

**Treatment Outcomes of Ectopic Pregnancy Among Women Managed
Medically at St. Paul's Hospital Millennium Medical College
Addis Ababa/ Ethiopia.**

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ABSTRACT

Background: Ectopic pregnancy, a pregnancy in which the embryo implants outside the endometrial cavity, is an important cause of maternal mortality, especially in developing countries. It can be managed via multiple approaches including medical management using methotrexate. In Ethiopia, limited evidence exists regarding the treatment outcome of its medical management.

Methods: This retrospective study was conducted based on medical records of ectopic pregnancy patients managed medically using methotrexate. The data of all women who had unruptured ectopic pregnancy and managed medically in the study period at St.Paul's Hospital Millennium Medical College were included in the study. Data were extracted from patients medical records using a structured and pretested format by trained data collectors and analyzed using SPSS software.

Results: During the period of study, 81 women among patients diagnosed with unruptured ectopic pregnancy were managed medically using methotrexate with the success of 93.8% (n=76). Methotrexate was administered intramuscularly to all patients in either a single dose (60.5%, n=49) or multiple dose regimen (39.5%, n=32). Although 53% (n=26) of patients on single dose regimen required second dose and 25% (n=8) on multiple dose regimens did not complete all 4 doses, the success rates were comparable between the two groups of regimen. Five out of the 81 patients underwent surgical intervention for either ectopic rupture or persistent ectopic mass. There was no fatal complication.

Conclusion: Methotrexate is a successful and safe alternative to surgical management of unruptured ectopic pregnancy in our settings. It should be given a trial in patients who meet the selection criteria in a setting ready for emergency surgical intervention and blood transfusions.

Key words: Ectopic pregnancy, Methotrexate, Medical management, beta hCG, Addis Ababa, Ethiopia, st. Paul's Hospital Millennium Medical College.

INTRODUCTION

An ectopic pregnancy (EP) is any pregnancy that implanted outside the uterine endometrium (1). It is a potentially life-threatening condition and obstetric emergency. Once gone undiagnosed, it ruptured spontaneously with increase of gestational age causing hemorrhage. Despite the improvement in diagnostic modalities that lead to early intervention, hemorrhage from EP is still the leading cause of pregnancy-related maternal mortality in the first trimester and accounts for 4% of all pregnancy-related deaths (2).

Studies have shown that EP is more common in young adult women who are nulliparous or still in need for their fertility. The recurrence rate has been found to be as high as 15% and in some cases, EP may be a recurrent one in a woman who had unilateral salpingectomy previously but did not start or complete her family size. Researches in Ethiopia reported its incidence to be higher among the age group of 20 to 29 years with the ranges of 51.9% to 57.9% and the higher rates reported to be among the unmarried and nulliparous women (1,3,4).

Ectopic pregnancy remains a leading cause of maternal mortality and morbidity in the first trimester of pregnancy in developing countries and Ethiopia has been reported to be among the countries with higher contribution to the maternal deaths worldwide with the EP being the leading cause in the first trimester (5,6). This put it (EP) a major public health problem in the developing countries and in Ethiopia.

As the search for alternative treatment options continue, many researches have been conducted and medical management of ectopic pregnancy has been confirmed as a genuine alternative to the surgical approach in some selected cases with methotrexate (MTX) being the preferred medication. Beside preservation of fertility, medical management of EP helps in avoiding immediate and late complications of surgery and anesthesia, reducing the treatment costs and therefore the burden of EP. Unfortunately, most of these studies were conducted in developed countries with different setting and practice causing knowledge gap and controversies in their application in the developing countries.

Although medical management using MTX is being practiced in some referral hospitals in Ethiopia, there are no documented information on its effectiveness. Despite that studies have been conducted on EP in different hospitals in Ethiopia (1,3,4), none of them addressed the treatment outcome of its medical management

leaving a wide gap in the knowledge of this treatment modality in local practice. Thus this study is done with much concentration on the treatment outcomes and the criteria in favor of the success of medical management of EP using MTX. It was conducted at SPHMMC in Addis Ababa with hope that its result will be helpful in decision making on management plan of cases of unruptured EP. Beside, it will be used as baseline reference and source of information in future researches.

METHODOLOGY

This retrospective study was conducted in Addis Ababa /Ethiopia based on medical records of ectopic pregnancy patients managed medically using methotrexate at St. Paul's Hospital Millennium Medical College during a five year-period of study from January 1st 2015 to December 31st 2019. All patients with unruptured ectopic pregnancy who were given methotrexate as their initial treatment were included in the study. Patients' medical record numbers were extracted from the medical registry books in both wards and emergency Outpatient and recorded in a designed form. Through these medical record numbers, patients' charts were retrieved in the card room. Data were then extracted from patients medical charts by trained data collectors - under direct supervision of the principal investigator- using a structured and pretested data extraction format and after confirmation of the accuracy and completeness, were analyzed using SPSS software.

RESULTS

During the five year-period of study at SPHMMC, among women diagnosed and managed for ectopic pregnancy (EP), 81 of them were managed medical using methotrexate. The diagnosis of EP was made based on both trans-abdominal and transvaginal sonography and serum beta human chorionic gonadotropin (hCG). Most of the women (60.5%, n= 49) were among the age group of 20 to 29 years, with only 4 patients (4.9 %) below the age of 20. The rests were 30 years and above. While most of these patients were married (86%, n= 70), 39% were nulliparas, 25.95% each were para 1 and para 2 and above. Although none of them has a recorded history of PID, 12 (14.8%) of them had a positive history of EP for which unilateral salphingectomy was done, and 16% (n= 13) had history of at least one abortion.

Only 3 patients (3.7%) presented with complaint of abdominal pain only, the rests presented with either amenorrhea alone or in association with lower abdominal pain, no documented complaint of vaginal bleeding. The gestational age was below 8 weeks for 40.7% (n=33) and equal or greater than 8 weeks for 45.7% (n= 37) of patients based on the last menstrual period (LMP). Only 11 patients had unknown LMP but claimed to be amenorrhic for not more than two months.

The pretreatment serum beta hCG levels for most of the patients (70.4%, n=57) was below 5,000 iu, with the levels above 10,000 iu for only 8.6% (n=7).

There was no cardiac activity visualized on ultrasound for all patients and the gestational sac(GS) diameter was below 3.5 cm for most (93.8%, n=76) patients and only one patient had a GS diameter above 4 cm.

Methotrexate was given intramuscularly for all patients in either a single dose regimen (60.5%, n=49) or multiple dose one (39.5%, n=32). While 53% of all cases who were initially started on a single dose regimen required a second dose, 75% of those placed on multiple dose regimen completed all four doses. Leucovorin was given to all patients on multiple regimen. However, only two patients from the study group developed symptom of mild vomiting.

Of all these 81 cases, 5 patients (6.2%) underwent surgical intervention (2 for ectopic rupture and 3 for persistent ectopic pregnancy).

All the successful medically treated patients (93.8%, n=76) were discharged within ten days, with 40.8% discharged in 7 days or less. The serum beta hCG levels at the time of discharge were below 1,500 iu for the majority of them (90.8%, n= 69).

The first post-treatment visit was after one week from discharge and the serum beta hCG levels were for all of them below 1,000 iu with most below 500 iu and the GS diameter reduced by more than 50% of the pretreatment size for all patients. The second post-treatment visit was after one week from the first visit and serum beta hCG levels were below 200 iu for all patients with most in the normal ranges and the GS has already disappeared for most patients.
(See table 1 and 2 below for details).

Table 1: Details of the pretreatment patients information.

Variables		Number (n)	Percentage (%)
Maternal age groups in year	below 20	4	4.9%
	20 - 29	49	60.5%
	30 and above	28	34.6%
Marital Status	Single	11	14%
	Married	70	86%
Parity	Nulliparous	39	48.1%
	Para 1	21	25.95%
	Para 2 or greater	21	25.95%
Gestational age in weeks	< 8 weeks	33	40.7%
	>8 weeks	37	45.7%
	Unknown	11	13.6%
History of Abortion	Nil	68	84%
	1 Abortion	8	9.9%
	2 Abortions	2	2.5%
	3 Abortions or greater	3	3.6%
History of PID	Yes	00	00
	No	81	100%
Current use of contraceptive	Yes	0	0%
	No	81	100%
History of EP	Yes	12	14.8%
	No	69	85.2%
Presenting Complaint	Amenorrhea	42	51.9%
	Abdominal pain	03	3.7%
	Both	36	44.4%
Gestational sac diameter	< 3.5cm	76	93.82%
	3.5 - 4cm	04	4.93%
	> 4cm	01	1.23%
Fetal Cardiac activity on US	Present	00	0%
	Absent	81	100%
Pretreatment Serum beta hCG	< 1,000	23	28.4%
	1000 - <5,000	34	42%
	5,000 - 10,000	17	21%
	>10,000	7	8.6%

Table 2: Details of the treatment and its outcomes.

Variables		Number (n)	Percentage (%)
MTX dose protocol	Single (1dose)	23	28.4%
	Single (2 doses)	26	32.1%
	Multiple (3 doses)	8	9.9%
	Multiple (4 doses)	24	29.6%
Leucovorin	Given	31	38.2%
	Not given	50	61.8%
Side effects	Yes	02	2.6%
	No	74	97.4%
Treatment Outcome	Discharged	76	93.8%
	Ruptured	2	2.5%
	Persistent	3	3.7%
Serum Beta hCG on discharge	< 1,000	61	80.3%
	1,000 - <1500	8	10.5%
	> 1,500	7	9.2%
GS diameter on discharge	< 3.5 cm	76	100%
	> 3.5 cm	00	0%
Period of hospital stay	7 days or less	31	40.8%
	>7 days	45	59.2%
Serum Beta hCG On the 1st Visit	< 15 iu	20	26.3%
	< 500 iu	45	59.2%
	500 - < 1000 iu	11	14.5%
GS diameter on the 1st Visit	< 2 cm	76	100%
	> 2 cm	00	0%
Serum Beta hCG On 2nd Visit	<15 iu	49	64.5%
	15 iu - < 200 iu	27	35.5%
	200 - < 500 iu	00	0%
GS diameter on the 2nd Visit	< 0.5 cm	63	82.9%
	0.5 - < 1 cm	13	17.1%

DISCUSSION

The success rate of medical management of EP using MTX was 93.8%, a rate within the reported overall success ranges (7).

Our study shows no difference in the treatment outcomes between both single and multiple doses regimen groups (7,8,9). Fifty three percent of patients in the single dose regimen group required second dose of MTX, a rate higher than reported in India and Jordan (10,11). This was dictated by the unsatisfactory reduction of the serum level of beta hCG after the first dose and the pretreatment serum hCG levels were higher for all of them, although were below 5,000 iu. Because of the decline of more than 15% in the level of serum beta hCG between the doses, 25% of patients started on multiple dose regimens did not complete all four doses. Again, pretreatment serum hCG and GS diameter played a role. The hCG levels was above 5,000 iu and GS diameter close to or equal to 3.5 cm for most patients who completed all four doses.

In this study, the failure rate was 6.2%, a rate comparable to previous studies findings (7) but lower than reported in India (10). From the five patients for whom medical management was not successful, the pretreatment serum beta hCG levels were above 15,000 iu for 3 patients, while the gestational mass size was above 4 cm for the fourth patient. Overall, the ectopic mass sizes were equal or above 3.5 cm for all of the 5 patients. The size of the ectopic mass and beta hCG levels were in the recommended ranges for medical treatment in only one patient who later on underwent laparotomy for ruptured EP. Although such levels of serum beta hCG and the size of ectopic mass were reported to affect the success rate of medical management (12,8,13), treatment using MTX was given a trial in these patients most likely because four of them had a unilateral salpingectomy for previous EP, two were nulliparas and the other two were primiparas. None of them required blood transfusion. It is observed from this study that, the earlier the GA, the lower the pretreatment serum hCG and the smaller the GS diameter, the rapid the rate of decline of the serum hCG and the resolution of the ectopic mass and therefore, the earlier the hospital discharge. So the levels of serum beta hCG above 10,000 iu and the ectopic mass size greater than 3.5 cm were the identified factors affected the success rate of this treatment modality.

Longer hospital stay (more than 7 days for 59% of patients) and costs for the medication (especially for those who completed all four doses) and serial investigations were the drawback of this treatment modality. There was no serious morbidity reported and overall, there was no fatal complication encountered.

CONCLUSION

It's convincing from the findings of this study that MTX in our settings is a successful alternative to surgical management for patients with unruptured EP who meet certain criteria. We expect success rate to be higher if strict selection of patients were made based on the reported criteria.

Although treatment was successful in many patients whose pretreatment serum beta hCG levels were above 5,000 iu, we agree with previous studies that reported serum beta hCG levels to be the most important determinant for treatment success and recommend levels of 5,000 iu or below to be used as the main selection criterion till a study with larger sample size is conducted in our setting.

And because of the small sample size, as well the study did not address long term outcomes of this treatment option, we recommend future study with larger sample size and address long term outcomes.

Because early detection of EP before tubal rupture gives both the patient and physician opportunity to give medical treatment option a trial and as well, increases the success rates, we recommend proper counseling of patients at high risk for EP to seek early medical attention once missed their periods.

Finally, we recommend this alternative management option of EP to be carried out in settings ready for emergency surgical intervention and blood transfusion.

LIST OF ABBREVIATIONS

EP	Ectopic pregnancy.
GA	Gestational age.
GS	Gestational Sac.
hCG	Human chorionic gonadotropin.
Hx.	History.
IU	International Unit.
LMP	Last menstrual period.
MTX	Methotrexate
PID	Pelvic Inflammatory Disease.
SPHMMC	St. Paul's Hospital Millennium Medical College.
SPSS	Statistical Package for the Social Sciences
US	Ultrasound.

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DECLARATION

It's with my consent to declare that this thesis is an original report of my research, has been written by me and has not been submitted for any previous degree. The experimental work is almost entirely my own; the collaborative contributions have been indicated clearly and acknowledged. Due references have been provided on all supporting literatures and resources.

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