

Reproductive Outcome After Combined Local and Systemic Methotrexate Treatment of Unruptured Tubal Pregnancy

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A prospective study was carried out to assess the effectiveness of systemic methotrexate treatment in combination with its local injection under ultrasound guidance in unruptured ectopic pregnancy. This was carried out in Mayo Hospital, Lahore in collaboration with Lady Aitchison Hospital, Lahore. A total of 152 women admitted with diagnosis of extrauterine pregnancy but only 30 women fulfilled the criteria for our protocol. In 90% women no further surgical intervention was required (27/30) and 80% had intrauterine pregnancy within 15 months of treatment. However, 10% failed to respond to medical treatment and needed surgery.

Key words: Unruptured tubal pregnancy, local and systemic methotrexate injection therapy

Ectopic pregnancy has been recognized for centuries as major life threatening complication of gestation. First described by Albucasis in 963 A.D. management of this emergency remained unchanged until Lawton Tait¹ advocated surgical intervention in 1884. Until that time the management was expectant, carrying a mortality rate of approximately 60% with improved surgical and medical management, mortality rates dropped from 35.5/10,000 pregnancies in 1970 to 5 deaths per 10,000 pregnancies in 1987. However, ectopic pregnancy remains the most common cause of maternal death during the first half of pregnancy in USA². The decline in the mortality rate is remarkable, because the incidence of ectopic pregnancy increased as much as five fold during same period.

The increased sensitivity of serum β hCG (β -human chorionic gonadotrophin) immunoassay coupled with improved quality of transvaginal ultrasonography (TVS) has allowed early detection of ectopic gestation and so changed the goal of management from life saving to conservation of tubal and fertility preservation. Early detection of unruptured tubal pregnancy has led to less invasive and non-surgical methods of treatment, which have almost eliminated the need for laparotomy and in many cases the need for laparoscopy. As medical management different modalities are being used like, RU-486; prostaglandins; KCl (Potassium chloride) and actinomycin-D, methotrexate emerged as the drug of choice for this purpose. There is little information about the future fertility outcome after the medical management of unruptured ectopic gestation.

Methods

Between January 1999 and December 2000, 152 women were admitted with the diagnosis of extrauterine gestation. Thirty fulfilled the inclusion criteria of the present study.

- Intact gestational sac located within fallopian tube of less than 3cm in diameter.
- No evidence of intra-uterine pregnancy by TVS.
- Haemodynamically stable patient .

- No evidence of fetal cardiac activity.
- Maternal serum β -hCG not >10,000miu/ml.
- Woman wants to retain fertility. The remaining 122 women, who did not confirm to the inclusion criteria of this study underwent different interventions such as salpingectomy (n=110) and salpingostomy (n=10) and two women left against medical advice.

Thirty women with unruptured tubal pregnancy were treated with methotrexate at Lady Aitchison Hospital and Mayo Hospital, Lahore. Informed written consent were taken from all women. The management protocol included:

- Identification of extrauterine pregnancy by TVS and injection of 12.5mg Methotrexate into gestation sac under ultrasound guidance.
- Administration 0.5mg/kg of body weight, Methotrexate given intramuscularly daily upto 5 days.
- Administration of 0.1mg/kg of Folic Acid 12-15 hours after each Methotrexate injection upto five days.

Each woman was carefully observed for changes in vital signs and tests for haemoglobin percentage, white cell count, platelets count, liver function tests, renal function tests and serum β hCG levels were performed on alternate days. The patients were discharged from hospital when β -hCG level dropped to 50% of the basic level and were managed at outpatient department till β -hCG level becomes ≤ 2 mlU/ml. Twenty five women agreed to have hysterosalpingography 2-3 months after resolution of β -hCG.

Data on reproductive outcome were obtained at periodic visits, until an addition pregnancy occurred or fertility becomes irrelevant. Since intention to conceive was the part of inclusion criteria, so we regard time to conception as time from treatment.

Statistical analysis

Results are presented as average (SD)[range] and percentages.

Results

The total number of deliveries during this time was seven thousand, six hundred and twelve (7612) for a prevalence of 1:50 at our hospitals, but in our set up patients may choose freely a hospital for delivery or for the management of any complication of pregnancy, so this prevalence rate is not the true representation of national prevalence or incidence rate, as number of known pregnancies and number of fertile women during the study period is not available. The average age of the women was 26.7 (3-5) years and average gravidity was 2.5(1.7)[1-7] and average parity was 2.0 (1.2) [0-5]. Twelve women 40% were nulliparous. About 2/3rd tubal pregnancies occurred in the left tubes and the average gestational age at diagnosis was 5-8 weeks. Serum β -hCG level ranged between 180-8,510miu/ml. The duration of hospital stay was averaged 5.5 days (2.2)[4-10]. Three out of 30 women (10%) failed to respond to methotrexate therapy and needed further surgical intervention (salpingectomy). Higher level of serum β -hCG was associated with failure of treatment i.e., ≥ 5000 iu/ml. The resolution time of serum β -hCG levels was also longer in women with higher serum β -hCG levels. The remaining 27 women, the resolution time of serum β -hCG was 19 days (10.6) on average and the median time was 15 days. Except for stomatitis (one case) and GIT upsets (another case) no other complications of methotrexate treatment, were observed.

Twenty five women agreed to undergo hysterosalpingography following treatment. In all but one, hysterosalpingography confirmed form 15 months (11)[7-22]. Four women did not have additional pregnancy, one had tubal sterilization, another had intrauterine device and remaining two opted for oral contraceptives. Twenty four women (80%) had intrauterine pregnancy within 15 months. Three women aborted spontaneous (16.5%) and remaining 21 gave birth at term with no report of malformation. Three women had tubal pregnancy again (13.3%) but on contralateral side.

Discussion

Since decades ectopic pregnancies had been managed by surgery. However, in recent past, there is emergence of different treatment modalities i.e., ranging from minimal invasive to non-invasive medical management, and with them fertility prospects have significantly improved. One problem with either systemic or local medical treatment

remains persistent ectopic gestation requiring additional surgery. In our study 3 women (10%) required salpingectomy following medical treatment, a rate similar to the reported 9% for systemic methotrexate and much better than the reported 20%-24% for local methotrexate treatment⁴. The only factor that can be figured out in our study for failure of medical treatment was initial high level of serum β -hCG.

Methotrexate has been widely used for ectopic gestation during last decade and offers an alternative to the surgical approach. Some groups have treated ectopic gestation by local methotrexate injection into the gestational sac either by laparoscopic route or guided by transvaginal ultrasonography. Others have administered it by systemic route. We tried a combination of both and got better results in terms of both intrauterine pregnancy (80%) and low rate of recurrent ectopic pregnancy (13.3%).

Conclusion

The methotrexate treatment of unruptured extrauterine pregnancy as proposed in our combined protocol is very efficient. While the failure rate of our protocol was similar to other treatment modalities, subsequent tubal patency and reproductive performance were felt better than that of surgical treatment or other protocols of methotrexate treatment previously reported^{3,4}.

Serum β -hCG level on admission may help to decide about primary surgical approach in cases where high serum β -hCG level is obtained (≥ 5000 IU/ml) or opting medical treatment when level is low.

References

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