ROLE OF INJECTION METHOTREXATE IN THE MANAGEMENT OF ECTOPIC PREGNANCY

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ABSTRACT

Objective: To evaluate the success rate of injection 'methotrexate' in the management of ectopic pregnancy.
Study Design: A single group interventional study.
Place and Duration of Study: NESCOM Hospital Islamabad, from Jan 2014 to Dec 2017.
Methodology: All patients admitted with ectopic pregnancy fulfilling the inclusion criteria i.e, a stable clinical condition, no evidence of rupture on ultrasound, normal liver and renal functions were included in the study, while the patients who were showing signs of rupture ectopic or with abnormal liver and renal functions were excluded from the study. Data was collected on predesigned performa. Diagnostic tools were Transvaginal Sonography and serial serum β-human chorionic gonadotropin levels .These patients were treated with injection methotrexate 50 mg/kg body weight. Serum β-human chorionic gonadotropin levels were done on day 4 and day 7 and weekly thereafter till ≤5 mIU/ml.
Results: The total number of patients (88) with 18-39 years, fulfilling the inclusion criteria were given injection methotrexate. Medical treatment was successful in 81.8% of patients whereas failure was observed in 18.2%. Among which 67 patients were given single dose, 20 patients received 2 doses and only 01 patient needed 3 doses. The mean resolution time for β-human chorionic gonadotropin level was 21 days (11-58). Average resolution time for adnexal masses (<3cm) was 19 days and for adnexal masses (>3cm) was 39 days.
Conclusion: Methotrexate was found to be safe, cost effective and fertility preserving alternative to the surgical management of ectopic pregnancy.

Keywords: Ectopic pregnancy, Methotrexate, βHCG level.

INTRODUCTION

Ectopic pregnancy could be a life threatening event if not timely addressed. Ectopic pregnancy is defined as when an embryo implants at a site other than the uterine cavity. The most frequent extra uterine location is the fallopian tube, accounts for 98 percent of all ectopic gestations. But other possible sites includ e cervical, interstitial, intramural, ovarian or abdomina[1]. In majority of cases the etiology is unknown but there are some risk factors that can damage the fallopian tubes such as infections, tumors, scars after operation, endometriosis, smoking and congenital defects in the fallopian tube[1]. Increasing maternal age is also an important risk factor.

Management of these pregnancies has changed dramatically over the years[2]. It is important to remember that haemorrhage from ectopic pregnancy is still the leading cause of pregnancy related maternal death in first trimester and accounts for 4-10 percent of all pregnancy related deaths[3].

Ruptured ectopic pregnancy is still the major cause of maternal mortality in first trimester. With improved diagnostic facilities its Early detection of ectopic pregnancy is possible which led to the introduction of medical treatment with injection Methotrexate in 1988[4].

The significant increase in the incidence of ectopic pregnancy has been observed in the last thirty years, specially in developed countries. The reported annual incidence rates vary between 100 and 175 per 100,000 women[5,6]. The factors contributing to the rising incidence are adequate treatment of pelvic inflammatory disease, use of

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contraceptive device, tubal reconstructive surgery, advances in the assisted reproductive technology and increasing maternal age.

Medical treatment with injection methotrexate is now being widely used and has gained popularity. The beauty of treatment is that patient can be managed at outdoor with avoidance of surgery[1]. Nearly 90 percent success rate can be achieved in a properly selected patient[7-9].

The aim of this study was to evaluate the success of injection methotrexate in the treatment of ectopic pregnancy. The author suggests that medical treatment with injection methotrexate is safe, cost effective and fertility preserving and should be used as first line treatment in unruptured ectopic pregnancy.

METHODOLOGY

The study was conducted in the Gynae department of NESCOM Hospital from a period of January 2014 to December 2017. This is a single group interventional study. Total number of 88 patients who were fulfilling the inclusion criteria were included in the study.

The patients who were asymptomatic and haemodynamically stable with normal renal and liver functions were included in the study and the patients who were showing signs of rupture with haemody namic instability or having abnormal liver or renal functions were excluded from the study. These patients were diagnosed on the basis of history, examination and specific investigation including serial β-human chorionic gonadotropin (β-HCG) levels and transvaginal ultrasonography (TVS). The data was collected on predesigned proforma and results were prepared by using computer programme SPSS-17. All the women with ectopic pregnancy who were fulfilling the inclusion criteria were given injection methotrexate (50 mg/kg) bodyweight and serum β-human chorionic gonadotrophin levels were done on day 4 and day 7. In those patients where the fall in serum βHCG level was more than 15 percent between the day 4 and 7 were successfully treated and further followed by weekly levels till less than 5 IU/L. Second dose of methotrexate was given when there was <15% fall in serum βHCG level between the day 4 and 7. These patients were followed till the complete resolution of adnexal masses and serum βHCG level. Sampling technique was non probability consecutive sampling.

RESULTS

The total number of patients with ectopic pregnancy, reported to Gynae department of NESCOM Hospital during the study period were 99 out of which 88 patients were selected for medical treatment and rest 11 patients underwent surgical treatment (fig-1 & 2) (table-I).

On ultrasonography, adnexal masses were detected in 51 (56.8%) patients. Size of the mass was ≤3cm in 21 patients and >3cm in 30 patients. Minimal fluid in pouch of douglas was detected in 19 patients. No adnexal mass was detected in 37 (43.1%) patients.

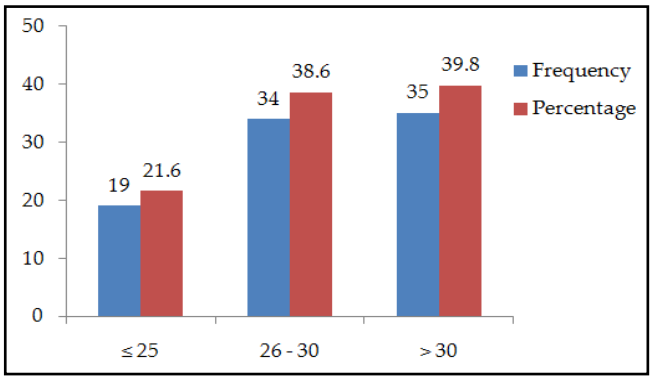

Figure-1: Frequency distribution of age groups (n=88).

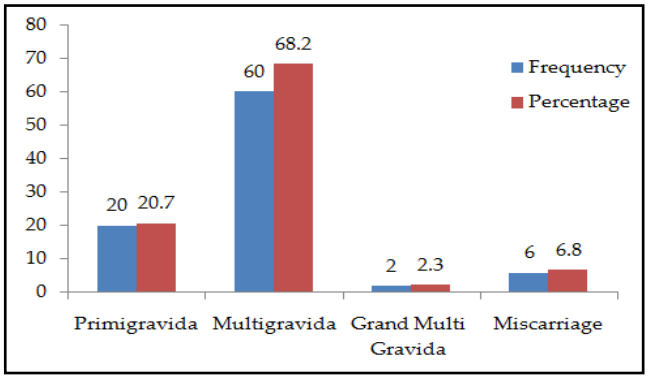

Figure-2: Frequency distribution of parity groups (n=88).

A total of 88 patients were given injection 'methotrexate', among which 67 (76.1%) patients were successfully treated with a single dose, 20 (22.7%) patients were given 2 doses and 1 (1.1%) patient was treated with 3 doses (table-II).

Table-I: Relationship of ectopic pregnancy with various risk factors.

Risk factors	Frequency	Percentage
History of Infection	29	33
Previous Surgery	33	37.5
History of Subfertility	21	23.9
Previous Ectopic	8	9.1
History of Contraception	4	4.5

Table-II: Relationship between doses of methotrexate with outcome.

Dose of Methotrexate	Outcome (%)	
	Failure	Success
Single	17.9	82.1
Double	20	80
Triple	-	100
Total	18.2	81.8

In our study 81.8% of the patients were successfully treated with injection methotrexate while a failure rate of 18.2% was observed. A success rate of 83.8% was observed in patients in whom adnexal masses were not detected. While a success rate of 95.2% was observed in adnexal masses of ≤3cm, and 70% in adnexal masses of >3cm (fig-3) (table-III).

In majority of patients (n=26), complete resolution of serum β HCG was achieved in 21 days, while in 8 patients, it took even longer time that is more than 40 days (table-IV).

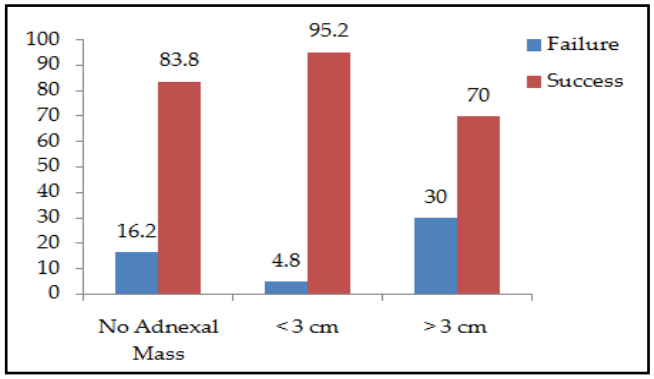

Figure-3: Relationship of Adnexal masses with success.

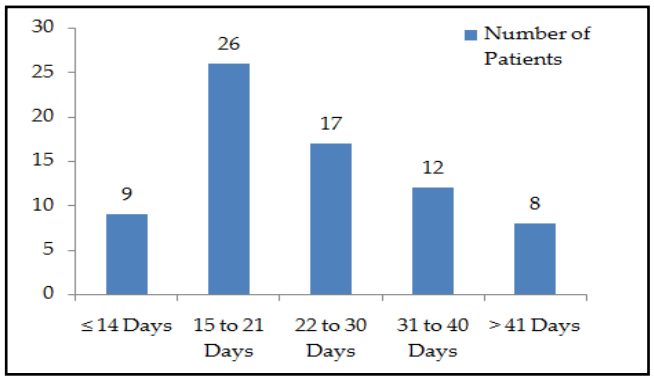

Figure-4: Resolution time of BHCG to ≤5.

Higher success rate of 84.6% was observed in patients having initial BHCG level of ≤10,000.

Table-III: Resolution time of Adnexal mass.

Adnexal Mass Size	No.	Minimum	Maximum	Mean	Std. Deviation
Less or equal to 3cms	21	7	41	19.14	7.933
More than 3cms	30	8	120	39.53	24.255

Table-IV: Association between baseline βhCG levels with outcome.

βhCG Levels at Baseline	Outcome (%)		*p*-value
	Failure	Success	
Less or equal to 10,000	15.4	84.6	0.043
Between 10,000 to 20, 000	60.0	40.0	
More than 20, 000	20.0	80.0	
Total	18.2	81.8	

Resolution time for adnexal masses of size ≤3cm was 19 (7-41) days whereas in size of adnexal mass >3cm mean resolution time was 39 (8-120) days. Mean resolution time for the βhCG levels was 21 (10-54) day (fig-4).

Hence there is association between baseline βhCG level with outcome having *p*-value 0.043 which is significant at 5% level of significance. In our study of 88 patients,we have 82% sample with resolution βhCG level ≤5. We conclude that

at least 74% outcome will be success with *p*-value 0.031. Out of 88 patients, 18 (20%) conceived spontaneously in one year.

DISCUSSION

Despite of the fact that the survival rate is increasing, rupture of tubal ectopic pregnancy is still a major contributor in pregnancy related death in the first trimester of pregnancy[9,10]. It may seriously compromise the woman's health and future fertility. Transvaginal ultrasound and serum βHCG measurement has become the cornerstone of early diagnosis. Pharmacological treatment of ectopic pregnancy has gained popularity due to its safety, easy administration and cost effectiveness.

Overall success rate in our study is 81.8% which is comparable to 80% success rate with single dose methotrexate reported by Mehboob *et al*[11]. In contrary, a higher success rate of upto 90% was reported by Lipscom and colleagues 2005, based on 643 methotrexate treated women for ectopic pregnancy. This difference is probably due to large population size in Lipscom study. 82% of success rate was achieved in patients who were treated with single dose of methotrexate, and 80% of success rate in double dose group[12]. Similarly in Lipscom study from 1998, 81% of patients were successfully treated with single dose[13]. A similar success rate of 83.9% was reported by Johannes *et al*[14]. Another observation to explain the comparatively lower success rate in our study is early surgical intervention on appearance of abdominal pain and when the rise in BHCG levels were noticed following methotrexate administration. Initially a single dose protocol was suggested in 1991. However, it was observed later on that the multidose protocol was more successful in resolving ectopic pregnancy[7]. Same has been observed in our study. In another study done by Taejong *et al*, in 2015, no significant difference was noticed in success rate between the single dose and two dose groups[15]. A success rate of 84.6% was observed when the initial BHCG level was <10,000 and the same is reduced to 40% in patients having initial BHCG level to >10,000. On the other hand we have been able to achieve success even with initial BHCG level as high as 31000. Lee reported a success rate of 96% with BHCG <6000 mIU/mL and 58% when BHCG was >6000 mlU/L. We have also noticed that initial BHCG level is the strong predictor of success for the repeated injection of Methotrexate.

Many risk factors for ectopic pregnancy have been detected in various studies. Infection and previous surgery, associated with tubal damage, were responsible for 29 (33%) and 33 (37%) of cases respectively in our study. Subfertility accounts for 21 (23%) of the total cases. There was history of contraception and previous ectopic in 4 (4.5%) and 8 (9.1%) of cases. No cause can be detected in remaining 23 (26%).

The mean resolution time of serum BHCG in our study was 25 days with a single dose and 28 days with double doses of methotrexate. Similarly a resolution time of 33 days with one dose and 55 days with two doses was noted in a study done by Thia *et al*[16]. Erdem reported the mean time of resolution as 26.5 (10-37) days in a successfully treated patients[17]. The mean resolution time for adnexal masses of ≤3cm is 19 days, whereas a resolution time of 39 days was observed in adnexal masses >3cm.

Minimal side effects were observed with injection methotrexate. More significant were lower abdominal pain and vaginal bleeding, easily managed with analgesics. According to a research made by Stovall and colleagues in 1993, about 50% of women experienced abdominal pain during first few days following methotrexate administration[18]. Same is observed in this study. Regarding the fertility, 18 (20%) patients subsequently acquired a healthy intrauterine pregnancy, 36.79% of patients achieved pregnancy after treatment with injection Methotrextae as explained by Demirdag *et al*[19].

CONCLUSION

The author concludes from this study that the medical treatment with injection Methotrexate is best alternative with the benefits of cost

and fertility preservation other than the surgical intervention.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Hoffman B, Schorge J, Schaffer J, Bradshaw K, Halvorson L, Corton M. Chapter 7: Ectopic pregnancy. Williums Gynecolog 2nd ed; 2012.p.2. Available from: https://accessmedicine.mhmedical.com/book.aspx?bookid=1758.
2. Yao M, Tulandi T. Current status of surgical and nonsurgical management of ectopic pregnancy. Fertile Sterile 1997; 67(1); 421-25.
3. Fylstra DL. Tubal pregnancy; a review of current diagnosis and treatment. Obstet Gynaecol 1998; 53(5): 320-28.
4. Lipscomb GH. Medical therapy for ectopic pregnancy. Semen Reprod Med 2007; 25(2): 93-99.
5. Guiustina DD, Denny M. Ectopic pregnancy. Emerg Med Clin North Am 2003; 21(1): 565-84.
6. TenoreJL. Ectopic pregnancy. Am Fam Physician 2000; 61(1): 1080-88.
7. Barnhart KT, Gosman G, ashby R. The medical management of ectyopic pregnancy; a Meta analysis comparing single and multidose regimens. Obstet Gynaecol 2003; 101(4): 778-84.
8. Farquhar CM. Ectopic pregnancy. Lancet 2005; 366(1): 583-85.
9. Goldner TE, Lawson HW, Xia Z, Atrash HK, Surveillance for ectopic pregnancy-United States, 1970-1989. MMWR CDC Surveill Summ 1993; 42(6): 1259-60.
10. Trabert B, Holt VL, Yu O, Van Den Eden SK, Scholes D. Population-based ectopic pregnancy trends, 1993-2007. Am J Prev Med 2011; 40(5): 556-60.
11. Mehboob U, Mazhar SB. Management of ectopic pregnancy: a two year study. J Ayub Med Coll Abbotabad 2006; 18(4): 34-37.
12. Lipscom GH, Givens VM, Meyer NL, Bran D. Comparison of multidose and single dose methotrexate protocols for the treatment of ectopic pregnancy. Am J Obstet Gynecol 2005; 192(6): 1844-47.
13. Lipscom GH, Bran D, Mc Cord ML, Portera JC, Ling FW. Analysis of three hundred fifteen ectopic pregnancies treated with single dose methotrexate. Am J Obetet Gynecol 1998; 178(6): 1354-58.
14. Johannes L, Petra S, Sebastian M, Oppelt P, Thiel FC, Renner SP, et al. Low dose methotrexate treatment in ectopic pregnancy: a retrospective analysis of 164 ectopic pregnancies treated between 2000 and 2008. Arch Gynecol Obstet 2013; 289(2): 329-35.
15. Taejong S, MiKyoung K, Mi-La K,Yongwook J. Single dose versus two dose administration of methotrexate for treatment of ectopic pregnancy:a randomized controlled trial. Hum Reprod 2016; 31(1): 332-38.
16. Thia EW, Loi, K, Wang JJ, Siow A. Methotrexate for ectopic pregnancy at the KK Women's and Children's Hospital, Singapore. Singapore Med J 2009; 50(11): 1058-61.
17. Erdem M, Erdem A, Arsalan M, Oc A, Biberoglu K, Gursoy R. Single-dose methotrexate for the treatment of unruptured ectopic pregnancy. Arch Gynecol Obstet 2004; 270(4): 201-04.
18. Stovall TG, Ling FW. Single-dose methotrexate: an expanded clinical trial. Am J Obstet Gynecol 1993; 168(6 Pt 1): 1759-62.
19. Demirdag E, Guler I, Abay S, Ogus Y, Erdem M. The impact of expectant management, systemic methotrexate and surgery on subsequent pregnancy outcomes in tubal ectopic pregnancy. Ir J Med Sci 2016; 186(2): 1-6.