Introduction

An ectopic pregnancy (EP) results from implantation outside the uterine cavity.\(^1\) It is an obstetric emergency. Undiagnosed it leads to rupture and haemorrhage. Despite the improvement in diagnostic techniques haemorrhage from EP remains the leading cause of pregnancy-related maternal mortality in the first trimester, accounting for 4% of all such deaths.\(^2\) The recurrence rate is as high as 15%.\(^3,4\) Studies in Ethiopia reported a higher incidence among 20 to 29-year-olds and unmarried and nulliparous women.\(^1,5,6\) Ethiopia is among the countries with a high incidence of EP being the leading cause of death in the first trimester.\(^7,8\) Research indicates that medical management of EP is a possible alternative to surgery. Methotrexate (MTX) seems to be the preferred medication. Medical management avoids the complications of surgery and anaesthesia and reduces costs. Most of these studies were conducted in developed countries with different settings and practices.\(^9\)
Medical management using MTX is being practiced in some referral hospitals in Ethiopia but there is no information on effectiveness. Studies conducted on EP in Ethiopia [1,5,6] have not addressed its surgical or medical management outcomes. This study focused on treatment outcomes, with the hope that the results will inform decisions on the management of unruptured EP, as well as being a reference for future research.

**Methodology**

This retrospective study was based on medical records of EP patients managed medically using MTX at St. Paul’s Hospital Millennium Medical College from January 1st 2015 to December 31st 2019. All patients with unruptured EP, who were given MTX (50mg/dose by intramuscular injection) as initial treatment, were included. Medical record numbers were extracted from the medical registry books in wards and emergency outpatients. The patients’ charts were retrieved and data were extracted, using a structured and pretested format, and after confirmation of accuracy and completeness, were analysed using SPSS software.

**Results**

Eighty-one patients had been managed using MTX. The diagnosis of EP was made with trans-abdominal and transvaginal sonography and serum beta human chorionic gonadotropin (hCG). Table 1 shows that most of the women (60.5%) were aged 20 to 29 years, with only four (4.9%) under 20 years; most were married (86%), 39% were nulliparous, 26.0% each were para 1 and para 2 and above. None had a recorded history of pelvic inflammatory disease. Twelve women (14.8%) had a history of EP for which unilateral salpingectomy was done, and 13 (16%) had at least one abortion.

Three patients (3.7%) presented with abdominal pain only. The remainder presented with either amenorrhoea alone or with lower abdominal pain. None had vaginal bleeding. The gestational age of the fetus was below eight weeks in 40.7% (n=33) and equal or greater than 8 weeks in 45.7% (n= 37) based on the last menstrual period (LMP). Eleven patients had unknown LMP dates but claimed to have had amenorrhoea for not more than two months.

The pre-treatment serum beta hCG levels for most of the patients (70.4%) was below 5,000 iu, with the levels above 10,000 iu for 8.6%. No foetal cardiac activity was seen on ultrasound for all patients and the gestational sac (GS) diameter was below 3.5 cm for most (93.8%). One patient had a GS diameter above 4 cm.

MTX was given intramuscularly to all patients in either a single dose (60.5%) or multiple doses if the beta hCG did not reduce (39.5%). Leucovorin, a drug to alleviate side effects of methotrexate, was given to all patients who had multiple doses. However, only two patients had mild vomiting.

Of the 81 patients, five (6.2%) underwent surgical intervention (two for ectopic rupture and three for persistent EP).

All with successful medical treatment (93.8%) were discharged within ten days. The serum beta hCG levels at the time of discharge were below 1,500 iu for most (90.8%).

---

**Table 1. Details of the pre-treatment patients’ information (N=81)**

| Variables                        | n (%)       |
|----------------------------------|-------------|
| **Maternal age groups (years)**  |             |
| 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 (26.0)   |
| Para 2 or greater                | 21 (26.0)   |
| **Gestational age (weeks)**      |             |
| < 8                              | 33 (40.7)   |
| >8                               | 37 (45.7)   |
| Unknown                          | 11 (13.6)   |
| **History of abortion**          |             |
| Nil                              | 68 (84)     |
| 1                                | 8 (9.9)     |
| 2                                | 2 (2.5)     |
| 3 or more                        | 3 (3.6)     |
| **History of EP**                |             |
| Yes                              | 12 (14.8)   |
| No                               | 69 (85.2)   |
| **Presenting complaint**         |             |
| Amenorrhoea                      | 42 (51.9)   |
| Abdominal pain                   | 3 (3.7)     |
| Both                             | 36 (44.4)   |
| **Gestational sac diameter**     |             |
| < 3.5cm                          | 76 (93.8)   |
| 3.5 – 4cm                        | 4 (4.9)     |
| >4cm                             | 1 (1.2)     |
| **Foetal cardiac activity on ultrasound** | 0 (0) |
| Present                          | 81 (100)    |
| Absent                           |             |
| **Pre-treatment Serum beta hCG i.u.** |       |
| < 1,000                          | 23 (28.4)   |
| 1000 - <5,000                    | 34 (42)     |
| 5,000 - 10,000                   | 17 (21)     |
| >10,000                          | 7 (8.6)     |
The first post-treatment visit was after one week from discharge and the serum beta hCG levels were all below 1,000 iu with most below 500 iu and the gestational sac (GS) diameter reduced by more than 50% of the pre-treatment size. The second post-treatment visit a week later found serum beta hCG levels were below 200 iu for all patients. The GS had disappeared for most patients. See Table 2.

After 5 patients underwent surgical intervention, only 76 patients remained on treatment and follow up.

Discussion

The success of medical management of EP using MTX was 93.8%.\[^9\] If selection criteria were strictly followed, we would have concluded that the treatment outcomes between single and multiple doses is comparable.\[^9,10,11\] Fifty three percent of patients in the single dose regimen group required a second dose of MTX, a rate higher than reported in India and Jordan.\[^12,13\] This was dictated by the unsatisfactory reduction of the serum level of beta hCG after the first. In this study, the failure rate was 6.2%, similar to a meta-analysis of previous studies\[^9\] but lower than reported in India.\[^12\] For the five patients for whom medical management was unsuccessful, the pre-treatment serum beta hCG levels were above 15,000 iu for three patients, while the GS size was above 4 cm for the fourth patient. The size of the ectopic mass and beta hCG levels were in the recommended ranges\[^11,15\] for medical treatment in only one patient who underwent surgery 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\[^10,14,15\], treatment using MTX was given a trial in these patients, probably because four of them had a unilateral salpingectomy for previous EP. None of them required blood transfusion. It is observed from this study that, the earlier the gestational age, the lower the pre-treatment serum hCG and the smaller the GS diameter, the more 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 affecting the success rate of this treatment.

Longer hospital stays (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. There was no serious morbidity reported and no fatalities.

Conclusion

We have confirmed that MTX in our setting 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 these criteria.

Although treatment was successful in many patients whose pre-treatment 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.

Our study included a small sample size and did not address long term outcomes of this treatment option. Therefore, we recommend that further research with larger numbers is undertaken with attention to long term outcomes.
detection of EP before tubal rupture gives the obstetrician an opportunity to give medical treatment a trial. We recommend proper counselling of patients at high risk for EP to seek early ante-natal attention. Finally, we recommend this medical approach to be carried out in settings ready for emergency surgical intervention and blood transfusion. All patients were placed on follow-up.

Acknowledgements: We are grateful to the staff of both Departments of Obstetrics and Gynaecology and of Statistics of St. Paul’s Hospital Millennium Medical College for retrieving patients’ medical records.

Declaration: The thesis from which this paper is drawn is the work of Dr Jok Thikuiy Gang. It has not been submitted for any previous degree. There was no external funding for this research, so the authors have no conflict of interest.

References

1. Abebe D, Tukue D, Aregay A, Gebremariam L. Magnitude and associated factors with ectopic pregnancy treated in Adigrat Hospital, Tigray region, Northern Ethiopia. Int J Res Pharm Sci 2017;7(1): 30 – 39 http://www.ijrpsonline.com/pdf/7110.pdf

2. Creanga AA, Shapiro-Mendoza CK, Bish CL, Zane S, Berg CJ, Callaghan WM. Trends in ectopic pregnancy mortality in the United States: 1980-2007. Obstet Gynecol.2011;117(4):837.

3. Allison Petrini and Steven Spandorfer. Recurrent Ectopic Pregnancy: Current Perspectives. Int J Womens Health. 2020; 12: 597–600.

4. Kuroda K, Takeuchi H, Kitade M, et al. Assessment of tubal disorder as a risk factor for repeat ectopic pregnancy after laparoscopic surgery for tubal pregnancy. J Obstet Gynaecol Res. 2009;35(3):520–524.

5. Yoseph S. Ectopic pregnancy at Tikur Anbessa Hospital, Addis Ababa, Ethiopia, 1981-1987: a review of 176 cases, Ethiop Med J. 1990 Jul;28(3):113-8.

6. Kebede Y, Dessie G. Determinants of ectopic pregnancy among pregnant women who were managed in Nekemte Referral Hospital, Oromia Region, Ethiopia. J Preg Child Health 5:370.

7. Yifru Berhan, Asres Berhan. Review of Maternal Mortality in Ethiopia: A Story of the Past 30 Years. Ethiop J Health Sci. 2014 Sep; 24(0 Suppl):3–14.

8. Igerase GO, Ebeigbe PN, Igbekoyi OF, Ajufob BI (2005) Ectopic pregnancy: 11 year review in a tertiary centre in the Niger Delta. Trop Doct 44:175-177.

9. Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing “single dose” and “multidose” regimens. Obstet Gynecol. 2003 Apr;101(4):778-84 https://pubmed.ncbi.nlm.nih.gov/12681886/

10. Lipscomb GH, Stovall TG, Ling FW. Nonsurgical treatment of ectopic pregnancy. N Engl J Med. 2000 Nov 2;343(18):1325-9.

11. Mergenthal MC, Senapati S, Zee J, et al. Medical management of ectopic pregnancy with single-dose and 2-dose methotrexate protocols. Am J Obstet Gynecol. 2016; 215(5):590.e1–590.e5.

12. Sumant R Shah, Sandip Sonata, Bhavesh Patel, Nidhi Patel, Medical Management of Ectopic pregnancy with Methotrexate . Indian Journal of Clinical Practice. 2014:24(11)

13. Shehab M, Nusair B. Medical treatment of ectopic pregnancy. Rawal Medical Journal 2008;33(2):186-188. http://www.rmj.org.pk/?mno=7745

14. Nazac A, Gervaise A, Bouyer J et al. Predictors of success in methotrexate treatment of women with unruptured tubal pregnancies. Ultrasound in Obstetrics and Gynecology 2203;21(2):181-185

15. Bonin L, Pedreiro C, Moret S, et al Predictive factors for the methotrexate treatment outcome in ectopic pregnancy. Eur J Obstet Gynecol Reprod Biol. 2017;208:23-30.