

## COMPARATIVE STUDY OF MEDICAL AND CONSERVATIVE SURGICAL METHODS FOR UNRUPTURED ECTOPIC PREGNANCIES

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### ABSTRACT

#### AIMS AND OBJECTIVES

To study and compare medical (Methotrexate) versus surgical (Laparoscopic salpingostomy) conservative management for unruptured ectopic pregnancy.

#### MATERIALS AND METHODS

This is a prospective study conducted at CKM Government Maternity Hospital, Warangal, Telangana. The recruitment period was from July 2012 to June 2013 and these patients were followed for 2 years from July 2013 to June 2015. An institutional ethical clearance was obtained and an informed consent was taken from the patients who were selected for the study. Of the 63 unruptured ectopic pregnancy cases, 31 patients were given multiple dose methotrexate and 32 underwent conservative surgical management (Laparoscopic salpingostomy) according to the inclusion and exclusion criteria. The distribution of patients was studied according to the age, parity, literacy status, presence of risk factors and followed up with serum  $\beta$  HCG levels. The success and failure with both the treatments were defined and the patients were followed up till 2 years for fertility outcome.

#### RESULTS

Most of the patients were nulliparous (71.4%), illiterates (77.7%) and belong to age group 21–25 years (53.9%). Half of them had prior risk factors (55.5%) for ectopic pregnancy. Mean  $\beta$  HCG levels came down to normal from day 4 after salpingostomy, but there was a consistent fall till day 28 after methotrexate treatment. Complications were seen with both the treatments. The rate of success was comparatively more for salpingostomy patients (84.3%), but the difference is not statistically significant. The successful patients were followed up for tubal patencies, ectopic pregnancies and recurrent ectopic pregnancies and the differences were not statistically significant with both medical and conservative surgical treatments.

#### CONCLUSION

Conservative surgical treatment and medical treatment are both almost equally effective to preserve the subsequent fertility of the women. According to our study, the difference in success and failure for both the treatments (Medical and surgical) and the difference in fertility outcome in 2 years - pregnancy rate and recurrent ectopic with both medical and conservative surgical is not statistically significant. However, for firm conclusion to be drawn randomized multicentric trials have to be done.

#### KEYWORDS

Unruptured Ectopic Pregnancy, Methotrexate, Salpingotomy.

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#### INTRODUCTION

There is increased incidence of ectopic pregnancy in the present years due to early diagnosis, popularity of contraception, extensive use of Assisted Reproductive Technology, tubal surgery and due to increased incidence of sexually transmitted diseases.<sup>1</sup> The incidence of ectopic pregnancy is 2.1.<sup>2</sup> there is also increased incidence of recurrent ectopic pregnancy.

According to Ankum and Colleagues.<sup>3</sup> recurrence after one ectopic is about 10%. The incidence of heterotopic pregnancy after ART is about 0.5-1% according to Mekel and Teal.

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The incidence after ZIFT is 4.3% and after IVF is 1.8% (SART and ASRM 2007).

In developed countries improvements in the diagnosis and treatment of ectopic pregnancy have shifted concerns from the immediate health of the women towards preserving her subsequent fertility. This is one of the goals of conservative treatment.

Conservative surgical treatment was first advocated by Kelly in 1898. Stromme.<sup>4</sup> was the first surgeon for successful use of salpingostomy. It is the preferred surgical method when patients desire future fertility. Medical treatment by methotrexate was developed more recently. Tanaka.<sup>5</sup> and associates were the first to use methotrexate for ectopic pregnancy.

#### AIM

To assess the success, safety and future fertility in patients of ectopic pregnancy when managed by conservative methods - medical and surgical.

**OBJECTIVE**

To study and compare medical (Methotrexate) versus surgical (Laparoscopic salpingostomy) conservative management for unruptured ectopic pregnancy.

**MATERIAL AND METHODS**

This is a prospective study conducted at CKM Government Maternity Hospital, Warangal, Telangana. The recruitment period was from July 2012 to June 2013 and these patients were followed for 2 years from July 2013 to June 2015. An institutional ethical clearance was obtained before starting the study. An informed consent was taken from the patients who were selected for the study.

Sixty three cases of unruptured ectopic pregnancy were diagnosed by transvaginal sonography and serum  $\beta$  HCG levels. Medical management with Methotrexate was done in 31 cases and conservative surgical management (Salpingostomy) was done in 32 patients and the success rate for fertility and complications in both groups were compared in the study.

**Inclusion Criteria for Medical/Conservative Surgical Management**

- Hemodynamically stable patients.
- Asymptomatic motivated compliant patients.
- Size of ectopic sac  $\leq 4$ cms.
- Cases with or without cardiac activity included.
- Initial  $\beta$  HCG levels 5000 mIU/mL.
- Patients who had single/no live child.

**Exclusion Criteria for Medical/Conservative Surgical Management**

- Acute intraabdominal haemorrhage.
- Hemodynamically unstable women.
- Interstitial pregnancy.
- Initial  $\beta$  HCG level  $>5000$ mIU/mL.
- Size of gestational sac  $>4$ cms.
- Immunodeficiency.
- Chronic hepatic or pulmonary disease.
- Blood dyscrasias.
- Peptic ulcer disease.

The distribution of the patients was studied according to the age, parity, literacy status, previous history of ectopic pregnancy and the results were compared. The presence of risk factors (1 or more), history of primary or secondary infertility and any treatment undertaken for the same were noted. History of prior tubal surgeries were also noted. These patients were monitored after treatment with  $\beta$  HCG levels.

Multiple dose regimen of methotrexate was followed for medical management. Methotrexate 1mg/kg was given intramuscularly on days 1, 3, 5, 7 and leucovorin 0.1mg/kg was given intramuscularly on days 2, 4, 6, 8. Serum  $\beta$  HCG levels were monitored on day 1, 3, 5, 7. If the decrease is  $\geq 15\%$ , then the values were repeated weekly until undetectable. These patients were monitored with weekly hemogram and liver function tests.

After salpingostomy, the values were repeated on day 4 and on day 7 and weekly if decreased values were not obtained. When the  $\beta$  HCG levels came down to undetectable levels, the conservative management was considered to be successful.

When the  $\beta$  HCG levels were increasing or not declining in spite of giving multiple doses of methotrexate, then those cases were taken as failures. Those cases which ruptured during medical treatment were also taken as failures. Those who were diagnosed to have persistent trophoblastic disease on follow up were also taken as failures.

When salpingostomy was not possible because of hemorrhage during procedure or when  $\beta$  HCG levels did not come to normal within 3 weeks after the procedure (Persistent trophoblastic disease), they were considered as failure of conservative management.

Long term follow-up for the successful cases was done to evaluate the fertility by noting number of tubal patencies, intrauterine pregnancies and recurrent ectopic pregnancies.

**RESULTS**

Total number of deliveries during recruitment period were 7749. Total number of ectopic pregnancy cases were 242 during the recruitment period. Out of these, 179 cases were ruptured ectopic pregnancies/tubal abortions, which were admitted in emergency ward and treated immediately by laparotomy/operative laparoscopy after improving the general condition. The remaining 63 cases were unruptured ectopic pregnancies, which were taken as cases for the present study (Figure 1).

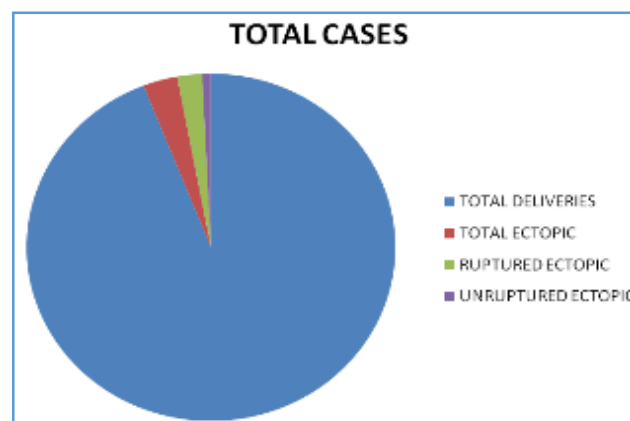


Fig. 1: Total Number of Cases

AGE IN YEARS	METHOTREXATE n=31 (%)	SALPINGOSTOMY n=32 (%)
16 – 20	3(9.6)	2(6.2)
21 – 25	16(51.6)	18(56.2)
26 – 30	10(32.2)	11(35.4)
30 – 35	2(6.4)	1(3.1)

**Table 1: Distribution of Patients According to Age**

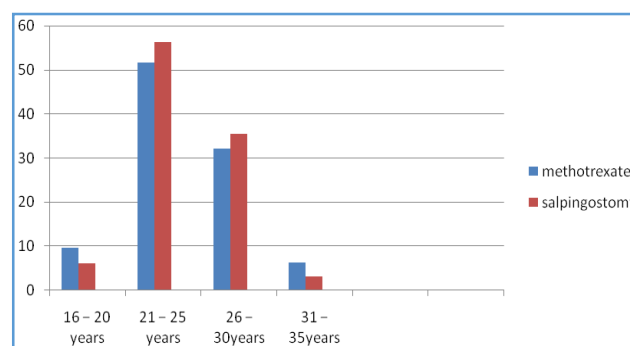
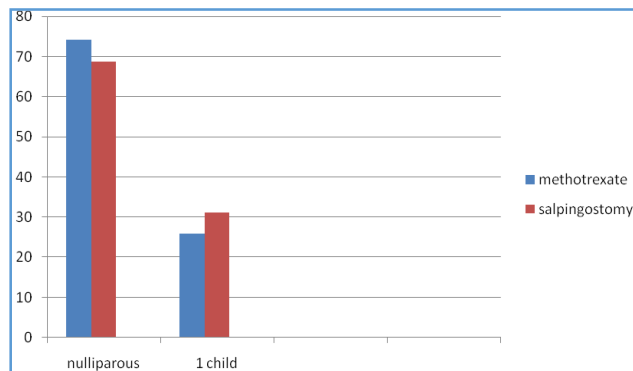


Fig. 2: Distribution of Patients According to Age

PARITY	METHOTREXATE n=31(%)	SALPINGOSTOMY n=32(%)
Nulliparous	23(74.1)	22(68.7)
1 Child	8(25.8)	10(31.2)

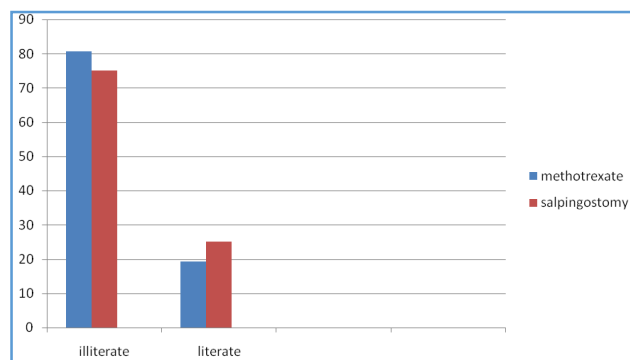
**Table 2: Distribution of Patients According to Parity**



**Fig. 3: Distribution of Patients According to Parity**

STATUS	METHOTREXATE n=31(%)	SALPINGOSTOMY n =32(%)
ILLITERATE	25(80.6)	24(75.0)
LITERATE	6(19.3)	8(25)

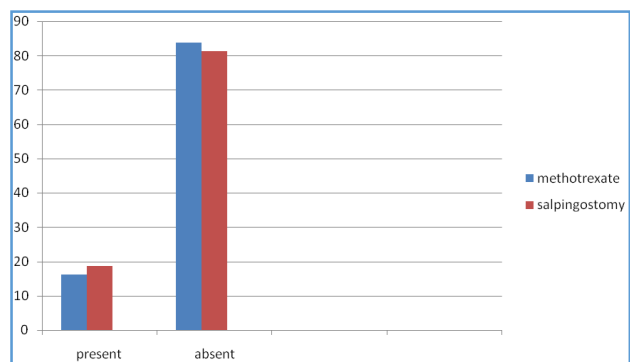
**Table 3: Distribution of Patients According to Literacy Status**



**Fig. 4: Distribution of Patients According to Literacy Status**

PREVIOUS ECTOPIC	METHOTREXATE n=31 (%)	SALPINGOSTOMY n=32(%)
Present	5 (16.2)	6 (18.7)
Absent	26 (83.8)	26 (81.3)

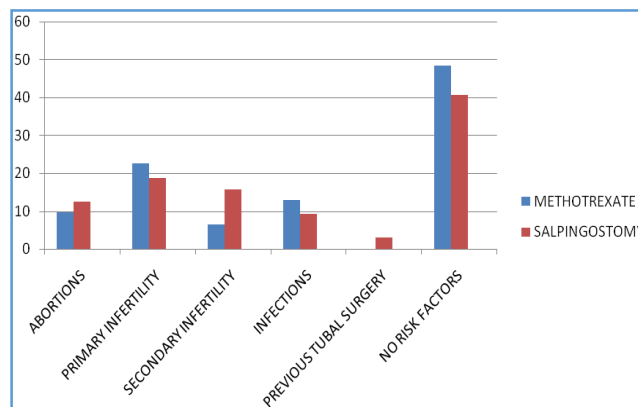
**Table 4: Previous H/O Ectopic Pregnancy**



**Fig. 5: Previous H/O Ectopic Pregnancy**

RISK FACTOR	METHOTREXATE n=31 (%)	SALPINGOSTOMY n=32 (%)
Induced/spontaneous abortion	3 (9.6)	4 (12.5)
Primary infertility	7 (22.5)	6 (18.7)
Secondary infertility	2 (6.4)	5 (15.6)
Infections/STD	4 (12.9)	3 (9.3)
Previous tubal surgery	0	1 (3.1)
No risk factors	15 (48.3)	13 (40.6)

**Table 5: Risk Factors in Both the Groups**



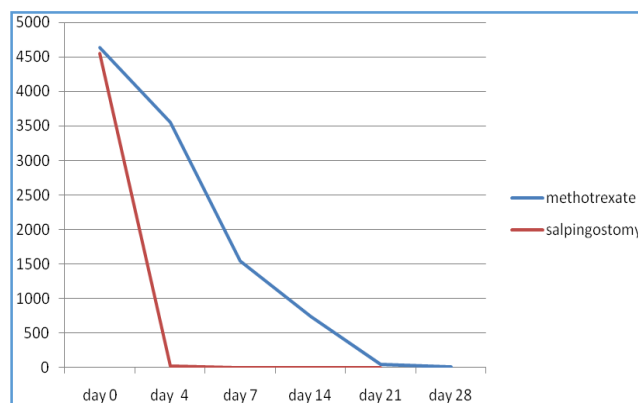
**Fig. 6: Comparison of Risk Factors**

SALPINGOSTOMY	4557
METHOTREXATE	4632

**Table 6: Mean  $\beta$  HCG Levels Before Treatment**

DAYS	METHOTREXATE	SALPINGOSTOMY
4	3546	20
7	1543	6
14	732	1
21	38	0.3
28	5	
35	0.5	

**Table 7: Mean  $\beta$  HCG Levels after Treatment in Both Groups**



**Fig. 7: Mean  $\beta$  HCG Levels before and after Treatment**

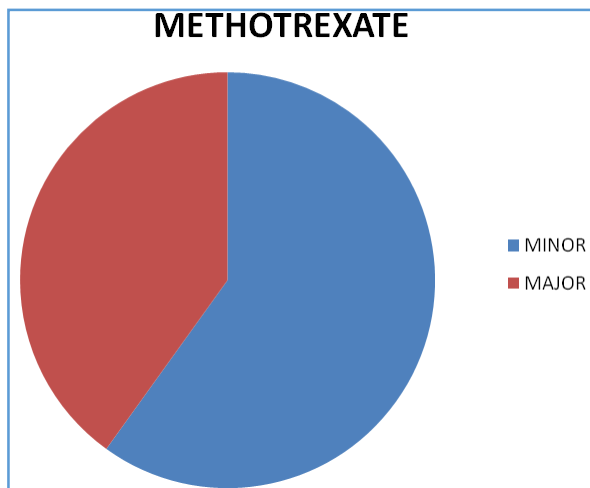


Fig. 8: Complications

Complications were seen with both the groups. Minor complications with methotrexate like stomatitis, alopecia, loss of appetite was seen in 6 cases. Major complications like abdominal pain due to intraperitoneal hemorrhage and leucopenia that led to hospital admission for observation were seen in 4 cases where methotrexate was given; 5 cases needed surgical management because there was no response to multiple doses (Persistent trophoblastic disease) and in 2 cases surgery was done due to rupture.

Hemorrhage was seen as a complication during laparoscopic salpingostomy intraoperatively in 5 cases. Hemostasis was achieved and blood transfusion given in 2 cases, whereas in 3 cases salpingectomy was done to control the hemorrhage; 2 patients were diagnosed to have persistent trophoblastic disease and were subsequently given methotrexate.<sup>(6,7)</sup>

RESULT	METHOTREXATE n=31(%)	SALPINGOSTOMY n=32(%)
SUCCESS	24(77.4)	27(84.3)
FAILURE	7(22.5)	5(15.6)

Table 8: Comparison of the Results of the Treatment

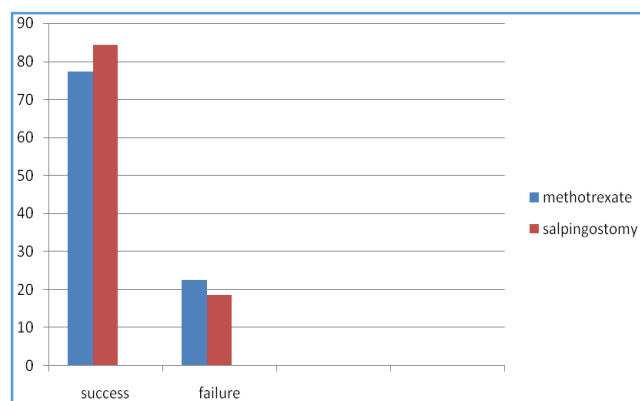


Fig. 9: Comparison of the Results of Treatment

Among the successful cases after salpingostomy (29), 3 cases were lost for followup. In the methotrexate group, 2 cases were lost for followup. These patients were followed up for the future fertility outcome.

OUTCOME	METHOTREXATE n=20(%)	SALPINGOSTOMY n=23(%)
TUBAL PATENCY	14(70)	18(78.2)
PREGNANCY RATE	12(60)	14(60.8)
REPEAT ECTOPIC	3(9.6)	4(12.5)

Table 9: Fertility Outcome

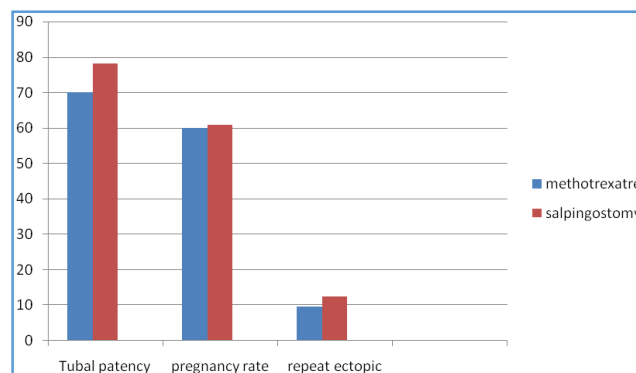


Fig. 10: Fertility Outcome

DISCUSSION

In our study, majority of the patients were in the age group of 21–25 years in both groups. Most of the patients are nulliparous with 20.6% incidence of primary infertility in these patients.

In Hemodynamically stable patients with unruptured tubal pregnancy, systemic methotrexate and laparoscopic salpingostomy were successful in treatment of majority of the cases.

The average methotrexate resolution rate among the study included was 77.4%. Of the 63 patients who were included in the trial, 31 patients were allocated systemic methotrexate of whom salpingectomy was necessary in 6.4% of these patients for tubal rupture.

Of 32 patients allocated laparoscopic salpingostomy, 6.2% needed methotrexate for persistent trophoblast and there was no case of tubal rupture noted.

The rate of failure of conservative surgical treatment (15.6%) was lower than that reported in other studies. The failure rate of medical treatment (22.5%) was consistent with that reported in some studies.<sup>8-11</sup>

In our study comparing fertility after medical and conservative surgical treatment showed that reproductive performance was slightly better with salpingostomy than that of medical management. This may be because of persistence of mass for a long period that may impair tubal patency and future fertility. Most other studies found little or no difference.<sup>(1,12-15)</sup> Lipscomb and Associates found no difference of fertility outcome either with Methotrexate of Salpingostomy.<sup>16</sup> The sample size in the present study may be too small for conclusion to be drawn.

In the study done by Fernandez et al.<sup>9</sup> comparing fertility after medical and conservative surgical treatment showed that spontaneous reproductive outcome was similar in both groups. During follow-up after 6 months of treatment tubal patency was assessed in both groups. The tube was patent in 45.1% of 31 patients in the methotrexate group and in 56.2% of 32 patients in the salpingostomy group.

In our study, the overall 2-year cumulative rate of recurrent ectopic pregnancy was 16.2%. The overall 2-year cumulative rate of recurrent ectopic pregnancy was same with conservative surgery or medical therapy.

STUDY	TUBAL PATENCY	INTRAUTERINE PREGNANCY	REPEAT ECTOPIC
Buster and Krotz study 2007	75 – 81%	52 - 61%	8 – 13%
Present study 2015	70 – 79%	60 – 61%	9 – 13%

**Table 10: Comparison of Fertility Outcome with Other Studies**

Buster and Krotz.<sup>17</sup> study showed that there is no difference in tubal patency (75–81%), intrauterine pregnancy (52–61%) or recurrent ectopic pregnancy (8–13%) treated with either laparoscopic salpingostomy or with methotrexate.

Stovall and Colleagues.<sup>18</sup> used single dose methotrexate 50mg/m<sup>2</sup> and found complete resolution (94.2%), mean time of resolution (35.5 days); 3.5% needed second course of methotrexate on day 7 and laparotomy in 5.8%. Tubal patency with HSG was seen in 82.3% cases.

Rates of intrauterine pregnancy were significantly higher if the contralateral tube was normal, lower if the woman was older or had a history of infertility.

Salpingostomy is a conservative surgical procedure, which requires expertise and the initial cost is more. The medical management with methotrexate requires long-term followup with serum  $\beta$  HCG levels. Also it may require frequent readmissions and laparotomy in case of persisting levels, which might increase the overall cost.<sup>19</sup>

## CONCLUSION

Conservative surgical treatment and medical treatment are both almost equally effective to preserve the subsequent fertility of the women. According to our study, the difference in success and failure for both the treatments (Medical and surgical) was not statistically significant. The difference in fertility outcome in 2 years - pregnancy rate and recurrent ectopic with both medical and conservative surgical is not statistically significant. However, for firm conclusion to be drawn randomized multicentric trials have to be done.

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