

Ectopic pregnancy comparison of different treatments

Fatmir Kopani
Arben Rrugia
Nikita Manoku

Obstetrics-Gynecologic University Hospital
"Queen Geraldine" of Tirana, Albanie

Corresponding Author:
Fatmir Kopani M.D.
Obstetrics-Gynecologic University Hospital
"Mbretresha Geraldine"
Department of Obstetric and Gynecology
Bulevadi "Zogu I"
Tirane, Albanie
Tel.: ++ 355 42 222609
Mobile: ++ 355 684008314

Summary

Objectives We would like to determine the best treatment option depending of ectopic pregnancy situation. **METHODS.** This is a retrospective and cohort study that registered all women admitted in Obstetrics and Gynecologic "Queen Geraldine" Hospital during June 2003 until 2008. There are admitted 228 women diagnosed with Ectopic Pregnancy that are treated in our Hospital. **Results.** Unruptured ectopic pregnancy is diagnosed in 5,2 week of pregnancy and ruptured ectopic in an average of 6,4 weeks. Surgical intervention is registered in 170 patients and we did tubectomy. Success rate of Methotrexate application regarding β -hCG level. This treatment was more successful if β -hCG level was lower. If the β -hCG level is higher over 10 000 the success rate will decrease in 83 % and in β -hCG levels over 15 000 the success rate will be very low until 50%. **Conclusions.** The treatment will be determined by combination of clinical symptoms, ultrasound examination and β -hCG levels. MTX is recommended for all women without hemodynamic problems, unruptured pregnancy and not high β -hCG level (β -hCG < 5000 mIU/mL). It is confirmed that the reduce rate of 15% of β -hCG in the fourth day after application of MTX is a success guide.

Key Words: Ectopic pregnancy, β -hCG, MTX, Ultrasound.

Introduction

Ectopic pregnancy is described for the first time in the 11th Century and later on it was described as pregnancy complication.

Ectopic pregnancy is potentially life-threatening and remains the leading cause of maternal death.

The incidence of ectopic pregnancy is increased during last years all over the world (1,2,3).

The incidence is higher between 35 and 44 years and it

is counted 27,2 per 1,000 reported pregnancy (3). The reoccurrence of ectopic pregnancy is 7 until 13 times high (4). Etiology includes tubal damage from different reasons like inflammation, infections and surgical interventions.

Risk factors include previous tubal surgery, previous ectopic pregnancy, previous genital infections, assisted reproductive technology, smoking (the risk is increased by number of cigarettes), age (increased over 40 years), intrauterine device (IUD), OC only with progestin, multiparity, previous abortion (spontaneous or induced), DES exposure in utero (5,6,7).

Clinical manifestation is connected with localization of ectopic pregnancy. Fallopian tube is the most common area of ectopic implantation, represented in 97% of all ectopic pregnancies.

Approximately, 80% of all ectopic pregnancies are localized in tubal ampula, 12% in isthmic part, 5% in fimbrias and 2% in interstitial part (corneal). Other localizations are not common; approximately 1% and most common are ovarian, cervical and abdominal (1).

The clinical manifestations of ectopic pregnancy complicate the diagnose because of their broad spectrum that run from asymptomatic until acute abdomen and hemodynamic shock. Combination of β -hCG levels and transvaginal ultrasound has a sensitivity of 97% and specificity of 95% avoiding application of other invasive tests like D & C (2). The classic clinical triade is: abdominal pain, amenorrhea and vaginal bleeding. The border of 66% increase level of β -hCG within 48 hours (confidence level 85%) is the lower border for normal vital intrauterine pregnancy (8).

Normally, the seric progesterone level in ectopic pregnancy is lower than in normal intrauterine pregnancy. Ultrasound examination represents complex adnexal mass or a solid mass accompanien an ectopic pregnancy, but this could be a corpus luteum, endometrioma, hydrosalpinx, ovarian neoplasia (e.g. dermoid cyst), or a pedunculated myoma. Free liquid in Douglas is another sign of ectopic pregnancy, but is not significant of ruptured ectopic. Presence of intraabdominal free liquid is shows more often for ruptured ectopic. The exact ultrasound comments are in correlation with β hCG levels (discriminatory zone). All viable intrauterine pregnancies can be visualized by transabdominal ultrasonography for serum hCG levels higher than 6,500 mIU/mL.

The discriminatory zone for transvaginal ultrasound are reported in levels between 1.000 and 2.000 mIU/ml. Missing of intrauterine gestational sac 38 days or more after the last menstrual period or 24 days after conception is the evidence of ectopic pregnancy (9).

The treatment of ectopic pregnancy includes medical or surgical methods. Both are effective, but the selection depends on clinical situation, localization of ectopic pregnancy and diagnostic tools.

The aim of this study

We would like to determine the best treatment option depending of ectopic pregnancy situation. We will analyse the cases treated by conservative treatment, the protocol of methotrexate application. Depending of **β-hCG levels** we will determine the success rate of conservative treatment.

Materials and methods

This is a retrospective and cohort study that registered all women admitted in Obstetrics and Gynecologic "Queen Geraldine" Hospital during June 2003 until 2008. There are admitted 228 women diagnosed with Ectopic Pregnancy that are treated in our Hospital. In the first group of women are included all women that are operated because of ruptured ectopic pregnancy. There are 165 operations done for this purpose. In the second group are included all women diagnosed with unruptured ectopic pregnancy who are undergone the conservative treatment as comparative method. There are 63 women in this group. MTX is the drug used for conservative treatment. The first injection is done following the protocol by Stovall (19). If **β-hCG** level is reduced by 15% or more between 4 and 7 days than we measured **β-hCG** level every week until it was lower than 15 mIU/ml. If the clinical situation allowed us we injected another MTX dose only in cases when **β-hCG** is reduced less than 15%.

Results

The average age of women registered with ectopic pregnancy is 30,38 years old. Maximal age is 44 years and the minimal age is 18 years old. One of risk factors, at least one abortion in their history resulted in 52,6 % of patients (Fig. 1). Previous surgery was registered in 10% and previous gynecologic surgery was in 17,5%. Unruptured ectopic pregnancy is diagnosed in 5,2 week of pregnancy and ruptured ectopic in an average of 6,4 weeks. The presence of free abdominal liquid is registered in 156 patients or 68,4% of cases.



Fig. 1 - History of abortion in study population.

In 170 patients or 74,5% we detected adnexial mass and presence of FHR.

Amenorrhoea is recorded in 185 cases or 81% of patients. Pregnancy test (pregnosticon test) is performed in 179 patients or 78,5% and was 100% positive. Punction of Douglas is performed in 50 patients or 30,8%. Vaginal bleeding is registered in 178 patients or 78% (Fig. 2).

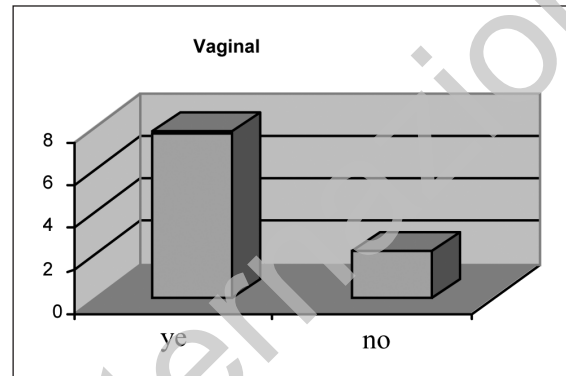


Fig. 2 - Distribution of vaginal bleeding in study population.

In 90% of patients the main complain was lower abdominal pain. No complains are registered in 3,5% of patients except amenorrhoea (Fig. 5).

71% of patients or 162 records are included in ruptured ectopic pregnancy (Fig. 3). Here we involved 5 patients that are converted from conservative treatment to surgical treatment.

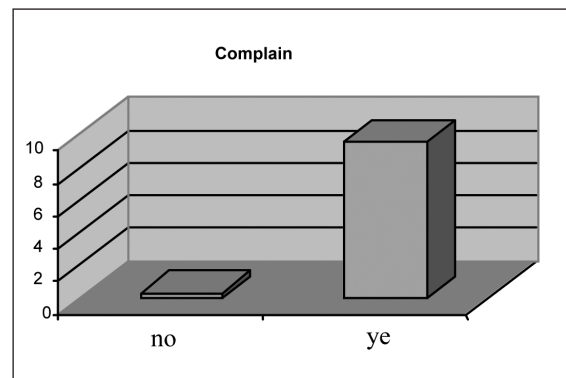


Fig. 3 - Distribution of complain in study population.

Surgical intervention is registered in 170 patients and we did tubectomy and adnexectomy. Left localization of ectopic pregnancy is recorded in 100 patients or 43,8% and the rest of 128 patients or 56,2% are recorded on the right side. The abdominal quantity of blood was measured in average of 1300 ml. Fertility rate is registered in 9 patients or 4%. Fertility rate after medical treatment is higher than after surgical intervention (Fig. 4).

In 27 patients or 15,8% is applied hemotransfusion. We used 300 until 900 ml of blood for hemotransfu-

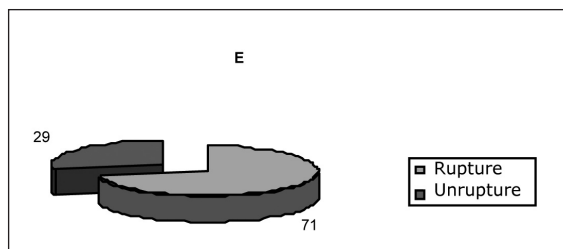


Fig. 4 - Percentage of rupture ectopic pregnancy.

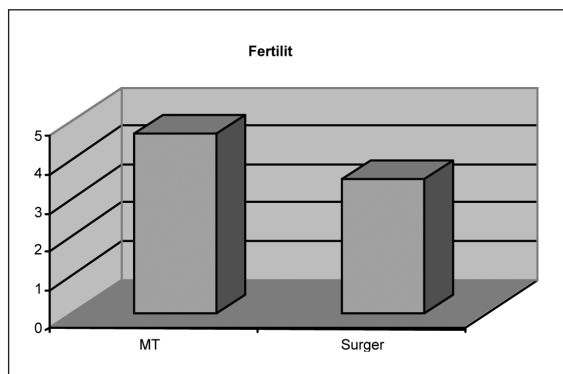


Fig. 5 - Fertility rate after medical treatment (MT) and surgical treatment.

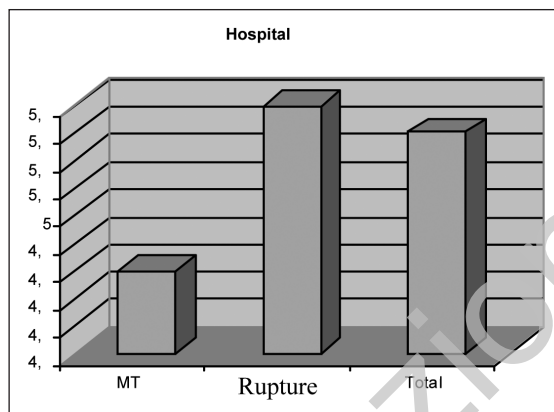


Fig. 6 - Average of days of hospital stay.

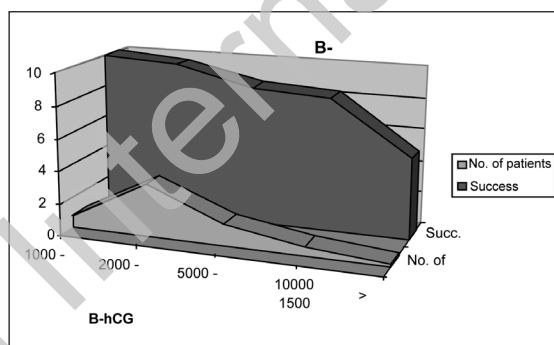


Fig. 7 - Success rate of Methotrexate application regarding β -hCG level.

sion. Fever is registered in 5 patients or 2,9%. The average hospital stay is registered in 4,8 days. Ruptured pregnancy are registered to have a mean hospital stay 5,4 days and the mean hospital stay for all ectopic pregnancies is 5,3 days. The graph shows the difference between medical treatment and surgical treatment deal with hospital stay.

The Fig. 6 shows the success rate of conservative treatment with MTX. This treatment was more successful if β -hCG level was lower. If the β -hCG level is higher over 10.000 the success rate will decrease in 83% and in β hCG levels over 15 000 the success rate will be very low until 50% (Fig. 7).

Table I - Success rate of medical treatment regarding different levels of B-hCG

Values	Nr. patients	Success
1000 - 1999	8	100
2000 - 4999	33	97
5000 - 5999	14	85,7
10000 - 15000	6	83,3
> 15000	2	50

Discussions

Risk factors

Previous surgery is registered in 26% of patients, even in our study it was 27,5% which 17,5% had previous gynecologic surgery. This percentage shows the same as

in literature without any difference. We registered in our study history of previous ectopic pregnancy in 7-8% of patients and it is lower than in literature where we found it 10% (5,6,7). This number is lower because conservative treatment has a short history in our country and surgical intervention with radicale tubal surgery was the main treatment until 4 years ago.

The best diagnostic tools are transvaginal ultrasound combined with β -hCG levels (10,11). Combination of these both methods can detect all ectopic pregnancies (12,13). We found the same result that the combination of transvaginal ultrasound with β -hCG levels could diagnose all ectopic pregnancies. Good interpretation of β -hCG levels referred from laboratory is the key point in early diagnose of ectopic pregnancy. There are three international standard used in the world but most common used is the third international reference standard (code 75/537). The same standard is used in our laboratory to measure β -hCG levels. Using the same standard will give us the possibility to compare our results with other studies in the world.

Fertility rate

There is not any significant difference after surgical or medical treatment of ectopic pregnancy for the future rate of ectopic or intrauterine pregnancy (14,15). The fertility rate for intrauterine pregnancy after ectopic preg-

nancy treated with MTX is 58-61%. We do not have an exact number of women that had intrauterine pregnancy after MTX treatment. This gap is because of problems in address system in clinical records of women admitted in our hospital. The intrauterine pregnancy rate after surgical treatment of ectopic pregnancy is 61-70% and the recurrence rate of ectopic pregnancy is 18% (2,7).

Medical treatment

The common criteria to include patients in medical treatment with MTX were: hemodynamic stability, normal hepatic and renal function, unruptured pregnancy, adnexial mass < 4 cm, β -hCG level less than 15.000 (1,14). Many different studies tried to describe factors that influence the success rate since before starting treatment with MTX. These factors include: previous obstetrical history, ultrasound findings and β -hCG levels (16).

There is a significant correlation between serum level of β -hCG and success treatment with MTX. Embryonal cardiac activity presence is increased as β -hCG levels are higher. Embryonal cardiac activity is present in 5% of ectopic pregnancies for β -hCG level less than 5000 mIU/mL and it is registered to be 27% for β -hCG level between 5000-10.000 mIU/mL and it will be 50% for β -hCG level over 15.000mIU/mL (5,13,17).

The possibility of ectopic pregnancy rupture is increased, if β -hCG level is higher after MTX application (11).

Table II

β -hCG level	Success rate
< 1 000 mIU/mL	98% (CI=96-100)
1 000 – 1999 mIU/mL	93% (CI=85-100)
2 000 – 4999 mIU/mL	92% (CI=86-97)
5 000 – 9999 mIU/mL	87% (CI=79-98)
10 000 – 14999 mIU/mL	82% (CI=65-98)
> 15 000 mIU/mL	68% (CI=49-88)

We did a comparison between β -hCG levels in our study and those from other studies and we found that success rate was 100% up to 1999 mIU/mL of β -hCG level. This high success is because of small number of patients in our study. The percentage of success is 97% for β -hCG level between 2000 and 4999 mIU/mL and this is still higher than other studies. The success rate for β -hCG level between 5.000 and 9999 mIU/mL is 85,7% and this is similar to other reference studies. The same success rate in our study and other studies is for β -hCG level between 10000 until 14999 mIU/mL is 83,3%. We concluded that this is the limit for conservative treatment and that of surgical treatment, because for β -hCG level higher than 15.000 mIU/mL the success rate will be very low and in our study it is registered to be 50%. We treated very few cases by conservative treatment in such β -hCG level.

We applied the second dose of MTX in only 17,4% of patients and this is similar with other studies. In a study from (18,19), it is registered that 18,8% of patients

where was used the single dose protocol needed to receive another dose of MTX.

MTX side effects

There are different side effects of MTX but those are not problematic complains. In different studies side effects reported to be between 5,5-8% of patients and in some other studies are registered until 28% (20, 21). Different more frequently side effects are: alopecia 28%, pelvic pain 8,2%, nausea 4,2%, headache 1,9%, weakness 1,3%; stomatitis 1,3%; light sensibility 1,3% and some patients had pneumonia from MTX hypersensibility (22). We followed single dose protocol and the side effects were registered in a low percentage. The same percentage of side effects is registered even in other studies when they applied single dose protocol. The most common complain was pelvic pain and cramps. The cause of pelvic pain is because of changes happened in ectopic pregnancy other than MTX itself. We did not register in our study any case with leucopenia or thrombocitopenia (thrombocit < 100.000; white blood cells 1500). We did not faced with any patients that had kidneys or hepatic problems and so we never interrupted treatment by MTX because of such complications.

Surgical treatment

In presence of other tube problems and when the women have the desire to save fertility, laparoscopic salpingotomy should be the preferred surgical treatment. Laparoscopic surgical treatment is the selected method for patients that have stabile haemodynamic level but surgeon skills are important influence factors for selection of surgical method (23).

In a study from (23,24) the preferred laparoscopic method is applied only in 26% of patients and other 63% are operated by open surgery. 11% received converted laparoscopy to open surgery. In our study 100% of surgical treatment is applied open surgery. Salpingectomy is applied in 95,8% of patients compared with 90% applied in different studies by (23). Adenectomy is applied in 4,2 % of patients because of co – problems detected during open surgery (e.g. pyosalpingitis).

The confirmation of ectopic pregnancy by pathology resulted in 100% of patients that received open surgery. The total number of patients is 170. Application of anti – D immunoglobuline is recommended by (25), for Rh negative patients but in our study we did not apply this treatment. We have to apply in the future treatment even anti – D and should be included in our protocol.

We found in our study that prophylactic application of anticoagulant treatment is not registered in all patients. In other studies this application is registered in 45% of patients (23). In our study we have a higher percentage of application until 66%. We recommended this because of predisposition of pregnant women to have thrombosis.

Conclusion

Ectopic pregnancy is a common serious problem with high morbidity percentage and possibility of maternal

mortality. We can diagnose ectopic pregnancy earlier than the clinic will be present and this will give us the possibility to apply the best treatment with fewer complications. Quantity β -hCG measure, ultrasound examination, D & C inform us for the diagnose of ectopic pregnancy and surgical treatment can be avoided. The treatment will be determined by combination of clinical symptoms, ultrasound examination and β -hCG levels. MTX is recommended for all women without hemodynamic problems, unruptured pregnancy and not high β -hCG level (β -hCG < 5000 mIU/mL) It is confirmed that the reduce rate of 15% of β -hCG in the fourth day after application of MTX is a success guide. It is recommended to apply measure of β -hCG levels after laparoscopic salpingostomy. In Rhesus negative women diagnosed with ectopic pregnancy we have to apply anti - D immunoglobuline. We should use anticoagulant therapy for all women that received a surgical treatment. We need to do more improvement in our ectopic pregnancy treatment protocol even we have good application and results from present experience.

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