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Methotrexate Treatment of Ectopic Pregnancy: Experience at Nizwa Hospital with Literature Review

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Abstract

Objectives: Ectopic pregnancy occurs when the embryo fails to implant within the uterine cavity. Methotrexate, a folic acid antagonist has been widely used to treat ectopic pregnancy. The aim of this study is to determine the efficacy of methotrexate treatment for ectopic pregnancies in our settings which will in-turn help us reduce maternal mortality and morbidity.

Methods: This was a retrospective review of 60 cases of ectopic pregnancy treated with single dose methotrexate in Nizwa hospital, Oman. Demographic data, clinical presentation, treatment progress, outcome, side effects and future fertility follow up were analysed using a computer database. Selection criteria included hemodynamically stable women with ß-hcg level of ≤5000 mIU/ml, adnexal mass ≤4 cm, absent cardiac activity and hemoperitoneum less than 100 ml. Human chorionic gonadotrophin (hcg) assay and clinical presentation were used to determine cases which warranted surgical intervention.

Results: The success rate of single dose methotrexate therapy in our study was 65% (n=39) and 35% (n=21) required surgical intervention compared to reported success rate of 67-100% published in various studies. Careful selection of cases and confining strictly to the criteria improved the success rate from 40% to 60% in five and half years of the study. The mean average time of resolution of ectopic pregnancy was 32 days for a single dose and 58 days for repeat second or third doses. Eight cases of pregnancy of unknown location were treated successfully with Methotrexate. No major side effects were noted. A successful fertility outcome of 30% in the first year followed by 13.3% in the subsequent second year with a secondary infertility rate of 11.6% was observed in this study.

Conclusion: Methotrexate treatment of ectopic pregnancies is safe and effective with no major side effects. Intramuscular methotrexate has the advantage of tubal conservation and saves patients from requiring surgery. It is easier to administer than intraoperative route, which is by laparoscopy and needs expertise. Our study showed single dose methotrexate to be an effective treatment option for selected patients with unruptured tubal ectopic pregnancy.

Keywords: Ectopic pregnancy; Methotrexate; Tubal rupture; Human chorionic gonadotropin.

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Introduction

Ectopic pregnancy is an acute emergency if not timely diagnosed and treated. Timely diagnosis and appropriate treatment can reduce the risk of maternal mortality and morbidity related to ectopic pregnancy. It is an important diagnosis to exclude when a woman presents with bleeding in early pregnancy.[1] Reports of the incidence from elsewhere is showing rise from 0.5-1-2%.[2] There has been a rise of 3-5% in pregnancies from assisted reproductive techniques.[3] The clinical presentation of ectopic pregnancy has changed from a life threatening disease to a more benign condition for which non-surgical treatment options are available with systemic methotrexate (MTX) or expectant management.[4]

Women with a visible ectopic pregnancy and pregnancy of unknown location (PUL) have been offered medical treatment with methotrexate.[5] Methotrexate can be administered systemically as a single dose regimen (MTX 1.0 mg/kg or 50 mg/m2 i.m without folinic acid) or as multiple dose regimen (MTX 1.0 mg/kg i.m daily 0,2,4,6 alternated with folinic acid 0.1 mg/kg orally on days 1,3,5,7). A single dose regimen was introduced to minimize side effects, to improve patient compliance and to reduce the overall costs. Methotrexate has been shown to be safe with virtually no adverse effects reported on reproductive outcome. Careful follow-up and assessment are required for all women presenting with pain in the few days following methotrexate therapy before assuming that the treatment has failed and if there is need for surgical intervention.

Methods

Between January 2005 and June 2010, 60 patients of diagnosed ectopic pregnancy treated as in-patients with single-dose methotrexate regimen were retrospectively identified from hospital records of the department of Obstetrics and Gynaecology, Nizwa hospital which is a regional and referral hospital. The diagnosis of ectopic pregnancy was made using both transvaginal ultrasound and measurement of ß-hcg. All cases selected for medical management gave their informed written consent before starting the treatment and the study was approved by the Regional research ethical committee of the hospital. A *p*-value of 0.05 or less was taken as statistically significant.

The selection criteria for patients suspected to have ectopic pregnancy but with low serum hcg, or cases with pregnancy of unknown location (PUL) were as follows:

Patients who were hemodynamically stable with beta human chronic gonadotrophin (ß-hcg) levels of ≤5000 mIU / ml, adnexal mass ≤4 cm, absent cardiac activity and the presence of hemoperitoneum less than 100 ml. The patients with hemoperitoneum more than 100 ml, adnexal mass >4 cm, and the presence of cardiac activity and ß-hcg >5000 mIU/ml were excluded from the study.

Baseline investigations such as full blood count, ß-hcg, renal and liver functions tests, and blood group RH factor were done on day 1 and single dose of 50mg/m^2 MTX was administered. Serial ß-hcg was repeated on days 4 and 7. If the ß- 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 ß-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 MTX. Follow-up serum ß-hcg was performed weekly until negative with a value of <5 mIU/ml.

Single dose MTX treatment was considered successful when ß-hcg levels became negative without further administration of MTX dose or surgery. The ultrasound examination was performed using 7.5 MHz transvaginal probe. Cases with persistent plateauing serum hcg concentration were defined as 15% fall or <15% rise in serum hcg concentrations. Second dose of MTX was installed in both cases of either increasing ß- hcg or plateauing ß-hcg. For patients with hemodynamic instability, signs of tubal rupture, increasing abdominal pain, falling haemoglobin level surgical intervention were considered.

The toxicity of MTX 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. Non-sensitized Rhesus negative women received anti-D immunoglobulins 250 µgms as per the department protocol. Women treated with MTX were advised to refrain from sexual intercourse until serum hcg was negative, and not to conceive within three months of treatment. Future pregnancy outcome for all cases were followed for three years.

Results

In this study, the mean age was 30 years ranging between 15-45 years (Table 1, p=0.355). The success rate of MTX decreased as maternal age increased. Gravidity was between one and seven with 60% (n=36) primipara, 33.3% (n=20) with parity 2-5, and 6.6% (n=4) with parity more than 5 (Table 2, p=0.469). The highest success rate of MTX was among those women who had 2-5 children (75.0%), followed by those women with 0-1 children (61.1%), and women with more than 5 children was (50.0%). The mean gestation age at diagnosis was 4.3 weeks (Table 3, p=0.472).

The success rate of MTX decreased with increasing gestational age. Adnexal mass ranged from 2-4 cm. In patients with adnexal mass more than 4 cm, the success rate was less, (Table 4, p=0.132). The highest success rate of MTX was among patients with PUL (100%) followed by women with 2-3 cm adnexal mass (64.2%). There was no marked difference in the site of ectopic gestation, however 45% (n=27) were on the right side, 40% (n=24) on left side and 1.6% (n=1) were bilateral ectopic pregnancies were observed.

Table 1: Maternal age in years

S. No	Age in years	Cases		Successful	
		n	%	n	%
1	15-25	11	18.3	8	72.7
2	25-35	40	66.6	27	67.5
3	35-45	9	15	4	44.4

Table 2: Parity wise distribution

S. No	Parity	Case		Successful	
		n	%	n	%
1	0-1	36	60	22	61.1
2	2-5	20	33.3	15	75.0
3	>5	4	6.6	2	50.0

Table 3: Gestational age at diagnosis

S. No	Weeks	Cases		Successful	
		n	%	n	%
1	0-4	7	11.6	5	71.4
2	4-6	41	68.3	28	68.2
3	>6	12	20.0	6	50.0

Table 4: Adnexal mass size

S. No	Adnexal mass (cm)	n	Successful n (%)
1.	0-2	18	10 (55.5)
2.	2-3	28	18 (64.2)
3.	3-4	6	3 (50)
4.	PUL	8	8 (100)

The average value of ß-hcg on day 1 in patients treated with single dose of MTX was 1234 (range 109-5269) and those treated with two doses or more was 1319.20 (range 865-6885). An increase in the day 4 value was observed in some cases, mainly due to the trophoblastic tissue breakdown releasing the hormone. (Table 5)

Methotrexate has a cytotoxic effect on trophoblastic tissue. Although it arrests mitosis in cytotrophoblast, the syncytiotrophoblast mass may still increase and produce β-hcg.

Table 5: Mean β-hcg range

Day	Single dose (mean range)	≥Two doses (mean range)
1st	1234 (109-5269)	1319.20 (865-6885)
4th	1350 (162-6241)	1508.13 (128-6990)
7th	895 (30-1518)	940 (158-2947)
Time of resolution	32 days	58 days
Cases: n (%)	45 (75%)	15 (25%)

The average time of resolution for ectopic pregnancy was 32 days for single dose of methotrexate and 58 days for those receiving two doses or more. Time of resolution for ectopic pregnancy was defined as the total number of days from the beginning of treatment until β-hcg level became negative (<5mIU/ml).

The total number of women treated with single dose was 75% (n=45) and 25% (n=15) received two doses or more. Patients with apparently normal ultrasound findings, no pregnancy (intra or extrauterine) visible on transvaginal ultrasound scan with serum hcg below the discriminatory zone (<1000mIU/ml) were grouped as PUL (pregnancy of unknown location). Thus 13.3% (n=8) patients of PUL were all treated successfully with single dose of MTX in the current study.

The overall success rate of treatment in our study was 65% (n= 39). Surgical intervention was required for 35% (n=21) of patients with tubal rupture and abdominal pain. Twenty-five (n=15) patients complained of lower abdominal pain between days 2-7 and out of them 25% (n=12) required early surgical intervention by diagnostic laparoscopy followed by salpingectomy or salpingotomy by open laparotomy. Two cases were managed by laparoscopic salpingotomy. Seven cases received intraoperative MTX instillation into the fallopian tube during tubal preservation by salpingotomy or tubal milking procedures. Mild vaginal bleeding not more than the initial bleeding was noted in 25% (n=5) with no reported case of gastrointestinal side effects.

A rare case of bilateral tubal ectopic pregnancy on single dose of MTX failed and later underwent salpingectomy for one fallopian tube and tubal conservation by salpingotomy for the other. The incidence of infertility was 15% (n=9) in the studied group. Out of these, two women had conceived spontaneously and the rest with assisted reproductive technique. There were 8.3% (n=5) women with history of previous ectopic pregnancy and 21.6% (n=13) with history of miscarriages. None of the women were using birth control measures except a few who used natural method of birth control, which is very common in Oman.

On the other hand, 30% (n=18) women reported successful pregnancy outcome after one year and 13.3% (n= 8) cases after 2 years. Three cases suffered missed miscarriage after one year. While 16 cases were lost to follow-up and may have followed at other health institutions in the Sultanate. Moreover, 11.6% (n= 7) cases suffered secondary infertility and the rate of repeat ectopic pregnancy in our study was 1.6% (n= 1).

Discussion

Ectopic pregnancy occurs in around 1% of pregnant women and may seriously compromise women's health and future fertility.[6] 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.[7]

Single dose methotrexate appears effective not requiring citrovorum recovery and has better patient compliance. Treatment success is inversely correlated to β-hcg concentration.[8] The most important selection criteria for medical management is the absence of pain and the prediction that the pregnancy will not rupture before its resolution. Surgery and medical management are the two ways to treat ectopic pregnancy. Both are effective and choice depends on clinical situation, site of ectopic mass and access to technology.[9] Systemic single dose methotrexate seems to offer the greatest benefits in terms of efficacy and tolerability. It has proved to be a good alternative to laparoscopy in selected cases.

Pregnancy of unknown location was treated in 10% of women by systemic methotrexate compared to a success rate of 13.3% (n=8) in our study and 29 women in Thia's study.[1,10,11] The success rate of systemic MTX in our study was 65% (n=39) and 35% (n=21) required surgical intervention. Thus, 25% (n=15) were treated with two doses of MTX and one among these patients received a third dose for plateauing β-hcg levels on day.[9] Thirty patients with small unruptured ectopic pregnancies achieved a success rate of 86.7% with five women requiring a second dose and one woman was successfully treated with three doses.[12]

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.[13] Success reached 90% (n=10) in patients out of 11 with single dose treatment in Merisio's series.[8] Literature published so far shows a success rate ranging from 67% to100% in single versus multidose treatment for ectopic pregnancies.[14]

In all comparative studies, the success rate was found to be much higher than in our 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. With more experience of using the drug the success rate improved. Careful selection of cases and confining strictly to the criteria of low β-hcg levels, adnexal mass ≤4 cm and proper clinical assessment avoided unnecessary surgical intervention and improved the success rate year by year. (Table 6)

Treatment failure based strictly on a high increase in β-hcg level from day 4 to 7 may be a hasty judgment. Pain after MTX treatment could be due to tubal abortion or stretching of the tube by hematoma contributing to increased failure rate in most of the studies.[15] Fear of rupture misleads clinicians to operate early on unruptured ectopic pregnancies that would otherwise resolve with

medical management. Differentiating 'separation pain' due to tubal abortion from pain due to tubal rupture can be difficult and may lead to early surgical intervention.

Table 6 : Yearly success rate of treatment at Nizwa hospital

S. No	Year	n	Successful (n)	Successful (%)
1.	2005	5	2	40
2.	2006	10	6	60
3.	2007	8	5	62.5
4.	2008	15	9	60
5.	2009	10	7	70
6.	2010 (June)	12	10	83.3
Total		**60**	**39**	**65**

Mahboob reported a success rate of 80% by treating 12 out of 15 women with single dose MTX with initial β-hcg levels equal to 5000mIU/ml.[16] In our study, all patients with β-hcg more than 5000 mIU/ml failed to respond to medical treatment. Mamdoh demonstrated that β-hcg of 2000 mIU/ml is an optimum cut off value for selecting potential cases for medical failure using the single dose approach as cases with intial β-hcg value of >2000 mIU/ml and or an embryonic sac of >3.4 cm should be closely monitored for treatment failure.[17] This correlates with our study as failure rate was highest with adnexal mass of ≥4 cm. In the same series, an increase in the treatment failure group with advanced maternal age ≥35 years and history of spontaneous abortions was noted corresponding to our study where success rate of MTX treatment decreased as maternal age increased.

In our study, nine women aged over 35 years had a failure rate of 55.5% (n=5). While Lee reported a success rate of 96% with β-hcg less than 6000 mIU/ml and 58% when β-hcg is greater than 6000 mIU/ml.[18] He noted that initial β-hcg is the only predictor of success for repeated injection of MTX in single dose regimen.[18]

The incidence of infertility as a risk factor reported in literature was 30% for ectopic pregnancy.[9] However, it accounted for 15% (n=9) in our study (primary-7 and secondary-2). Many studies have identified the risk factors for ectopic pregnancy.[19,20] A third of cases are associated with tubal damage caused by infection or surgery, and another third with smoking which is a rare factor among Omani women. No cause can be established for the remaining third. Techniques of assisted reproduction increase the risk of ectopic pregnancy by 2-4%.

Multiple dose regimen for haemodynamically stable women with an unruptured tubal EP with serum hcg concentrations <3000 mIU/ml and a single - dose MTX for serum hcg <1500 mIU/ml is recommended.[6] Women with a pretreatment β-hcg level of 3000-4000 mIU/ml have a greater probability of surgery or multiple dose treatment.[12]

The time of resolution in our study was 32 days with a single dose, and 58 days with ≥two doses of methotrexate as compared to 27.3 days and 35 days respectively in other series.[8] Thai noted the time of EP resolution was 33 days with one dose and 55 days with two doses, similar to our study.[1] (Table 7)

Table 7: Time of resolution of ectopic pregnancy in days

MTX	Merisio study	Thia study	Nizwa study
Single dose	27.3	33	32
Two doses	35	55	58

Erdem reported the mean time of resolution as 26.5 (10-37) days in patients who were successfully treated with MTX.[21] These results are consistent with other studies.[22]

Laparoscopy is less costly than open surgical approach. Laparoscopic surgery was compared with open surgery in three randomized controlled trials and was found to be associated with shorter operation time, less intraoperative blood loss, less hospital stay and less analgesic requirement.[23] This is the preferred mode of treatment provided suitable equipment and surgical expertise is available and so long as the patient's inclusion criteria is fulfilled. In the same study, the rate of persistent ectopic pregnancy after laparotomy with tube conserving surgery was 3-5% and after laparoscopy was 3-20%. Methotrexate regimen reduces the incidence of persistent trophoblast. Persistent trophoblast is detected by the failure of serum hcg levels to fall as expected after initial treatment, often a problem occurring after salpingotomy rather than salpingectomy. In 12 cases treated with laparoscopy, one case of persistent trophoblast was observed and can be reduced with medical management of ectopic pregnancy and β-hcg follow up to avoid complications such as delayed hemorrhage owing to persistent trophoblast.[6]

In our study, 25% (n=15) of women complained of lower abdominal pain, and 25% (n=12) were treated surgically due to increasing hemoperitoneum. Most studies showed increased lower abdominal pain between 2-7 days after treatment. This complication of methotrexate is disturbing in an outpatient with an ectopic pregnancy. In Thai's series, 40% (n=4) of patients were hospitalized for pelvic pain two days after treatment and their pain regressed without surgery.[1] One patient developed mild rash in light exposed skin areas. No such complaint was observed in the studied patients managed as inpatients. In the same study, 28.2% (n=9) of patients complained of abdominal pain a between days 4 and 8, and one patient was found to have a ruptured cornual ectopic pregnancy at laparoscopy. Minor side effects reported in the same series were mucositis in 19.1% (n=21), and 10.9% (n=12) of the patients suffered gastric pain and diarrhea. No side effects were reported with single dose treatment in a series of 30 patients with a success rate of 97%.[24] Increased abdominal pain on days 5-10 after medical management of ectopic pregnancy has to be closely monitored for possible rupture.[25]

Future fertility outcome was followed for 3 years in our study. Methotrexate therapy was associated with high rates (80%) of subsequent fertility compared to our study, where successful

intrauterine fertility was 30% in the first year, followed by 13.3% in the second year with a secondary infertility rate of 11.6%.[26] In our study, of the 60 diagnosed cases of unruptured ectopic pregnancies, a 36 year para 4 reported with ectopic pregnancy of six weeks gestation, which was managed surgically by right salpingectomy for leaking EP. Subsequently after two years, she reported with EP of the other side which was treated conservatively with two doses of MTX corresponding to a rate of 1.6% repeat ectopic pregnancy. Successful pregnancy rate following methotrexate was 87% and that of repeat ectopic pregnancies was 13%.[25] In another study following medical treatment of ectopic pregnancy, conception rate was 60%, recurrent ectopic was 20%, spontaneous miscarriage was 30% and subsequent live birth was 30%.[27] These results are comparable to our study where 30% live births, 50% (n=3) spontaneous miscarriages and 1.6% (n=1) of recurrent ectopic pregnancies were observed.

Conclusion

Methotrexate has proven to be an effective medical management for ectopic pregnancies in a society where tubal conservation is of utmost importance. The medical management by MTX seems to offer several benefits over surgical treatment. It is less invasive, less expensive and can be given on an outpatient basis and does not need expertise like laparoscopy. Future reproductive expectations are better with methotrexate with higher intrauterine pregnancy rates and lower ectopic rates subsequently. However the risk of tubal rupture after medical treatment combined with a prolonged follow up for an ectopic pregnancy to resolve requires outpatient monitoring for rupture and methotrexate side effects making compliance important in patient selection. 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.

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