



COMPARING SINGLE DOSE METHOTREXATE TO SALPINGECTOMY FOR TREATMENT OF UNRUPTURED TUBAL PREGNANCY: A PROSPECTIVE CASE STUDY AT A TERTIARY CENTRE

Obstetrics & Gynaecology

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ABSTRACT

Objective: To compare success of treatment and failure rates between single dose systemic methotrexate (50mg/m²) and salpingectomy for the treatment of unruptured tubal pregnancy.

Material and methods: this is a prospective case study done in department of obstetrics and gynaecology at a tertiary centre of government in Patna medical college and hospital. All clinically stable women with clinical diagnosis of unruptured tubal pregnancy were selected from January 2015 to January 2020 who were admitted in labour room ward in Patna medical college and hospital. The ethics committee approval was taken. A total of 62 women were selected for study. All clinically stable women with history of amenorrhea, pain abdomen and vaginal bleeding and positive pregnancy test along with serum β hcg concentration below 5000 IU/L and adnexal mass of less than 3.5cm in diameter by transvaginal ultrasound and minimum hemoperitoneum and no adnexal foetal heart were included as cases of unruptured tubal pregnancy. Exclusion criteria were an unstable vital sign, generalised peritonism on abdominal palpation, a falling β hcg, diagnostic uncertainty, ultrasonically diagnosed interstitial cervical, ovarian or heterotopic pregnancy and contraindication to methotrexate.

Result: a total of 62 patients of unruptured tubal pregnancies were registered at a tertiary centre for a period of 5 years in labour room emergency ward. All patients fulfilled the eligibility criteria. 34 patients underwent surgery and required no further treatment compared to 28 women who were given systemic methotrexate. 14 out of 28 responded to single dose of methotrexate well. 9 out of 28 patients required more than one dose of methotrexate. 5 out of 28 underwent surgery during follow up. Women treated with methotrexate experienced greater and more prolonged vaginal bleeding and pain abdomen. The likelihood of methotrexate treatment failure was greater at higher serum concentration.

Conclusion: The study showed that in treatment of unruptured tubal pregnancy, single dose systemic methotrexate is a less effective treatment than surgical salpingectomy. Methotrexate can be offered as an alternative to salpingectomy in cases of low serum β hcg under close and regular follow up.

KEYWORDS

Apical plug, Apexification, Biodentine, Calcium hydroxide, Open apex

Introduction:

Ectopic pregnancy is a serious medical and surgical condition. It can affect patient's fertility and can even be life threatening in cases of tubal rupture. In normal pregnancies fertilization occurs in the ampulla of the fallopian tube and then the fertilized egg travels to the uterine cavity for implantation. In ectopic pregnancy the implantation occurs outside the uterine cavity. The common extrauterine site for implantation being ampulla of tube [1]. The other reported implantation sites include the abdomen, cervix, caesarean section scar and ovary[3,4]. While improvements in diagnostic techniques and treatment have been made, ectopic pregnancy can be initially missed and remains a significant contributor to pregnancy related deaths and decreased fertility [1,2,5]. Classic presenting symptoms include lower abdominal pain, vaginal bleeding and amenorrhea [5]. Half of the patient present asymptotically at an early gestation [1,5]. A confident diagnosis and management of ectopic pregnancy can now be made when we combine transvaginal ultrasound and quantitative serum β hcg measurement. This diagnosis is increasingly being made before tubal rupture and with earlier diagnosis it has become apparent that many tubal pregnancies follow a relatively indolent course with a low chance of sudden haemorrhage. This has resulted in increasing interest in the use of medical therapy for the treatment of ectopic pregnancy.

Many agents have been tried, but the great majority of women receiving medical therapy for ectopic pregnancy have been treated with methotrexate. This has been administered either locally or systemically as a multiple or more recently a single dose regimen. Local administration is necessarily invasive and multiple doses of systemic methotrexate have been associated with a high incidence of side effects making these approaches relatively unattractive. If effective and well tolerated the most appropriate treatment for suitable women could be a single intramuscular dose of methotrexate. Such a treatment regimen would permit the management of ectopic pregnancy entirely within an outpatient setting. This would considerably reduce treatment costs and cause less disruption to the lives of women undergoing treatment. From our clinical experience prior to initiating this study we were uncertain whether methotrexate was as effective as salpingectomy our most frequently used treatment for ectopic pregnancy. The aim of this study was to test the hypothesis that systemic methotrexate as a single dose regimen is less effective

than operative salpingectomy for treatment of unruptured tubal pregnancy.

Methods:

A total of 62 women with clinical diagnosis of unruptured tubal pregnancy were included from January 2015 to January 2020, over a period of 5 years, from labour room ward of a tertiary centre, Patna medical college and hospital, Patna. The ethics committee approval was taken. Quantitative serum β hcg measurement and transvaginal ultrasound was used to diagnose the presence of an ectopic pregnancy along with positive patient history of amenorrhea pain abdomen and vaginal bleeding. Women were eligible for entry into the trial if they had a serum β hcg concentration below 5000 IU/L, adnexal mass less than 3.5cm in diameter, minimal hemoperitoneum or transvaginal ultrasound (estimated to be <300ml), diagnosis confirmed, clinically stable, and no adnexal foetal heart, serum β hcg not falling after 48hrs, uterine cavity empty, fit for surgery or methotrexate. Both women with or without any desire for future fertility were eligible for entry into the study. Exclusion criteria were unstable vital sign, generalised peritonism on abdominal palpation, a falling serum β hcg concentration, diagnostic uncertainty requiring laparotomy, an ultrasonically diagnosed interstitial, cervical, ovarian or heterotopic pregnancy, contraindications to methotrexate (i.e. leukopenia, thrombocytopenia or elevated serum liver enzymes or creatinine). Patient consent was taken. Women who underwent surgery as soon as they had been adequately prepared and theatre space was available. Women allocated to methotrexate received a single intramuscular methotrexate dose of 50 mg/m² of body surface area. women were treated on an outpatient basis and were reviewed clinically on day 4 when a serum β hcg was measured. Patients were reviewed again clinically on day 7 and a serum β hcg, full blood count and serum aspartate transaminase was measured. Thereafter women were seen weekly for a clinical review and measurement of serum β hcg. A second dose of methotrexate was given if serum β hcg concentration had failed to fall by more than 15% between day 4 and day 7 or was plateauing or rising after day 7. Further dose of methotrexate was given if serum β hcg concentration still failed to fall and no contraindication to methotrexate has developed. Laparotomy was performed if patient showed signs clinically or on ultrasound scanning of tubal rupture during follow up, or if she required further medical therapy but developed return of the patient's serum β hcg concentration to <5IU/L

following initial therapy without the need for any further medical or surgical intervention. Primary hypothesis tested by this study was that a single dose of systemic methotrexate is less effective than operative salpingectomy.

Statistical methods:

All statistical analysis was undertaken using SPSS version 7.0. Where appropriate results were given as mean values with 95% confidence intervals (CI) or median with a range.

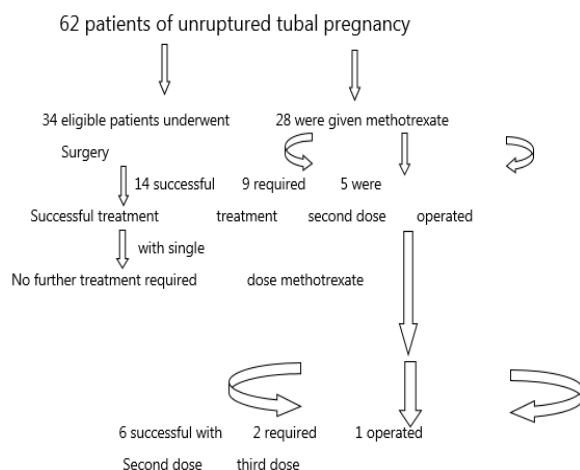
Result:

A total of 62 women with clinical diagnosis of unruptured tubal pregnancy were admitted in the labour room ward in 5 years from January 2013 to January 2018. All patients fulfilled the eligibility criteria. All patients were given option of medical and surgical treatment. Patient consent was taken. Mean age of patient with ectopic pregnancy was 26.7 years in our study group. The mean gestational age was 43.1 days. The most common presenting symptom in our study with patients of unruptured tubal pregnancy was amenorrhea in 93.1% followed by abdominal pain in 71% of cases. The duration of amenorrhea varied between 6.3 weeks to 9 weeks. All patients had a quantitative β hcg assay done and in 56% serum β hcg was below 1000 IU/L and in 33% serum β hcg was more than 3000 IU/L. All patients also had a transvaginal sonography done. The major sonographic finding was empty uterine cavity in 91% of cases, pseudogestational sac in 4.9% cases endometrial thickness in 71.3% and adnexal mass in 32.6%. Out of 62 patients of unruptured tubal pregnancy, 34 opted for surgical method and were operated. These patients required no further treatment. 28 out of 62 patients were given injection methotrexate. 9 required more than one dose of methotrexate. 5 out of 28 underwent surgery during follow up and were found to have ruptured fallopian tube at time of surgery. Rest 14 out of 28 responded to single dose of methotrexate well.

Table. 1: Baseline characteristics of two treatment groups

Sl. No.	Characteristics	Methotrexate (n=28)	Salpingectomy (n=34)
1	Age	26.4	27.1
2	Parity	0	0
3	Duration of gestation(days)	43.4	42.8
4	Clinical symptoms		
	a. None	1	1
	b. Vaginal bleeding only	2	2
	c. Abdominal pain only	1	3
	d. Abdominal pain and vaginal bleeding	22	30
5.	Duration of bleeding (days)	20-64	14-60
6.	Duration of pain(days)	8-31	20-16
7.	Pre-treatment serum β hcg(IU/L)	922-4066	704-4400
8.	Pre-treatment haemoglobin(g/dl)	12.4	11.8
9.	Ultrasound finding of adnexal mass<3.5	All (1.5-2.4) cm	All (1.9-2.9)

Study outcome



All 34 women who were treated with surgery required no further treatment. Of the 28 women in methotrexate group 14 were treated successfully with a single dose of methotrexate. 9 women failed to demonstrate an adequate fall in serum β hcg concentration on day 7 and were given a second dose of injection methotrexate. 5 women had to undergo laparotomy during first week of follow up. In three of these women tubal rupture was suspected and rest 2 requested surgical management after first dose of methotrexate. Of the 9 women who were given a second dose of methotrexate, 6 required no further treatment, 2 required a third dose of methotrexate on day 14 and one required a fourth dose of methotrexate when her serum β hcg concentration again started rising during fifth week of follow up and was finally operated upon patients request.

Table 2: Women in methotrexate group who underwent surgery during follow up

Sl. No.	Initial serum β hcg (IU/L)	Day of operation	Serum β hcg on day of operation	Operation	Finding(hemoperitoneum)
1.	1100	1	1154	Salpingectomy	Unruptured tubal pregnancy(50ml)
2.	2310	9	1910	salpingectomy	Leaking hematosalpinx 200ml
3.	2200	10	2210	salpingectomy	Tubal rupture(250ml)
4.	2185	3	2298	salpingectomy	Tubal rupture(800ml)
5.	1595	2	1660	salpingectomy	Tubal rupture(400ml)

The first patient of table 2 was operated on patients request and rest four patient's clinical and ultrasound finding were consistent with tubal rupture.

Complications- In surgical group, 2 patients developed wound sepsis and were prescribed oral antibiotics and daily dressing post operatively for wound infection. In methotrexate group one women had an elevated liver enzymes level and mild neutropenia following second dose of methotrexate. These haematological abnormalities returned to normal within a week.

Follow up-the median time for β hcg level to fall to less than 5 IU/L was 28 days (range 14-71) in the methotrexate group and in surgical group where salpingectomy was done no follow up with β hcg was done.

Initial serum β hcg level were significantly lower in patients who required only a single dose of methotrexate (median β hcg 345 IU/L) when compared with women requiring either more than one dose of methotrexate or surgery (median β hcg 1508 IU/L) ($P < 0.01$). Other side effects were reported by 4 women who had received methotrexate and included minor mouth ulceration (two women), dry eyes (two women) and vaginal dryness in one women. Women who had undergone laparotomy reported no additional side effects.

Discussion:

To decide between medical treatment by systemic methotrexate and surgical treatment by salpingectomy for an unruptured tubal pregnancy is in a way challenging. There has been an increase in incidence of ectopic pregnancy due to multiple factors such as sexually transmitted infections, tubal surgeries, use of intrauterine devices, smoking and medically assisted procreation. In our study the mean age of patients presenting with ectopic pregnancy was 26.7 years. In literature it ranges between 25 and 35 years [6,7]. The risk of ectopic pregnancy increases with age. This can be explained by changes in tubal function with age. The most common symptom in our study was amenorrhea (93.1%) and pain abdomen (71%) which correlates with the range in literature as well [8].

Medical management using methotrexate has been used for treatment of ectopic pregnancy since 1982. It can be given locally or systemically and is effective in all the ectopic pregnancy location. Most commonly methotrexate is given intramuscularly at dosage of 1mg/kg of body weight. There are many possible treatment regimens with single dose or multiple injections. In our study we hoped to determine the promising results for single dose systemic methotrexate. Medical treatment of ectopic pregnancy needs rigorous monitoring.

Inclusion criteria were based on previously published uncontrolled trials [9] and ACOG guidelines [10]. According to CNGOF [11], ectopic pregnancy is highly suspected when β hcg level is over 1500 IU/L and there is no intrauterine gestation sac in the transvaginal ultrasound. Serum β hcg kinetic is more important and informative than a single β hcg value. Transvaginal ultrasound has a specificity of 99% and a sensitivity of 69% [12]. In our study the diagnosis of ectopic pregnancy was confirmed in 88% of cases by transvaginal ultrasound. Although TVS has been shown to achieve a very high specificity in the diagnosis of ectopic pregnancy [13], it is an operator dependent investigation with result sometimes requiring interpretation in light of clinical history and symptoms. It may be less reliable in the evaluation of women with minimal symptoms such as those likely to be eligible for medical therapy [14]. TVS will readily demonstrate the presence of even small quantities of free fluid in the pelvis but is unable to reliably determine whether there is any active bleeding or if tubal rupture has occurred [15]. Less 5% of our patients population had no pelvic pain at time of diagnosis [table 1] and while entry criteria such as serum β hcg level and adnexal mass size may be useful objective criteria for patient selection; more subjective criteria such as clinical and examination findings also play a central role in determining a patient's suitability for medical therapy.

Management of ectopic pregnancy has greatly progressed during last years. Medical treatment is known to be less costly and there are many scores used to decide the treatment regimen in cases of ectopic pregnancy like Carson and Buster, Elito, Fernandez. However, these scores are not commonly used.

We found in our study that treatment with a single dose of intramuscular methotrexate had a 50 % success rate with 32.1% of women requiring further injection of methotrexate and 21.4% undergoing surgery during follow up. This success rate is significantly lower than 100% success rate we found with operative salpingectomy (95% CI of difference 10% to 47%). 3 women (10.7%) in methotrexate group also experienced tubal rupture during follow up. These results are comparable to the results of 14 uncontrolled studies that have been published to date [16,17,18]. These have shown a success rate varying from 52%-94% for single dose systemic methotrexate and a surgical intervention rate varying from 0%-22%. The difference in the success rate of methotrexate in these studies could be explained by the variability of inclusion criteria and the definition of failure.

Two other randomised trials have compared single dose systemic methotrexate with conservative surgery [19,20]. Saraj et al. using a dose of 1mg/kg, found a 78% success rate (30 out of 38 women) for single dose methotrexate compared with 92% (34 of 37) for surgery (difference not significant). In second randomised trial 29 comparing single dose methotrexate with conservative surgery success rate of 88.2% (45 of 51 women) were reported for methotrexate and 95.5% (47 of 49) for surgery (difference not significant).

One possible influence on the likelihood of successful treatment with methotrexate is initial serum β hcg concentration [21]. In our study women who required more than one dose of methotrexate or surgical intervention had a significantly higher initial serum β hcg concentration than those women who were treated successfully with only one dose. There was also a significant correlation between initial serum β hcg and the time taken for serum β hcg concentration to fall to less than 5 IU/L. Other authors have reported reduced success rates at initial serum β hcg concentrations as low as 1500 IU/L with single dose methotrexate and 3000 IU/L with a multiple dose regimen [22]. Another factor that will affect apparent success rates is an individual centre threshold for surgical intervention.

The definition of failure with methotrexate treatment of ectopic pregnancy varies according to authors. In our study failure was when we resorted to surgical treatment. In our study failure rate was 21.4%. The most common cause of failure were suspicion of tubal rupture, increase in abdominal pain, increase in hemoperitoneum, unfavourable evaluation of β hcg level and patient refusal of getting another dose of methotrexate. Methotrexate can cause multiple adverse effects such as stomatitis, colitis, nausea, abdominal pain, vomiting, leukopenia and transitory hepatic enzymes elevation. However, these side effects are more common with multiple dosage regimen than single dose regimen, therefore in our study these side effects were seen in only 10.7% of patients. Studies have shown that pregnancy rate after an ectopic pregnancy is 60% with recurrence rate of 10-30%.

Conclusion:

Our study showed that a single dose of systemic methotrexate is only likely to be an effective alternative to surgical salpingectomy in women presenting at relatively low serum β hcg concentration. At serum β hcg concentration over 1500 IU/L women are likely to need more than one dose of methotrexate and a significant proportion will require surgical intervention. If methotrexate is used strict inclusion criteria and meticulous follow up are essential. Surgical salpingectomy will continue to be treatment of choice for most women with ectopic pregnancy.

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