

Treatment of Ectopic Pregnancy with Methotrexate: Opportunities and Challenges in a Developing Country Context

VM Lema*

FCOG Professor of Obstetrics and Gynaecology, Vice President - ECSACOG, Nairobi, Kenya

***Corresponding Author:** VM Lema, FCOG Professor of Obstetrics and Gynaecology, Vice President - ECSACOG, Nairobi, Kenya.

Received: March 09, 2024; **Published:** March 22, 2024

Abstract

Management of ectopic pregnancy has improved globally in the past four or so decades, resulting in reduced associated morbidity and mortality, despite an increase in its incidence. Improved awareness, availability of and access to quality healthcare services, as well as diagnostic capabilities, have enabled early and accurate diagnosis thereof.

Early diagnosis gives the clinicians a wider range of treatment options among which is the medical approach using intramuscular methotrexate, a folic acid antagonist. This is now widely used as first-line treatment for haemodynamically stable patients. It however has its limitations and requires adherence to strict guidelines and instructions. The patient is required to make weekly follow up visits, after initiating treatment, with estimation of β -hCG level until it drops to non-pregnant levels, which considered an indicator of successful treatment among other instructions.

While methotrexate has been and continues to be used successfully for the treatment of ectopic pregnancy in developed countries, its use in developing countries such as those in sub-Saharan Africa remains very limited. There's paucity of published data from the Region despite having the highest incidence rates of ectopic pregnancy globally. However there're potential opportunities for its use in the region, if we address the related challenges.

This paper presents an initial experience with the use of methotrexate in East Africa by the author. It shows possible opportunities and situations it can be used successfully while highlighting inherent challenges with its use.

Keywords: *Ectopic Pregnancy; Methotrexate; Opportunities and Challenges; Developing Counties*

Introduction

The incidence of ectopic pregnancy, defined as implantation of a fertilised ovum outside of the uterine cavity [1], continues to increase in some regions of the world, especially sub-Saharan Africa [2]. The actual incidence is unknown, but the region is said to have the highest incidence rates globally [3].

The aetiology of ectopic pregnancy is uncertain, but available evidence indicates that both abnormal embryo transport and an alteration in the tubal environment are responsible for tubal implantation. Majority of ectopic pregnancies (95 - 98%) occur in the uterine tubes with the rest occurring in the uterine cervix, the ovary and abdominal cavity [4,5].

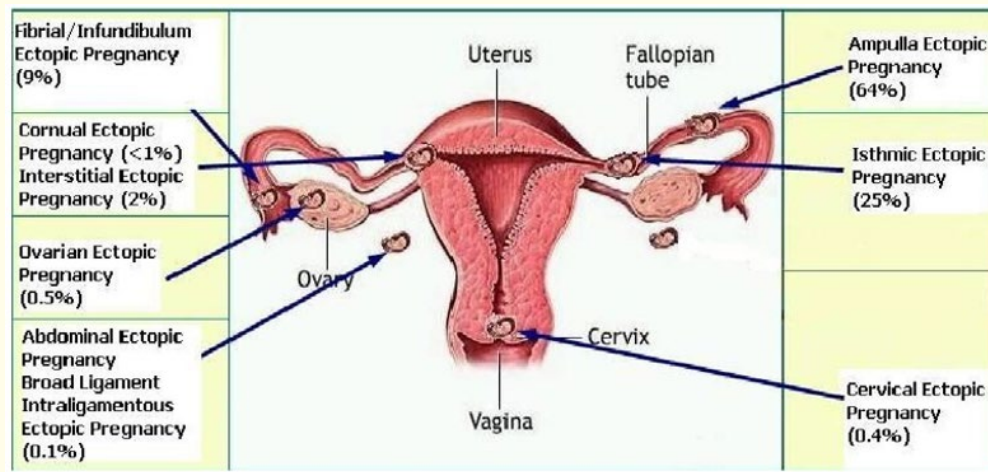


Figure 1: Sites of ectopic pregnancy.

Increased public awareness and improved diagnostic capabilities have contributed to reduction of associated morbidity and mortality in developed countries. The use of high-resolution transvaginal ultrasound (TVUS) with a high sensitivity and specificity, combined with the highly sensitive serum β -hCG [6-8] has made early and accurate diagnosis possible, which has in turn widened available management options [9]. These include expectant, surgical and medical strategies.

Intramuscular injection of methotrexate is the most preferred medical option. It has gained popularity and is increasingly being used as first-line treatment of unruptured ectopic pregnancy. A folate antagonist which blocks DNA synthesis by inactivating dihydrofolate reductase enzyme. It acts on rapidly dividing cells at the implantation site, notably the trophoblastic cells [9,10]. It is given either as a single dose of 50 mg/m² on day 1 or two dose of 50 mg/m² on days 1 and 4 or fixed multiple doses of 1 mg/kg body weight given on alternate days, with leucovorin 0.1 mg/kg 12 hours later, until the β -hCG levels drop to < 5 mIU/ml over 2 days [9]. The single dose is preferred because of fewer visits and injections especially if the β -hCG level is < 5000 mIU/ml [9,10]. If the β -hCG level does not decrease by at least 15% between days four and seven after initiating the treatment, a second dose of methotrexate of 50 mg/m² is given on day seven. If the drop is more than 15% between day four and seven, or after the second dose, β -hCG levels are monitored weekly until a normal level of \leq 5 mIU/ml is attained [9,10]. The two-dose protocol is recommended for those with higher β -hCG levels (>5000 mIU/ml) [11-13]. Subsequent weekly follow up visits are necessary because of potential of failure, persistence of trophoblastic tissues and rupture [14,15] which may necessitate recourse to surgery.

In deciding on the treatment option it is essential to take cognizance of the size of the adnexal mass, the initial β -hCG level or rise in 48 hours in some cases, the patient’s general health and ability to adhere to instructions. While the medical approach with use of methotrexate has increased and a higher percentage of patients are being treated with it successfully [16,17], the situation in sub-Saharan African is different. Majority of patients with ectopic pregnancy are still treated surgically for various reasons, including late diagnosis often after it has ruptured [18,19]. The situation is likely to change as healthcare services continue to improve and public awareness increases.

This paper presents initial experiences with the use of the medical approach on two patients by the author in his private practice in Nairobi, Kenya, over the past two years. It highlights the potential opportunities as well as challenges of using it in our context.

Case Presentations

KCW: A 32 year old lady, para 0+0, presented to my clinic mid-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. She had been married for two years. . On physical examination she was not pale, 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 an intrauterine or ectopic pregnancy and no free fluid in the cul-de-sac. She was seen two weeks later at which point 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. After counselling the couple opted for the medical approach. 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 author in case of any unusual symptoms.



Figure 2: Showing the ectopic pregnancy - Case 1.

Note the empty Uterine Cavity on the left side and the ectopic with an empty gestational sac on the right.

Four days later, 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. The couple was reassured that she was responding well to the treatment, but they insisted on receiving 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 12 months later, in early May 2023, with a history of amenorrhea for 5 weeks. An initial 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. A repeat pelvic sonographic examination two weeks later confirmed a live intrauterine pregnancy of 7 weeks. The pregnancy progressed well and she delivered a healthy baby girl at term. The mother and baby are doing well to date.

JNM: A 28 year old para 0+1 married lady, was seen in late March 2023 with a history of 6-weeks amenorrhea. She had had a medical termination of pregnancy at 7 weeks of gestation two years before and had been using the copper intrauterine device for contraception for about 18 months, which was removed in late December 2022. She did not have history of STIs prior to that, and her menstrual cycles had been regular with normal flow and no dysmenorrhea.

A home urine pregnancy test was positive two weeks prior to the visit and had slight bleeding with a small clot two days prior to the presentation. She also had symptoms of pregnancy i.e. nausea but no vomiting, breast fullness and increased nipple sensitivity. Upon physical examination, she was in a good general condition, not pale clinically, normal vital signs, no abdominal tenderness or distention. There were positive breast signs of pregnancy. A pelvic examination was not done. An ultrasound examination revealed an unruptured right tubal pregnancy, with no free fluid in the cul-de-sac and an empty uterine cavity.

After counselling she opted for the medical approach. The serum β -hCG level was 1235 mIU/ml, the liver and renal function tests and haemogram were within normal limits (Hb was 14.3 gm/dl). She was given methotrexate 75 mg IM, and discharged home with clear instructions of what to observe for and to contact the author in case of any unusual symptoms.



Figure 3: Showing the ectopic pregnancy - Second case.

She did not come back as appointed on day four, but came back on day 9 after initiating treatment. She had not had any issues in the interim period. The earlier symptoms of pregnancy i.e. nausea and breast fullness and nipple sensitivity had disappeared. On examination she was in a good general condition, not pale, normal vital signs and no abdominal tenderness or vaginal bleeding. The β -hCG level was 6407 mIU/ml and had a normal haemogram (14.0 gm/dl). The liver and renal function tests were within normal limits. Since we did not have day 4 β -hCG levels, and that there was a more than doubling of β -hCG level between day one and nine, she was given a second dose of methotrexate, 75 mg IM and given the same instructions as before. She was seen again seven days later. She had not experienced any issues since the last visit and all the vital signs and laboratory tests were within normal limits and physical examination did not reveal any

abnormality. The β -hCG level had dropped to 1293.83 mIU/l. When seen a week later, the β -hCG level was 475 mIU/l. She had had slight bleeding for three days but no abdominal pains. She did not come back hereafter. Six months after the treatment she was contacted by phone and said she was doing well. She was advised to come back for further evaluation if after 12 months of adequate sexual exposure she will not have conceived, as well as come back if she misses her periods for two weeks, to determine the location of pregnancy if she'll have conceived and confirm the site of the pregnancy if pregnant.

Discussion

Increased public awareness coupled with improved access to quality healthcare services has greatly improved the management of ectopic pregnancy. The use of transvaginal ultrasound with an accuracy of 90%, a sensitivity of 87 - 99.0% and specificity of 94 - 99.9% [10,20], combined with the highly sensitive β -hCG with a low discrimination level (≤ 1500 mIU/ml) [21] has made early and accurate diagnosis of ectopic pregnancy possible [7,22]. This has availed the clinicians more opportunities for conservative management options, that do not only retain tubal anatomical structure and function [23,24], but also reduce the associated costs and related morbidity [25].

Methotrexate a folate antagonist, has gained popularity and is increasingly being used as a first-line treatment of unruptured ectopic pregnancy with up to 97% success rates [4]. Of the three regimens that have been proposed; single-dose, two-dose; and fixed multiple-dose regimens the single-dose regimen is the preferred option [9,14]. It involves intramuscular injection of methotrexate 50 mg/m², on day 1, for those clinically asymptomatic, with an adnexal mass < 4.0 cm, and initial serum β -hCG < 5000 mIU/ml. Others opine that it can be used safely and successfully regardless of the size of adnexal mass and β -hCG levels as long as all other criteria are met [26].

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| <ul style="list-style-type: none"> • Hemodynamically stable. • Low hCG (< 5000 mIU/ml). • Small mass (< 3.5 cm). • Unruptured mass. • No embryonic cardiac activity. • Certainty that there is no IUP. • Willingness for follow-up. • No known sensitivity to MTX. |
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Table 1: Criteria for use of single-dose methotrexate.

The two presented cases met the above criteria. They had small adnexal masses, low initial β -hCG levels (7092 mIU/ml and 1235 mIU/ml respectively), were clinically asymptomatic and haemodynamically stable, had no contraindications for its use, and expressed willingness and ability to follow given instructions. They received 50 mg/m², on day one. Despite a drop in the β -hCG level between day 4 and 7, the first patient was given a second dose because the couple requested it despite assurances that she was doing very well as the level of β -hCG was dropping as expected. The second one was given another dose on day 7 because we were not sure of day 4 β -hCG level, and there had been a significant rise from that of day 1. Some studies have shown better and faster resolution among patients who received the second single-dose [10,13].

Both patients did very well, the β -hCG levels were down to normal by the seventh week from initiation of treatment for the first case. We however did not know when the level for the second patient dropped to non-pregnant level, as she did not make more visits. The timeframe to resolution ranges from 3 - 7 weeks from initiation of therapy [9].

The medical approach requires strict adherence to instructions. These include avoidance of situations or conditions which may exacerbate a likelihood of adverse effects such as exposure to direct sunlight which may worsen dermatitis. Others may interfere with the efficacy of the drug, such as foods or folic acid supplements, non-steroidal anti-inflammatory drugs; or activities which may increase risk of rupture such as vaginal intercourse, vigorous exercises; or mask the symptoms of rupture e.g. narcotic analgesics, alcohol, gas-producing foods [4,27].

Protocol	Single dose
Medication	MTX 50 mg/m ² body surface area (ht x wt)
Laboratory values	LFTs, CBC, renal function tests and β-hCG at baseline, day 4, and day 7
Repeat medication	Repeat regimen if β-hCG level does not decrease by >15 percent between day 4 and day 7
Follow-up	β-hCG level weekly, and continue regimen until it's < 5 mIU/ml [9]

Table 2: The single-dose methotrexate regimen.

The patients were given all these instructions, as well follow up instructions on a weekly basis, and explanation on why and what would be done. The first patient was followed up as instructed until the β-hCG level had dropped to the non-pregnant level, end of the seventh week, which is in line with reported resolution timeframe of 3 - 7 weeks [9,27]. The second presented patient did not come back as appointed on day four, but came back day 9 after initiating treatment, when the levels of β-hCG had increased significantly from that of day 1. She was not seen again after the fourth week, when the β-hCG level was 475 mIU/l. Both were advised to avoid getting pregnant until at least six months after the treatment to allow time for elimination of the methotrexate from the system for fear of potential teratogenicity [28]. The first patient conceived spontaneously 12 months after the treatment and the pregnancy is going on very well so far. The second one has not, but has been getting regular menstrual periods since the treatment and has not had any medical issues related to the treatment.

Both patients did not report any major adverse effects after treatment. The first had mild muscle pains in both legs the first two days, while the second had slight vaginal bleeding for three days but no abdominal pains. Vaginal bleeding during treatment is said to be due to the sloughing off of decidual endometrium [29]. Since she did not have abdominal pains and was still haemodynamically stable, she was reassured.

These are the first 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, between February 2022 and May 2023. Majority of patients are treated surgically either laparoscopically or open laparotomy. There's paucity of published data on the use of methotrexate in the treatment of ectopic pregnancy in sub-Saharan Africa, only two published review articles from Nigeria and South Africa [30,31].

Conclusion

Ectopic pregnancy remains a serious acute emergency and a major cause of first trimester mortality and morbidity in sub-Saharan Africa, where a majority of the patients present late, often with clinical symptoms. This limits treatment options. However, with the advent and expansion of diagnostic technologies such as TVUS and serum β-hCG coupled with increased access and affordability of health care services, the situation is bound to change.

Use of the medical approach with methotrexate for ectopic pregnancies is still very low in sub-Saharan Africa. It is a safe and effective treatment of early ectopic pregnancy in well selected candidates. This reduces costs to the patients and facilities. Proper evaluation,

selection and counselling of patients is essential. The challenges of patient's adherence to instructions such as follow up visits can be mitigated by using phones to contact and follow up on those who might otherwise default, thanks to the expansion of technology even in remote areas of Africa.

There is need to raise public awareness on ectopic pregnancy, the importance of early attendance to a health facility, as well as improve on clinicians' diagnostic capabilities. As about one half of all women who have an ectopic pregnancy do not have any known risk factors, sexually active women should be made aware of the possibility of ectopic pregnancy, especially if they have symptoms of pregnancy, even in the absence of symptoms of ectopic pregnancy and encouraged to seek health care services early.

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Volume 13 Issue 4 April 2024

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