

# Medical management of ectopic pregnancy: Case series at a private tertiary hospital, Tanzania

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Gregory Ntiyakunze<sup>1</sup> , Daudi Gidion<sup>1</sup> , Willbroad Kyejo<sup>2</sup> ,  
Brenda Moshi<sup>1</sup> , Shweta Jaiswal<sup>1</sup>, Lynn Moshi<sup>1</sup>, Jane Muzo<sup>1</sup> ,  
Harrison Chuwa<sup>3</sup> and Muzdalifat Abeid<sup>1</sup>

## Abstract

Ectopic pregnancy is a pregnancy in which the developing blastocyst implants outside the endometrial cavity. An estimated 1.3%–2.4% of pregnancies end up outside the uterus. With prompt diagnosis and efficient treatment, the risks of morbidity and mortality associated with ectopic pregnancy can be reduced. For the treatment of carefully chosen ectopic pregnancies, methotrexate therapy, a folic acid antagonist that is highly toxic to rapidly replicating tissues, produces outcomes comparable to surgery. We describe six cases of ectopic pregnancy which were successfully treated with methotrexate and on follow-up two of them successfully conceived to term delivery. For patients who are physically fit enough, medical management of an ectopic pregnancy with methotrexate should be the first line of treatment to lower surgical morbidity and mortality. Following the administration of the medication, the patient is monitored with a clinical symptom interview and weekly plasma human chorionic gonadotrophin levels checks. When initial human chorionic gonadotrophin levels are extremely high, complete resolution of an ectopic pregnancy can take 6–8 weeks instead of the usual 2–3 weeks. Early diagnosis of ectopic pregnancies is necessary to improve their prognosis. Ectopic pregnancies can be managed medically with methotrexate to preserve fertility. Compared to surgical management, methotrexate therapy appears to have more advantages.

## Keywords

Ectopic pregnancy, methotrexate, medical management, case series

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## Introduction

Ectopic pregnancy occurs when the developing blastocyst implants outside the endometrial cavity.<sup>1</sup> It is estimated that 1.3%–2.4% of pregnancies are ectopic.<sup>2</sup> More than 95% of ectopic pregnancies are thought to take place in the fallopian tubes, with the remaining implanting on the cervix, ovary, myometrium, and other sites.<sup>3</sup>

Any woman in reproductive life can potentially have an ectopic pregnancy. Any damage or impaired fallopian tube functioning predisposes to ectopic pregnancy. Knowledge of risk factors and appropriate clinical history and physical examination can help identify women who may benefit from close monitoring and early treatment.<sup>4</sup>

High-risk conditions include previous ectopic pregnancy, history of tubal surgery (including a previous tubal sterilization), history of sexually transmitted infection, pelvic inflammatory

diseases, pelvic adhesions, conception resulting from assisted reproduction, cigarette smoking, and in utero exposure to diethylstilbestrol.<sup>5</sup>

Ectopic pregnancy may present with classic triad of symptoms including, abdominal or pelvic pain, amenorrhea with or without vaginal bleeding in the first trimester.<sup>4</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, The Aga Khan University, Dar Es Salaam, Tanzania

<sup>2</sup>Department of Family Medicine, The Aga Khan University, Dar Es Salaam, Tanzania

<sup>3</sup>Department of Oncology, The Aga Khan Hospital, Dar Es Salaam, Tanzania

### Corresponding Author:

Gregory Ntiyakunze, Department of Obstetrics and Gynecology, The Aga Khan University, P.O. Box 38129, Dar Es Salaam, Tanzania.  
Email: gregory.ntiyakunze@akhst.org



Ectopic pregnancy is a significant cause of morbidity and mortality in the first trimester of pregnancy. It is the leading cause of maternal mortality in the first trimester and has been contributing 10%–15% of all maternal death.<sup>6</sup> Early detection and effective care can lower the risk of maternal mortality and morbidity associated with ectopic pregnancy. While surgical treatment is the standard of care, advances in early diagnosis of ectopic pregnancy have provided an opportunity for medical management with methotrexate.<sup>7</sup> Treatment with methotrexate, a folic acid antagonist highly toxic to rapidly replicating tissues, achieves comparable results to surgery for the treatment of appropriately selected ectopic pregnancies and is now commonly used.<sup>7</sup>

The benefits and drawbacks of medical and surgical management of ectopic pregnancy must be kept in mind, as well as when a particular treatment is appropriate to use. Medical management may not always be the optimal choice for each patient.

Most African nations are experiencing an increase in the prevalence of ectopic pregnancies; according to a study by Etuknwa et al., the incidence has tripled over the past 30 years.<sup>8</sup> Due to delayed diagnosis, surgical care has remained the mainstay of treatment in resource-poor Africa despite this rise.<sup>9</sup> In this article, we review six cases of ectopic pregnancies that were successfully treated medically. Two of these cases later on had successful term pregnancies. This highlights the importance of medical management in fertility preservation.

Lower abdominal pain and vaginal bleeding symptoms were present in all six patients prior to the seventh week. One person only displayed the vague symptom of excessive vomiting. The diagnosis was confirmed by sonographic evaluation, and the initial serum beta hCG (human chorionic gonadotropin hormone) level was assessed before and after treatment. All patients received injection methotrexate at a dose of 50 mg/m<sup>2</sup> according to their body weight and height.

## Cases presentation

### Case 1

33 years gravida 3 Para 1+1 Living 2, with 4 plus 5 days weeks of amenorrhea presented with abdominal pain was sharp in more on the left side of the lower abdomen accompanied with per vaginal spotting for 2 days, she reported to have urine for pregnancy test at home that was positive. Had history of previous tubal pregnancy and right salpingectomy was done 1 year ago. Had previous twin delivery by cesarean section 3 years ago.

She had neither history of sexually transmitted diseases nor pelvic inflammatory diseases and no history of using assisted reproductive techniques.

On arrival had stable vital signs, with blood pressure of 133/82 mmHg, pulse rate of 80 beats per minute, respiratory rate of 18 breath per minute, body temperature 36.5°C,

oxygen saturation of 98%, body weight was 60.6 Kg, and height of 165 cm.

Per abdominal examination had non-distended abdomen, with old healed Pfannenstiel scar, soft abdomen, non-tender, no organomegaly with normal bowel sounds.

On systemic examination was essentially normal.

Laboratory workout done initial serum Beta HCG (human chorionic gonadotropin) level was 3834 mIU/ml, blood group O positive, had normal CBC (complete blood count), RFT (renal function test), and LFT (liver function test).

Transvaginal ultrasound revealed ectopic pregnancy on the left adnexa of 1.6 by 1.1 cm in size with no cardiac activities seen with endometrium thickness of 0.6 cm, not ruptured, and empty intrauterine cavity.

She was treated with methotrexate at the dose of 50 mg/m<sup>2</sup>, received 80 mg IM on day 0 and day 7.

Patient had lost follow-up, however was able to come after 6 months with successful intrauterine pregnancy and delivered at term via cesarean section 3.2-Kg female baby Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score 8/9 in 1st and 5th minute.

### Case 2

25 years, primigravida presented at 5 weeks amenorrhea presented with excessive morning sickness symptoms, on arrival at clinic urine pregnancy test was positive. She had no per vaginal bleeding, no abdominal pain, no weight loss.

Otherwise, no history of chronic illness, no food or drug allergy. No history of gynecological procedure, no familial history of chronic illness, no history of pelvic inflammatory diseases or sexually transmitted diseases and has been using calendar method for contraception.

On arrival had stable vital signs, with body weight of 66 Kg and height of 172 cm.

Per abdominal examination had non-distended abdomen, no scar, soft abdomen, non-tender, no organomegaly with normal bowel sounds.

On systemic examination was essentially normal.

Laboratory workout done initial serum Beta hCG level was 4734 mIU/ml, blood group O positive, had normal CBC, RFT, and LFT.

Transvaginal ultrasound revealed ectopic pregnancy on the left adnexa of 1.9 by 1.1 cm in size with no cardiac activities seen with endometrium thickness of 0.62 cm, not ruptured, and empty intrauterine cavity.

She was treated with methotrexate at the dose of 50 mg/m<sup>2</sup>, received 89 mg IM on day 0 and day 7.

### Case 3

32 years gravida 3 Para 2 Living 2 at 5 weeks gestational age, presented with gradual onset of per vaginal bleeding

for 2 days. Report passage of blood per vaginal changed sanitary pads four times, neither fully soaked nor blood clots. It was associated with easy fatiguability and palpitation at times on excessive exertion. She reports no history of difficulty in breathing, no chest pain, no headache, no blurry vision.

Otherwise, no history of chronic illness, no food or drug allergy. No history of gynecological procedure, no familial history of chronic illness.

On arrival had stable vital signs, with body weight of 74 Kg and height of 168 cm.

Per abdominal examination had non-distended abdomen, Old healed Pfannenstiel scar, soft abdomen, non-tender, no organomegaly with normal bowel sounds.

On systemic examination was essentially normal.

Laboratory workout done initial serum Beta hCG level was 5134 mIU/ml, blood group O positive, had normal levels on the CBC, RFT, and LFT.

Transvaginal ultrasound revealed ectopic pregnancy on the left adnexa of 1.8 by 1.1 cm in size with no cardiac activities seen with endometrium thickness of 0.8 cm, not ruptured, and empty intrauterine cavity.

She was treated with methotrexate at the dose of 50 mg/m<sup>2</sup>, received 100 mg IM on day 0, and beta hCG were followed up.

Was lost to follow-up, but was able to conceive intrauterine pregnancy after 8 months, delivered at term via cesarean section with an APGAR score of 8/9 in 1st and 5th minute.

#### Case 4

27 years, primigravida presented at 4 weeks gestation age, presented at Emergency Department with per vaginal bleeding for 1 day, report history of changing three pads per day which were partially soaked no blood clots. Not associated with palpitation, no easy fatiguability, no excessive sweating.

No excessive morning vomiting. Otherwise, no history of chronic illness, no food or drug allergy. No history of sexual transmitted infection, no history of gynecological procedure, no familial history of chronic illness.

On arrival had stable vital signs, with body weight of 62 Kg and height of 165 cm.

Per abdominal examination had non-distended abdomen, no scar, soft abdomen, supra-pubic tenderness, no organomegaly with normal bowel sounds.

On systemic examination was essentially normal.

Laboratory workout done initial serum Beta HCG level was 3734 mIU/ml, had normal CBC, RFT, and LFT.

Transvaginal ultrasound revealed ectopic pregnancy on the right adnexa of 1.3 by 0.7 cm in size with no cardiac activities seen with endometrium thickness of 0.7 cm, not ruptured, and empty intrauterine cavity.

She was treated with methotrexate at the dose of 50 mg/m<sup>2</sup>, received 85 mg IM on day 0 and day 7.

#### Case 5

32 years, G2p111 with amenorrhea of 6 weeks presented with per vaginal bleeding changed sanitary pads three times per day not blood soaked, or blood clots seen and left lower abdominal pain for 2 days. This was not accompanied with per vaginal bleeding, no fever, no vomiting, or any referred pain.

On examination of the patient stable with body weight 76 Kg and height 170 cm.

Abdominal examination had non-distended contour, moving with respiration, with mild tenderness on the left iliac fossa on deep palpation.

Other systems had essentially normal findings.

Radiological investigations found a left adnexa tubal pregnancy on the transvaginal ultrasound measuring 1.67 cm sac and no visible cardiac activities with empty uterine cavity endometrial thickness was 0.84 cm.

Laboratory workout found an initial level of serum B-HCG level of 2992 mIU/ml with normal range of parameters on the CBC, RFT, and LFT.

Was treated with methotrexate at a dose of 50 mg/m<sup>2</sup>, received a single dose 100 mg IM on day 1 and follow-up beta HCG.

#### Case 6

28 years, nulliparous, presented with lower abdominal pain accompanied with episodes of vaginal spotting for 3 days not mixed with blood clots. She reported to have amenorrhea of 5 weeks with prior history of regular menstrual flow.

No history of loss of consciousness, no referred pain, no urinary symptom. She was not on any contraception recently and had no chronic illness.

At arrival had stable vital signs with body weight 67 Kg and height 164 cm.

Per abdominal examination during inspection normal contour of the abdomen, moving with respiration, on palpation had no area of significant tenderness including the lower abdominal regions with no organomegaly. On systemic examination was essentially normal.

Initial laboratory workout found urinary test for pregnancy positive, Beta hCG level was 697.4 mIU/ml, normal CBC, RFT, and LFT. Transvaginal ultrasound found left tubal pregnancy of 2 cm by 1.7 cm with increased vascularity, no cardiac activities noted during the scan with empty uterine cavity and endometrial thickness of 0.67 cm.

Treated with methotrexate at a dose of 50 mg/m<sup>2</sup> received 100 mg IM on day 1. And on day 20 the Beta hCG was 3.2 mIU/ml.

The above table shows a summary of gestational age of pregnancy, detailed initial ultrasound, treatment, and follow-up.

Figure 1 Shows that the average resolution time during the treatment period was around 30 days depending on the initial serum beta human chorionic gonadotropin level.

## Discussion

Medical management protocols for methotrexate were established in the late 1980s and have become a widely accepted primary management for non-complicated ectopic pregnancy.<sup>10</sup>

An ideal case for medical management of an ectopic pregnancy with methotrexate should have the following criteria: hemodynamic stability, no severe or persistent abdominal pain, commitment to follow-up, size of gestational sac less than 3 or 4 cm, no cardiac flicker and serum beta human chorionic gonadotropin concentration less than  $\leq 5000$  mIU/ml, normal liver, and RFTs.<sup>7</sup> We used these criteria for patients' selections on our six cases who received medical management of ectopic pregnancy.

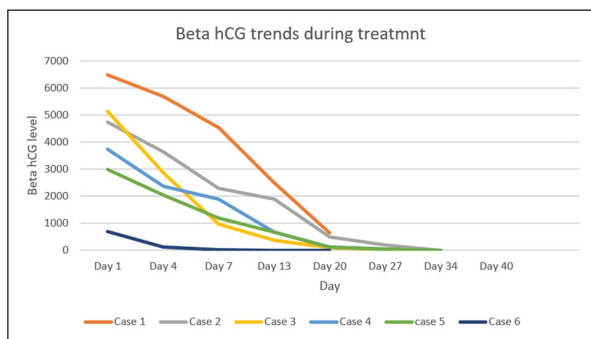
As with all medical interventions, the first line of evaluation is the clinical presentation. An immediate surgical

management is indicated if the patient is unstable or present with features of acute abdomen. Patients who presented at our center had stable vital signs that made them eligible for the medical management rather than surgical intervention.

Medical management has advantages to women with delayed conception or history of previous ectopic pregnancy and who received surgical management previously as the tube involved is being preserved if medical management is provided. In addition to these, medical management has more advantage in preserving fertility.

A full blood picture, liver enzymes, serum creatinine, and blood type should also be checked on the patient prior to the administration of the first dose of methotrexate.<sup>11</sup> Women having a history of pulmonary disease should have a chest x-ray to avoid the risk of interstitial pneumonitis since one of the side effects of methotrexate is interstitial pneumonitis.<sup>12</sup> Patient need to avoid alcohol and supplements or food products containing folic acid.<sup>13</sup>

There are two commonly used methotrexate treatment regimens, the multiple dose regimen and the single dose regimen. When the beta HCG levels fails to drop by 15% on day 4 to 7, second dose is provided as long as there is no clinical or radiological evidence of rupture. patient is informed and she require to provide consent for the second dose. The multiple-dose protocol was the first to be used to treat ectopic pregnancy. It alternates methotrexate treatment with folic acid (leucovorin) therapy.<sup>13</sup> It is continued until  $\beta$ -human chorionic gonadotrophin ( $\beta$ -hCG) falls by 15% from its peak concentration. Approximately half of patients treated with this regimen will not require a full 8-day regimen.<sup>13</sup> This is similar to our cases, where case numbers 3, 5, and 6 only received one dose of methotrexate while the



**Figure 1.** Trends of serum beta human chorionic gonadotrophin during treatment period.

**Table 1.** Shows the summary of the cases on initial Beta hCG levels, sonographic findings, treatment given, and the Beta hCG level follow-up.

	GA (Weeks)	Lab findings Day 0 (Serum B hCG levels mIU/ml)	Sonographic findings	Treatment methotrexate IM/ Oral. (50 mg/m <sup>2</sup> )	Outcome of follow-up Beta HCG levels (mIU/ml).
Case 1	4	3834	Left adnexa ectopic 1.6 × 1.1, no cardiac activity, endometrium 0.6 cm, empty uterine cavity	85 mg IM on day 1 and day 7	Day 4- 2848, day 7- 2097, day 13 910, day 21- 621, day 28- 52 and day 35- 4.7.
Case 2	5	4734	Left adnexa ectopic 1.9 × 1.1 no cardiac activity, endometrium 6.2mm empty uterine cavity	89 mg IM on day 1 and day 7	Day 4- 3645, day 7- 2300, day 13- 1890, day 20- 489 and day 34- 5.9.
Case 3	5	5134	Left adnexa ectopic 1.8 × 1.1 no cardiac activity, endometrium 0.8 cm, empty uterine cavity	100 mg per oral on day 1	Day 4- 2870, day 7- 980.68, day 13- 380.2, day 20- 88 and day 34- 3.52.
Case 4	4	3734	Right adnexa ectopic 1.1 × 0.9 cm, no cardiac activity, endometrium 6.2mm empty uterine cavity	85 mg IM on Day 1 and day 7	Day 4- 2369, day 7- 1890, day 13- 680, day 20- 123 and day 34- 3.1.
Case 5	6	2992	Left adnexa ectopic 1.67 cm no cardiac activity, empty uterine cavity	100 mg IM on Day 1	Day 4- 1396, day 7- 837.8, day 13- 235.7, day 20- 56.7 and day 34- 4.2.
Case 6	5	697.4	Left tubal ectopic 2 × 1.7 cm, empty uterine cavity	100 mg IM on Day 1	Day 4- 214.8, day 7- 78.8, day 13- 39.5, day 20- 3.2.



remaining case series received two doses, resulting in a significant drop in  $\beta$ -hCG levels after a follow-up (Table 1).

Following administration of treatment, the surveillance includes an interview for clinical symptoms and weekly surveillance of plasma  $\beta$ -hCG levels. A clinical examination and an ultrasound can be performed at any time of the onset of functional signs suggesting a hemorrhagic complication of ectopic pregnancy.<sup>14</sup>

If the drop in plasma- $\beta$ -hCG level on day 7 is less than satisfactory compared to the first injection (in practice, the  $\beta$ -hCG level on day 7 should be strictly lower than the level on day 0 or strictly lower at 85% of the  $\beta$ -hCG level on day 4 if it is available), a second methotrexate injection should be considered. They are weekly checked to ensure that their level is declining to become undetectable.<sup>15</sup>

When initial  $\beta$ -hCG levels are extremely high, complete resolution of an ectopic pregnancy can take 6–8 weeks instead of the usual 2–3 weeks. When declining  $\beta$ -hCG levels again rise, the diagnosis of a persistent ectopic can be made.<sup>16</sup> However, in our scenario majority of cases reached complete resolution of 85% on day 28 (4 weeks).

## Conclusion

Early detection of ectopic pregnancies is essential for improving their outcomes and lowering the morbidity and mortality. Medical management with methotrexate is efficient and ideal for proper selected patients because it offers a chance to preserve fertility, is less invasive, less expensive, and does not require specialized knowledge like laparoscopy or laparotomy. The compliance, however, plays a significant role in patient selection due to the risk of tubal rupture following medical treatment associated with a lengthy follow-up.

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## Authors contribution

G.N. Involved in the acquisition of data, data collection, manuscript drafting and its revision; D.G. Involved in the acquisition of data, manuscript drafting and its revision; W.K. Involved in the acquisition of data and manuscript drafting; B.M. Involved in the acquisition of data and manuscript drafting; S.J. Involved in the clinical care of the patient and manuscript revision; L.M. Involved in the clinical care of the patient and manuscript revision; J.M. Involved in the clinical care of the patient and manuscript revision; H.C. Involved in the clinical care of the patient and manuscript revision; M.A. Involved in the clinical care of the patient, manuscript revision and supervision.

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## Ethics approval


Our institution does not require ethical approval for reporting individual cases or case series.

## Informed consent

Written informed consent was obtained from all the patients for the anonymized information to be published in this article


## ORCID iDs

Gregory Ntiyakunze  <https://orcid.org/0009-0003-6326-8434>

Daudi Gidion  <https://orcid.org/0000-0002-1230-4074>

Willbroad Kyejo  <https://orcid.org/0000-0001-8251-8660>

Brenda Moshi  <https://orcid.org/0000-0002-8580-7852>

Jane Muzo  <https://orcid.org/0009-0003-3714-8447>

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