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RESEARCH ARTICLE

METHOTRAXATE : EFFICACY AND ANALYSIS OF MEDICAL MANAGEMENT IN TUBAL PREGNANCY

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ABSTRACT

Background: Ectopic pregnancy is the most life threatening emergency in pregnancy leading to maternal death. Ectopic pregnancy jeoparadizes the wish of attainmaint of motherhood also, But now therapy for ectopic gestation has evolved from a radical procedure to conservative treatment aimed at the preservation of fertility.

Objective: To assess the demographic profile, risk factors, clinical presentation & determine the efficacy of methotrexate treatment for ectopic pregnancies at our tertiary care centre which will not only help in reducing maternal mortality and morbidity rates but also go a long way in preservation of future fertility.

Method: A prospective, longitudinal and observational study was conducted in the Department of Obstetrics and Gynaecology, Umaid hospital, Dr. SN Medical college, Jodhpur during a period of two year from October 2013 to September 2015. 32 cases of ectopic pregnancy admitted in the hospital were analyzed in terms of demographic profile, risk factors, clinical presentation, management and efficacy of methotraxate. Finally all collected material and data were analyzed statistically to draw various informative conclusions.

Results: Most common age and parity affected by ectopic pregnancy were 21-30 years (63.75%) and para 1-3 (72.50%) respectively. No age and parity were immune to ectopic pregnancy. More than one clinical feature was present in most of the patients. Efficacy of methotraxate in our study was 81.25%. Successfullness of Methotraxate treatment in gestational sac size <4cm was 84% and in D1 β-hCG level <5000 mIU/ml was 88.46%. Effectiveness of methotraxate was decreased when gestational sac size and β-hCG level increased.

Conclusion: Medical therapy with MTX has an established place in the treatment of early EP in selected patients with hemodynamic stability and lower initial levels of hCG as the most reliable predictors of treatment outcome and advantage of tubal conservation and saves patients from requiring surgery.

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INTRODUCTION

Attainment of motherhood is the most cherished desire of every female. An ectopic pregnancy jeopardizes this wish and may permanently impair her reproductive capacity. Pregnancy is a perfection of marital bliss but no perfection is so absolute that impurity does not pollute so is the ectopic pregnancy. For a young maid whose womb is desirous of an offspring, advanced extrauterine pregnancy is but an illaned opportunity which kills life or else its quality. Surgical treatment of EP is the mainstay of management, and laparoscopic surgery is currently the 'gold standard' (Tulandi and Sammou, 2000; Bangsgaa *et al*., 2003).

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Improvement in non-invasive diagnostic methods, such as sensitive pregnancy tests in urine and serum β-hCG and high-resolution transvaginal sonography, has enabled early diagnosis of ectopic pregnancy (Ankum *et al*., 1996; Mol *et al*., 1998; Farquhar, 2005). As a consequence, the clinical presentation of ectopic pregnancy has changed from a life-threatening disease, necessitating emergency surgery, to a benign condition in frequently asymptomatic women for whom nonsurgical treatment options are available (Ankum *et al*., 1996; Mol *et al*., 1998; Farquhar, 2005). Medical treatment with several agents including methotrexate (MTX), hyperosmolar glucose, potassium chloride, prostaglandin F2 alpha, estradiol and trichosanthin has been the subject of numerous trials (Hajenius *et al*., 2000). It has an established place in the treatment of smaller unruptured EP where tubal integrity is usually

preserved, and in selected patients it appears to be as effective as surgery. It is clear, however, that many women with EP are not suitable for medical therapy and recent studies have investigated the possible ways of improving the efficacy of medical therapy and better predicting of cases where medical treatment will be successful (Sowter and Farquhar, 2004). MTX is a folic acid antagonist that binds to the enzyme dihydrofolate reductase, which is involved in the synthesis of purine nucleotides. It is ideally suited for inhibition of rapidly growing cells such as trophoblast. MTX is commonly used as the first-line agent in the treatment of newly diagnosed EP, as it is most thoroughly studied and established for clinical use. MTX can be administered systemically (intramuscular and intravenous injections), orally or by local injection under ultrasound or laparoscopic guidance. Contrary to the multiple-dose schedules that were prevalent in older studies, recent studies used more unified, single-dose MTX (Skubisz and Tong, 2012). In women with EP, who are hemodynamically stable and wishing to preserve their fertility, medical treatment with single dose MTX tends to be equal to the treatment with laparoscopic surgery regarding success rate, complications, and subsequent fertility. It seems to be a viable alternative to laparoscopic salpingotomy for a selected group of patients with EP (Krag *et al*., 2009).

MATERIALS AND METHODS

The present prospective, longitudinal and observational study was conducted in the Department of Obstetrics and Gynaecology, Umaid hospital, Dr. SN Medical college, Jodhpur during a period of two year from October 2013 to September 2015.During this period, (n = 32) patients of diagnosed ectopic pregnancy treated as in-patients with methotrexate regimen. The diagnosis of ectopic pregnancy was made using both transvaginal or transabdominal ultrasound and measurement of β-hCG. All cases selected for medical management gave their informed written consent before starting the treatment. The selection criteria for patients suspected to have ectopic pregnancy but with low serum β-hCG or cases of pregnant women patients who were hemodynamically stable with β-hCG level of ≤10,000 mIU/mL, adnexal mass ≤4 cm absent cardiac activity and the presence of hemoperitoneum >100 mL. Baseline investigations such as full blood count, β-hCG, renal and liver functions tests and blood group, RH factor were done on Day 1 and single dose of 50 mg/m2. Methotrexate was administered. Serial β-hCG was repeated on Days 4 and 7. If β-hCG on Day 7 was at least 15% lower than that on Day 4, the patient was discharged and followed up as an outpatient. If the β-hCG level on Day 7 was the same or higher than that on Day 4, the patient received a second dose of 50 mg/m2 methotrexate. Follow-up serum β-hCG and ultrasound was performed weekly. Single dose methotrexate treatment was considered successful when β-hCG levels became negative without further administration of methotrexate dose or surgery. Cases with persistent plateauing serum β-hCG concentration were defined as 15% fall or <15% rise in serum β-hCG concentrations. Second dose of methotrexate was installed in both cases of either increasing β-hCG or plateauing β-hCG. Follow-up β-hCG was performed weekly until negative with value of b-hCG <5 mIU/mL. For patients with hemodynamic instability, signs of tubal rupture, increasing abdominal pain, falling haemoglobin level surgical intervention were considered. The toxicity of methotrexate treatment was evaluated by noting side effects such as lower abdominal pain, vaginal bleeding, mouth ulcers, sore throat, gastrointestinal side effects or complaints of any rashes. Nonsensitized Rhesus negative women received anti-D immunoglobulins 50 μg as per the department protocol. Women treated with methotrexate were advised to refrain from sexual intercourse until serum β-hCG was negative, and not to conceive within 3 months of treatment.

RESULTS

In our study, the majority of patient (68.75%) were between 20-30 years (n =22) (Table 1). The success rate of methotrexate decreased as maternal age increased. Parity was between zero and six with 37.50% (n = 12) primipara (Table 1).

Table 1. Demographic picture of patients

AGE(years)	<20	20-25	26-30	31-35
	2(6.25%)	10(31.25%)	12(37.50%)	8(25%)
PARITY	0	1-3	4-7	>7
	12(37.50%)	18(56.25%)	2(6.25%)	0(0.0%)
RESIDENCE	RURAL	URBAN		
	18(56.25%)	14(43.75%)		

Table 2. Distribution of Cases According to Clinical Presentation

SYMPTOMS	NO.OF CASES	PERCENTAGE
Amenorrhea	28	87.50%
Pain Abdomen	20	62.50%
Bleeding Per Vaginum	22	68.75%
Vomiting	3	9.37%
Passing of fleshy cast	1	3.12%

Table 3. Distribution of Cases According to Predisposing Risk Factors

Predisposing Risk Factor	No. of cases	Percentage
PID	8	25.00
TB	2	6.25
MTP	2	6.25
Abortion	8	25.00
Infertility	1	3.12
IUCD	2	6.25
D & C	6	18.75
Previous Abdominal SurgeryLSCS	8	25.00
Previous Ectopic Pregnancy	2	6.25

Table 4. Size of ectopic mass and outcome

Size of mass	No. of patients	Percentage	No. of successfully treated patients	Success rate (%)
< 4cm	25	78.12	21	84.00%
>4cm	7	21.88	5	71.42%

Table 5. Success rate according to β-hCG level on D1

β-hCG on D1	No. of patients	Percentage	No. of successfully treated patients	Success rate (%)
≤ 5000	26	81.25	23	88.46%
>5000	6	18.75	3	50.00%

Table 6. Outcome according to fall in β-hCG level between D4 and D7

Fall in β-hCG	No. of patients	Percentage	No. of successfully treated patients	Success rate (%)
>15%	24	75.00	21	87.50%
< 15%	8	25.00	5	62.50%

Table 7. Time duration to return normal β-hCG and USG findings

Time duration to normalize	Serum β-hCG	Percentage	USG finding	Percentage
<2 Week	6	23.08	0	0.00
2 Week- 4 Week	6	23.08	3	11.54
5 Week – 8 Week	13	50.00	15	57.69
>8 week	1	3.84	8	30.77

Table 8. Overall efficacy of Methotraxate treatment

Outcome	No. of patients	Percentage
Successfull	26	81.25%
Unsuccessfull	6	18.75%

More than one clinical feature was present in most of the patients. Amenorrhea (87.50%) and pain abdomen (62.50%) were the common presenting symptoms (Table 2). The most common risk factor found was PID and previous abdominal surgery including caesarean section. These were present in 8 (25.00%) cases of ectopic pregnancy. History of D & C and IUCD were other common risk factor. Two cases had a previous ectopic pregnancy. In 4 (12.5%) patients no risk factor was present. Relative risk after previous one ectopic pregnancy was 6.25% (Table 3). The success rate of methotrexate decreased with increasing gestational age. Adnexal mass size measured by transvaginal and transabdominal ultrasound ranged from 1 to 5 cm. In patients with adnexal mass <4 cm, the success rate was high(84%). The success rate of methotrexate decreased (50%) with increasing adnexal mass size (Table 4). 26 patients having β-hCG on Day 1 <5000 mIU/ml (average value 1800 mIU/ml) treated with single dose of methotrexate, out of which 88.46% were successfully treated. Those patients had D1 β-hCG level >5000 mIU/ml , success rate was low or they needed second dose of methotraxate (Table 5). An increase in the Day 4 β-hCG level was observed in some cases, mainly due to the trophoblastic tissue breakdown releasing the hormone. Success rate of single dose methotraxate was very high (87.50%) in Patients, those D4 to D7 β-hCG level fall was > 15% (Table 6). The average time of resolution for serum β-hCG level was 36 days for single dose of methotrexate and 54 days for those receiving two doses. Time of resolution for serum β-hCG was defined as the total number of days from the beginning of treatment until β-hcg level became negative (<5 mIU/mL). Average time duration to return normal USG finding was 56 days (Table 7). The total number of women treated with single dose were 78.12% (n = 25) and (n = 7) 21.88% received two doses. Success rate in group of patient given single dose methotrexate was 80% and in patients with two dose methotrexate, it was 85.71%. The overall success rate of treatment in our study was 81.25% (n = 26). Surgical intervention was required for 18.75% (n = 6) of patients with tubal rupture and abdominal pain (Table 8). All 6 patients were managed by surgical intervention method laparotomy followed by salpingectomy.

DISCUSSION

Ectopic pregnancy occurs in around 1% of pregnant women and may seriously compromise women's health and future fertility (Mol *et al*., 2008). Ectopic pregnancy can be diagnosed before the patient's condition has deteriorated and cornerstone of diagnosis is the use of transvaginal ultrasound and serum human chorionic gonadotrophin measurement (Condous *et al*., 2004). Medical treatment with MTX for extrauterine gestations was initially used in cases of abdominal pregnancy (Lathtrop and Bowles, 1969) and also for the cervical and interstitial pregnancy (Tanaka *et al*., 1982). The rationale for the use of MTX in these instances was to bring about prompt destruction of placental trophoblastic activity, with the assumption that this would be associated with a concomitant decrease in placental vascularity and thereby marked restriction of the potential of hemorrhagic complications of the retained placenta. MTX therapy for tubal pregnancies has also been based on the expectation of similar effects. In our study Ectopic Pregnancies were encountered in women between ages 18 to 40 years. Highest incidence of ectopic pregnancy was found in the age group of 21-30 years (68.75%) and minimum incidence was found in age group <20 years (6.25%). It shows that reproductive age group is more prone to ectopic pregnancy. It is because increase incidence of sexually transmitted diseases and pelvic inflammatory diseases in this age group as well as efficacy of antibiotic treatment for PID. Most common age group involved was 21-30 years for ectopic pregnancy as reported by Mandelkar *et al*. (1990), Vyas and Vaidya *et al*. (2000), Abubakar A Panti *et al*. (2012), Premlata *et al*. (2014). Highest incidence of ectopic pregnancy was in para 1-3 (56.25%) and lowest incidence in para 4-7 (6.25%). It was found more in Para 1-3 because of increased use of intra uterine contraceptive devices for births spacing and increased tubal ligation in these patients as this is the time for small family norm, early marriage, and early completion of family and use of family planning methods. These findings correlate with the observations of Pendse (1981), Rose Jophy *et al*. (2002), Premlata *et al*. (2014) where average parity was found to be 2-3.

The most common etiological factor was pelvic inflammatory disease. It was found to be present in 20 (25.00%) cases this observation is in consonance with findings of Vyas and Vaidya (2000) and Jophy Rose *et al*. (2002), Abubakar A Panti *et al*. (2012), Premlata *et al*. (2014). Pelvic inflammatory diseases are responsible for causing peritubal adhesions, partial closure of lumen, intratubal adhesions, diverticuli & cysts. In the diverticuli the myoelectrical activity is diminished and limited to that segment of the tube only and therefore the fertilized ovum gets trapped in it. Mahboob reported a success rate of 80% by treating 12 out of 15 women with single dose MTX with initial β-hcg levels equalto 5000mIU/ml (Mahboob and Mazhar, 2006) which is comparable with our study (88.46%). Results support a substantial increase in failure of medical management with single-dose MTX when the initial hCG is above 5000 mIU/mL and MTX should be used with caution in patients with EP who present with hCG levels above this level (Menon *et al*., 2007). The time of resolution in our study was 36 days with a single dose, and 54 days with ≥ two doses of methotrexate as compared to 27.3 days and 35 days respectively in other series (Merisio *et al*., 2005). Thia noted the time of EP resolution was 33 days with one dose and 55 days with two doses, similar to our study (Thia *et al*., 2009). Erdem reported the mean time of resolution as 26.5 (10-37) days in patients who were successfully treated with MTX (Erdem *et al*., 2004). These results are consistent with other studies (Tawfiq *et al*., 2000). The success rate in our study (81.25%) was found to be lower than in other comparable study. The reason being that at the beginning of starting the methotrexate regimen in our institution women with increasing β-hcg values and complaints of abdominal pain were taken early for surgical intervention for fear of rupture of the ectopic pregnancy. Srivichai *et al*. reported a success rate of 90.6% in

96 out of 106 patients were successfully treated with methotrexate though four required a second dose (Srivichai *et al*., 2006). Success reached 90% (n=10) in patients out of 11 with single dose treatment in Merisio's series (Merisio *et al*., 2005). Literature published so far shows a success rate ranging from 67% to100% in single versus multidose treatment for ectopic pregnancies (Barnhart *et al*., 2003). Fear of rupture misleads clinicians to operate early on unruptured ectopic pregnancies that would otherwise resolve with medical management.

Conclusion

Ectopic pregnancy is a life-threatening condition occurring in women all over the world. With emphasis shifting from radical to conservative therapy; prevention of risk factors and early diagnosis become very important. Methotrexate has proven to be an effective medical management for ectopic pregnancies in a society where tubal conservation is of utmost importance because of its safety, effectiveness and require less expertise than laparoscopic. The predictors of success in our study are low β-hcg and adnexal mass less than 4 cm. Single dose methotrexate offers a safe and effective non-surgical method of treating selected patients and one important advantage of medical therapy is the potential for considerable savings in treatment costs and unnecessary surgical risk and also future fertility.

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