regardless of the serum β-hCG level or adnexal mass size.

It is heartening to see that we can make early and accurate diagnosis of ectopic pregnancy and offer non-surgical treatment option instead of the traditional surgical option, with good results in Africa. As the number increase we will be able to make sound judgment of the success rates of medical treatment option with more certainty.

There's need therefore for those of us working in the developing countries especially Africa to strive to raise public awareness on the risk factors, incidence of ectopic pregnancy, the need for women to report to a health facility as early as possible, ideally two weeks after a missed period to establish the location of the pregnancy, improve on diagnostic technologies [47] and ectopic to initiate appropriate therapeutic strategies. Strategies to ensure timely diagnosis and management of ectopic pregnancies can further reduce related mortality and morbidities.

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Volume 12 Issue 11 November 2023