How successful is treatment of ectopic pregnancy with methotrexate?

Gynecology Clinic at Örebro University hospital, between the years of 2013 and 2014

VERSION 2

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Abstract

Background: Ectopic pregnancy, the leading cause of maternal death in the first trimester, has been treated with surgery until the medical treatment methotrexate became an alternative in mid 1980s. Earlier studies show that the treatment success rate with methotrexate is best predicted by initial S-β-hCG values. The treatment success rate is about 92% when initial S-β-hCG levels < 5,000 IU/L and considerably lower; 68% when initial S-β-hCG levels > 15,000 IU/L. Medical treatment is priory over surgery for the reason that morbidity from surgery and general anesthesia is eliminated, theoretically less tubal damage and less cost and requirement for hospitalization.

Aim: The purpose of this research is to study the treatment success with methotrexate of ectopic pregnancy at Örebro University Hospital during the years of 2013 and 2014.

Materials and methods: A retrospective cohort study of 28 women with methotrexate treated ectopic pregnancies at Örebro University Hospital in Sweden during the years of 2013 and 2014. Information was extracted from patient records: patient history, laboratory tests and examination results. Students t-test was used in excel for statistical analysis.

Results: Methotrexate treatment success rate overall was 68% (19 of 28 women). In the success group, 63% had initial values < 1000 IU/l, 21% had values between 1000 and 5000, 11% had values between 5000 and 10,000 IU/l and only one woman (5%) succeeded with values > 10,000 IU/L. In the failure group the rates for the same S-β-hCG values were 25%, 38%, 25% 12% respectively. Only one dose was required in 79% to succeed. Average time until treatment completion was 48 days with a range of 10 to 100 days. In total 8 of 27 (30%) women did not report any side effects at all. Of those 19 (70%) women who did report side effects the two most common side effect were vaginal bleeding and abdominal pain.

Conclusion: In this retrospective cohort study we found a considerably lower treatment success rate overall with methotrexate up to two doses and a halved methotrexate side effect rate of what can be found in published studies. The trend between the initial β-hCG values and outcome of treatment seem to cohere with earlier studies but in our study no statistical significance was found regarding this trend. Our study showed also that a second dose was not required when initial S-β-hCG < 1000. Not all women experienced side effects when given only one dose but all women experience side effects when given two doses. At Örebro University Hospital expectants could be more commonly used as treatment when S-β-hCG < 1000. The small study population in this study makes the results uncertain.
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1. Background
1.1 Ectopic pregnancy and tubal rupture

Ectopic pregnancy or extra uterine pregnancy is a pregnancy that occurs outside the endometrial lining of the uterine cavity. In about 98% of all ectopic pregnancies the blastocyst attaches to the wall of one of the fallopian tubes and it is therefore named tubal pregnancy, other locations are cervix, ovary and abdominal cavity. In a few cases the ectopic pregnancy occurs together with an intrauterine pregnancy, named heterotrophic pregnancy. In majority of cases the etiology is unknown but there are some risk factors that can damage the fallopian tubes primary such as infections (inflammation), tumors, scars after operation, endometriosis, earlier ectopic pregnancy, smoking, or congenital defects in the fallopian tube. 

[1-4] Women who smoke more than one pack of cigarettes per day have three- to fourfold increased risk for ectopic pregnancy. Animal studies have shown that cigarette smoke affects the fallopian tubes cilia and smooth muscle which diffuses embryo transport through the tube to the uterus. [5,6] High maternal age is also an important risk factor, women between 35 and 44 years have a threefold increased risk of ectopic pregnancy compared with those between 15 and 35 years. [7,8]

The growing blastocyst can cause tubal rupture and this can lead to a severe hemorrhage which is the leading cause of fatality in ectopic pregnancy. In the past two decades, the tubal rupture rate caused by ectopic pregnancy ranged from 20 to 35 percent. Risk factors that increase the possibility of tubal rupture are ovulation induction, S-β-hCG > 10,000 IU/l when ectopic pregnancy is first suspected and no use of contraception ever. Estimation of these risk factors reliefs a timely diagnosis and quick surgical intervention. [9,10] Location of the EP determines partially timing of tubal rupture. If implantation has occurred in the isthmic or ampullary region of the fallopian tube, it will rupture earlier. While implantation of the trophoblast within the interstitial region of the tube (proximal tubal section that lies within the muscular uterine wall) often leads to late tubal rupture. Usually the tubal rupture happens spontaneously but it can also be induced by trauma such as bimanual pelvic examination. It seems to be that risk of tubal rupture in an ectopic pregnancy can determine if it is an “acute” or “chronic condition”. High initial S-β-hCG levels and rapidly raising levels lead to an immediate “acute ectopic pregnancy” diagnosis because of higher risk for tubal rupture. Static or negative S- β-hCG levels, very rare, are considered to be a “chronic ectopic pregnancy” since the risk is lower for tubal rupture. [11] In theory, “acute ectopic pregnancy” has a healthy developing trophoblast that does not cause an early bleeding and therefore women
develop symptoms at a later stage and search for care later. Whereas the chronic condition means an abnormal trophoblast that will cause small repeated ruptures which trigger an inflammatory response that forms a pelvic mass. Low or negative S-β-hCG levels, not so common, are due to an abnormal trophoblast, which is the case in “chronic ectopic pregnancy”. [12]

1.1.1 Prevalence and mortality

The ectopic pregnancy is estimated to occur in one of fifty pregnancies worldwide and the incidence is increasing. The mortality rate from ectopic pregnancy on the contrary has declined 10-fold during the past 35 years, because of improved diagnostic techniques and early surgical interventions. The mortality rate from ectopic pregnancy was 36 maternal deaths per 10,000 pregnancies in 1970, 19 years later, 1989, this number decreased to 3.8 maternal deaths per 10,000 pregnancies. During the same period nonwhite women had an overall risk of death 3.4 times higher than white women. Even though the survival rate is increasing, ectopic pregnancy remains the leading cause of pregnancy-related death in the first trimester of pregnancy due to tubal rupture. [4,7,13]

1.1.2 Symptoms

Majority of women in early stage of ectopic pregnancy with unruptured tube have no or mild symptoms and it is therefore often difficult to reveal the ectopic pregnancy early. But if any symptoms are present, they are amenorrhea followed by vaginal bleeding, abdominal pain and other ordinary pregnancy symptoms. [1,4,14]

1.1.3 Diagnostics

Combination of transvaginal ultrasound and serial sererum β-hCG measurements is most commonly used to confirm clinical suspicions of an ectopic pregnancy and these diagnostics are also used at Örebro University Hospital.

1.1.3.1 Serum β-hCG

β – Subunit of human chorionic gonadotropin, β-hCG, is a glycoprotein produced by synsyciotrophoblasts (cells surrounding the embryonic cavity that will form placenta) and can be detected in serum about 11 days after fertilization and is measured in International Units per liter, IU/l. β-hCG acts like a hormone and stimulates the corpus luteum in the ovary to continue producing progesterone, a necessary hormone for the pregnancy to continue, later when the placenta is formed in the end of the first trimester, it will take over the production of progesterone and β-hCG-levels will then decline. Non-pregnant women have S-β-hCG levels
below 5 IU/l. Levels above 25 IU/l are indicating pregnancy. β-hCG levels are individual and can vary widely between women, they should therefore not be used to date a pregnancy. A single β-hCG measurement is not giving much worthy information, the variation in β-hCG levels during a couple of days gives a more precise estimation of the condition. In normal pregnancies, serum β-hCG levels increase in a log-linear way until 60 or 80 days after last menstruation and then a plateau is reached at approximately 100 000 IU/L. In 85% of normal early pregnancies, the β-hCG level will double every 48-72 hours. Abnormal rising in S-β-hCG levels indicates an abnormal pregnancy but not its location. If there is a doubt about when a woman had her last menstruation, correlation between the S-β-hCG concentration and transvaginal ultrasound findings becomes particularly important. [15,16]

1.1.3.2 Transvaginal ultrasound

A gestational sac (fluid surrounding the embryo) should normally be detectable with transvaginal ultrasound between gestational week 4, 5 and 5, in intrauterine pregnancy. The yolk sac can be detected between gestational week 5 and 6. Fetal pole with cardiac activity can first be detected in the middle of week 5 and week 6.

If there is doubt about time of last menstruation, S-β-hCG measurement is used to determine expected ultrasound findings. Each hospital must define a prejudicial value, that is, the lower limit at which an examiner can reliably visualize pregnancy. At Örebro university hospital this lower limit is 1000 IU/l. There can be technical challenges, such as hemorrhage or myomas that can hinder the ability to exactly diagnose an intrauterine gestation even with S-β-hCG levels above 1000IU/l. [17] When no pregnancy is seen in the uterus at S-β-hCG levels above the discriminative value it will suspicion on an abnormal pregnancy that is either ectopic, incomplete abortion, or resolving completed abortion. But if S-β-hCG values lie below the discriminatory value and there are some ultrasound findings, in nearly 66% of case it is not predicting diagnose. [18] In cases where neither an intrauterine nor an extra uterine pregnancy is found, the term pregnancy of unknown location (PUL) or suspected X is used until further clinical information allows conviction of pregnancy location, very common occurrence. [1]

In intrauterine pregnancies the gestational sac is normally eccentrically located. While in ectopic pregnancy a pseudo gestational sac can be detected with ultrasound in the middle of the uterine cavity, it is an intracavitary fluid collection caused by shedding of the decidua. [19] Trilaminar endometrial pattern, adjacent edematous proliferative-phase endometrial
layers, is a further important intracavitary finding for diagnosing ectopic pregnancy. [20] No clear connection between endometrial stripe thickness and ectopic pregnancies exists yet. But it has been shown that in pregnancies where location is unknown at presentation, all normal intrauterine pregnancies had a stripe thickness >8 mm. [21]

Detection of an extra uterine yolk sac or embryo certainly confirms a tubal pregnancy, even though these findings are present in only 15-30% of cases. [22] In some cases subserosal edema will be seen as tubal ring (hypoechoic area) with ultrasound, also called a halo. [23] The best transvaginal ultrasound criteria for diagnosing ectopic pregnancy is finding of any adnexal mass that is not a simple ovarian cyst. But not all adnexal masses are indicating an ectopic pregnancy and besides the transvaginal ultrasound other information is needed to diagnose ectopic pregnancy. [24] Transvaginal ultrasound with color Doppler can detect placental flow around periphery of a pregnancy as "ring of fire" anywhere. But this phenomena can also be seen around a corpus luteum cyst, why it can be challenging for the examiner to differentiate a corpus luteum cyst from an ectopic pregnancy. [25]

Free fluid in the peritoneal cavity indicates an intraabdominal bleeding that can be detected with transvaginal ultrasound. Fluid (blood) in the paracolic gutters and Morison pouch indicates serious hemorrhage. Detection of fluid in the peritoneal cavity and finding of an adnexal mass is highly predictive for ectopic pregnancy. [26]

1.1.4 Treatment

Ectopic tubal pregnancy, if left untreated can result in tubal abortion (removal of products through the fimbrial ends) tubal rupture or spontaneous resolution. In the old days ectopic pregnancy was only treated with surgery until the mid-1980s when medical management became available. [1,27]There were a couple of candidates for medical treatment of ectopic pregnancy such as prostaglandins, progesterone antagonist mifepristone, traditional Chinese herbal medicines and potassium chloride or hyperosmolar glucose injected into the ectopic mass. [28]But because methotrexate is the only medical treatment widely studied as an alternative to surgical therapy, it is the most commonly used today for treating ectopic pregnancy. Medical treatment is priory over surgery for the reason that morbidity from surgery and general anesthesia is eliminated, theoretically less tubal damage and less cost and requirement for hospitalization. [1,27]
1.1.4 Medical treatment with methotrexate

Methotrexate is a folic acid antagonist that competitively inhibits the binding of folic acid to the enzyme dihydrofolate-reductase that is necessary for the production of nucleic acids included in DNA and RNA. This inhibition of the enzyme leads to decreased production of purines and thereby DNA and RNA and finally even decreased protein synthesis. Methotrexate inhibits the growth of fast dividing cells such as embryonic cells and cancer cells, and is therefore used as cancer chemotherapy and to terminate an early pregnancy. It is also used in treatment of autoimmune diseases such as MS, Chron’s disease, RA and psoriasis. There are several administrations ways; oral, intravenous, intramuscular and local injection. At Örebro University Hospital the most common administration way used for ectopic pregnancy termination is intramuscular injections. Methotrexate can be used in treatment of ectopic pregnancies that are located to fallopian tube, cervix and in cases where location can’t be found. Methotrexate has several side effects, the most common are stomatitis, conjunctivitis, transient liver dysfunction even though severe side effects such as myelosupression, mucositis, pulmonary damage and anaphylactic reactions have been reported with only one dose of 50 – 100mg. One third of women treated with methotrexate for ectopic pregnancy report side effects. Leucoverin (folic acid) is given post treatment to some patients to compensate side effects of methotrexate and this therapy is therefore called Leucoverine rescue. [1]

Before treatment with methotrexate there is a control made of following blood markers β-hCG, Hb, TPK, ASAT, ALAT, creatinine, total blood count and Rh - status. This control must be repeated prior to every additional dose of methotrexate. During treatment with methotrexate the patient should avoid everything that contains folic acid since it can competitively reduce methotrexate binding to dihydrofolate reductase. They should also avoid NSAID since it reduces the renal blood flow and thereby delay drug elimination, alcohol because methotrexate and alcohol are both risk factors for liver damage and together the risk increases of hepatic enzyme elevation, sunlight can cause methotrexate-related dermatitis and sexual activity can cause rupture of ectopic pregnancy. [29] Methotrexate is a teratogen that can cause severe embryopathy which is not wanted in a normal intrauterine pregnancy but wanted effect in ectopic pregnancy. [1]

Asymptomatic women who are motivated and who have resources to be compliant with surveillance are best candidates for methotrexate treatment. Absolute contraindications for
methotrexate treatment are hemodynamic instability, incapability to continue compliant with post therapeutic observing, and contraindications to methotrexate itself. [1]

There are some predicting factors for successful treatment with methotrexate; initial S-β-hCG, ectopic pregnancy size and fetal heart activity. Initial S-β-hCG levels is the single best prognostic factor for treatment success in patients given single-dose methotrexate. The prognostic value of the two other predicting factors seem to be directly related to S-β-hCG levels. There is no consensus yet about the upper limit of S-β-hCG levels that can best predict a successful treatment. However a study mad by Lipscomb and colleagues 1999, showed a success rate of 92% when initial S-β-hCG levels < 5 000IU/L and 68% when initial S-β-hCG levels >15 000 IU/L. [30] Menon and associates research in 2007 showed that there is nearly four times increased risk for treatment failure if the initial S-β-hCG levels were 5000-9999 IU/L than if they were 2000-4999. [31]

Not much data exists regarding blastocyst size on success rate with medical therapy. In a study made by Lipscomb 1998, cases with ectopic masses < 3.5cm had a treatment success rate of 93% with single dose treatment, whereas in cases where the ectopic mass > 3.5 cm the success rate was between 87 and 90%. [32] Majority of studies show an increased risk for treatment failure if there is cardiac activity detected by ultrasound when treatment starts. [32]

There are also some estimated predicting factors of treatment failure with methotrexate such as fast raising S-β-hCG levels before treatment and finding of extra uterine yolk sac, but the later cannot predict alone. [29,33]

Methotrexate treatment of previous ectopic pregnancy is not affecting the fertility and the subsequent pregnancies negatively. [34] It is though recommended to wait at least three months before trying to get pregnant again after an methotrexate treated ectopic pregnancy, this because of risk for embryopathy in the subsequent pregnancy from eventually left methotrexate concentrations from the treatment. [35]

Today two different treatment protocols exist for treatment of ectopic pregnancy; single dose protocol and multi dose protocol. The single dose protocol means intramuscular methotrexate given as a single dose. Several dose sizes have been studied but the most used is the 50mg/ m² body surface area (BSA) and this dose size is also used at Örebro university hospital. [36] BSA can be estimated by a nomogram or by using internet based BSA calculators.
Before administration the S-β-hCG-level is checked and it will be controlled again the fourth and seventh day after injection. It is common that levels increase until day four. If the decrease in S-β-hCG between day 4 and 7 is 15 percent or more no second dose is needed, but the control of S-β-hCG has to continue ever seventh day until they are < 5IU/L. But if the decrease in levels between day 4 and 7 is less than 15 percent, a second dose is given and the protocol is restarted. This unsuccessful decrease is seen in approximately 20 percent of cases. Estimated time to resolution for all cases is about 36 days but in a few cases it can take up to 109 days. [32] About 50 percent of cases experience abdominal pain the first days after methotrexate administration. This pain is often treated successfully with mild analgesics such as Alvedon. This pain is called separation pain and is caused by tubal distension, result of tubal abortion or hematoma formation or both. Transvaginal ultrasound and serial hematocrit helps reveal the need of surgical intervention. [36]

The difference between multidose protocol and single dose protocol is that in multidose protocol the S-β-hCG level control is made more frequent; every 48 hours and if the decrease in levels within this time is less than 15 percent a second dose is given immediately. The maximum doses that can be given are four and the patient will also receive leucovorin 24 hours after every new dose. There is also a difference in estimation of dose, in multiple dose protocol the dose is based on kilogram; 0.1 mg/ kg. The single-dose and multidose methotrexate protocols are associated with overall treatment success rates of ectopic pregnancy is around 90 percent. Many studies where treatment success rate between the two protocols is compared show about 5% higher treatment success rate when treated with multidose protocol. A study mad by Lipscomb and colleagues 2005 based on 643 methotrexate treated women for ectopic pregnancy, no significant differences in treatment duration, S-β-hCG levels, or overall success rates between the multi- and single-dose protocols—95 and 90%, respectively was found. [37,38] Besides single-dose protocol is more simple, costs less, is easily accepted because of less frequent post treatment monitoring, and less side effects and therefore is not require leucoverin rescue. Of these reasons the single dose protocol is most commonly used worldwide. [39,40]

1.1.4.2 Surgical treatment

Different surgical interventions are used to remove the ectopic pregnancy. The most common is laparoscopy, even called Keyhole surgery. If the pregnancy is located in one fallopian tube and the other tube looks healthy, then it is common that the tube enclosing the ectopic
pregnancy is removed, with a technique named salpingectomy. It is removed for the reason to avoid the 5-8% complication risk caused by persistent or repeated ectopic pregnancy in the same tube. While in women where the only one healthy fallopian tube is containing the ectopic pregnancy and the woman strongly desires to preserve fertility, the tube will be retained if patient is hemodynamically stable. The surgical technique in these cases is salpingostomy and it means that an incision is made in the fallopian tube and all free and tubal placental tissue is precisely removed without removing the tube. In cases where the fallopian tube has ruptured, emergency surgery is required. This emergency surgery means that an incision is med in the abdomen to stop the bleeding and, if possible, repair the fallopian tube with a surgical technique known as laparotomy.  [1,41]

1.1.4.3 Surgical versus medical treatment

In women who are hemodynamically stable and who have a small tubal diameter, no fetal cardiac activity, and S-β-hCG <5000 IU/L, similar results are reached with medical treatment as with surgical. Even if lower overall success rate with medical treatment is seen, it can be offered to women with larger tubal size, higher S-β-hCG levels, and fetal cardiac activity if she is motivated and aware of the risks that emergency surgery can lead to in the event of treatment failure.  [42,43]

2. Aim

The purpose of this study is to study the treatment success with single dose methotrexate of ectopic pregnancy at Örebro University Hospital during the years of 2013 and 2014.

3. Material and Method

3.1 Patient group

Patient selection was based on a register from Örebro university hospital pharmacy, Sweden, containing all ordinations of methotrexate made from the gynecological clinic at Örebro university hospital during 2013 and 2014. The register contained 32 patients, 5 of them were excluded because the methotrexate in these cases was used for other purpose than primary methotrexate treatment of suspected ectopic or confirmed ectopic pregnancy. After this exclusion 28 women with diagnose suspected ectopic or confirmed ectopic pregnancy, treated primary with methotrexate during 2013 and 2014 were included. Patients were diagnosed based on symptoms, transvaginal ultrasound and S-β-hCG. No restrictions regarding age were made.
3.2 Patient records and database

Patients’ ID number was retrieved from the pharmacy register and used in the journal system of the hospital, *kliniska portalen*, to find necessary data. Application for permission to review medical records was approved by the director of gynecological department at Örebro university hospital. Patient records were reviewed and data was extracted and compiled in a table in Excel.

Following data was extracted from the patient records:

1. Serum β-hCG-levels measurements before treatment.
2. Serum β-hCG-levels measurements at treatment start and following treatment until levels are <5 IU/l. Day 4, 7, 14, 21 ext.
3. Time until serum β-hCG-levels <5 IU/l.
4. Reported side effects of the treatment from patient.
5. Analysis by examiner of transvaginal ultrasound made before treatment.
6. The number of doses given to patient.
7. If surgical treatment was performed and the indication for the surgical treatment.
8. Patients’ age.

3.3 Statistics

Students’ t-test was used in excel to do a statistical analysis and see if a statistical significance can be found between initial β-hCG values and if the treatment succeeds or fails.

3.4 Ethical considerations

Patients’ ID-number was anonymized after retrieving data. But since this diagnose is fairly uncommon and the number of patients is small and the information is retrieved from one only specific hospital, there might be a risk that a patient can recognize herself. Besides the patients are unaware of that they are included in this study which can be questioned ethically. But since the outcome of this study will lead to a quality assurance of this treatment the advantage is considered to be greater than the disadvantage.
4. Results

4.1 Methotrexate treatment success rate overall

The total number women included in the study is 28. The definition of treatment success is no require for surgery when treated with methotrexate and the definition of failure is the opposite, required surgery although when treated with methotrexate. Treatment success rate overall with either single or double dose of methotrexate was 68% (19 of 28 women). For (15 of 19) 79% of women within this success group a single dose methotrexate was enough to suppress the S-β-hCG levels <5 with the speed required for not giving a second dose according to the single dose protocol. Twenty-five percent of all 28 patients included received a second dose.

Diagram 1

Comparison of methotrexate treatment success rate in the single dose group with the double dose group, based on 28 women. Requirement of surgery in both groups is seen, defined as methotrexate treatment failure.
4.1.1 Methotrexate treatment success rate within the single dose group

21 of 28 (75%) women received only one dose. The success rate in the single dose group was 71% (15 of 21).

![Diagram 2](image1.png)

**Diagram 2**

Require for surgery when treated with methotrexate is defined as methotrexate treatment failure.

4.1.2 Methotrexate treatment success rate within the double dose group

7 of 28 women received 2 doses, which is 25% of total number women included. The success rate within the double dose group was 4 of 7 women (57%).

![Diagram 3](image2.png)

**Diagram 3**

Require for surgery when treated with methotrexate is defined as methotrexate treatment failure.
4.2 Average time (days) until completion of treatment.

Table 1. Days until S-β-hCG <5 IU/l (completion of treatment) for the 19 patients where the methotrexate treatment was successful.

<table>
<thead>
<tr>
<th></th>
<th>1 DOSE</th>
<th>2 DOSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>25</td>
<td>70</td>
</tr>
<tr>
<td>Median</td>
<td>20</td>
<td>66</td>
</tr>
<tr>
<td>Range</td>
<td>10-43</td>
<td>43-100</td>
</tr>
</tbody>
</table>

4.3 The impact of initial S-β-hCG levels on methotrexate treatment success rate.

Data on S-β-hCG initial levels was missing of one woman and the number of patients included in table 2 is therefore reduced to 27. Table 2 is showing the impact of initial S-β-hCG on methotrexate treatment success rate up to two doses. There was only one patient where embryo heart activity was detected by transvaginal ultrasound, in this case the methotrexate treatment with one dose failed. The p-value was 0.238, which means that no statistical significant difference between initial S-β-hCG values and treatment success/failure was found.

Table 2. Impact of initial S-β-hCG levels on methotrexate treatment success rate up to 2 doses. Requirement for surgery is defined as methotrexate treatment failure.

<table>
<thead>
<tr>
<th>Initial S-β-hCG</th>
<th>1 DOSE</th>
<th>1 DOSE + SURGERY</th>
<th>2 DOSES</th>
<th>2 DOSES + SURGERY</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000</td>
<td>12 (86%)</td>
<td>2 (14%)</td>
<td>0</td>
<td>0</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>1001-5000</td>
<td>2 (29%)</td>
<td>1 (14%)</td>
<td>2 (29%)</td>
<td>2 (29%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>5001-10 000</td>
<td>0</td>
<td>1 (25%)</td>
<td>2 (50%)</td>
<td>1 (25%)</td>
<td>4 (100%)</td>
</tr>
<tr>
<td>&gt;10 000</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>0</td>
<td>0</td>
<td>2 (100%)</td>
</tr>
</tbody>
</table>

4.4 The impact of initial S-β-hCG level on average time (days) until completion of treatment.

Table 3. This table is showing the impact of initial S-β-hCG level on average time (days) until treatment completion (values <5 IU/l) for the 19 patients with successful methotrexate treatment up to 2 doses.

<table>
<thead>
<tr>
<th>Initial S-β-hCG</th>
<th>010-20</th>
<th>21-50</th>
<th>51-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000</td>
<td>8</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>1001-5000</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>5001-10 000</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>&gt;10 000</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL n</td>
<td>7</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>
4.5 Prevalence of surgical interventions and indication

The prevalence of surgical interventions, defined as methotrexate treatment failure, was 9 of 28 (32%). The indication for surgery was in 4 of 9 women (44%) insufficient decrease in S-β-hCG values, whereas in the rest 5 of 9 women (66%) discomfort able side effects in combination with suspect intraabdominal bleeding was the indication.

4.6 Prevalence of reported side effects post methotrexate treatment

Table 4. Number of women reporting side effects in the four different groups. Abdominal pain and vaginal bleeding are side effects of methotrexate treatment while the other four are side effects of methotrexate itself. The same patient can have more than one side effect. Requirement for surgery is defined as methotrexate treatment failure.

<table>
<thead>
<tr>
<th>Side effects</th>
<th>1 DOSE</th>
<th>1 DOSE + SURGERY</th>
<th>2 DOSES</th>
<th>2 DOSES + SURGERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>6 (40%)</td>
<td>4 (67%)</td>
<td>3 (75%)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>2 (13%)</td>
<td>3 (50%)</td>
<td>4 (100%)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0</td>
<td>0</td>
<td>1 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1 (17%)</td>
<td>0</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>0</td>
<td>1 (17%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No side effects</td>
<td>8 (53%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Because data about side effects is missing on one patient, she is excluded here and 27 patient is the new total number. In total 8 of 27 (30%) women did not report any side effects at all. Of those 19 (70%) women who did report side effects the two most common side effect were vaginal bleeding and abdominal pain. These two side effects are actually not side effects of methotrexate itself, they are rather side effects of methotrexate treatment that causes resolution of the pregnancy and separation of the blastocyst from the tube that can cause the pain (tubal separation pain). 12 (44%) of them reported both vaginal bleeding and abdominal pain as side effects. While 1 (5%) reported only vaginal bleeding with no pain and 6 (32%) women reported only abdominal pain with no bleeding. 13 of 21 women (62%) in the single dose group reported side effects, whereas all women (100%) reported side effects in the double dose group. 4 of 27 patients (15%) reported side effects caused by methotrexate itself, such as stomatitis, nausea and photophobia.
5. Discussion

In this study we found that the methotrexate treatment success rate overall with up to 2 was 68% (19 of 28 women). The difference in success rate between single and double dose group was 71% and 57% respectively. Average time until treatment completion (S-β-hCG <5 IU/l) was 25 days in the single dose group and 70 days in the double dose group; 48 days average time if both groups average time added together. Initial S-β-hCG was in 80% of women in the single dose success group very low <1000 IU/l but one woman had initial value of 24 534 IU/l. While in the double dose success group all women had initial S-β-hCG between 1000 and 10 000 IU/l. In the failure group the initial S-β-hCG values were widely spread. Lower initial S-β-hCG lead to a faster decrease in S-β-hCG levels. The indications for surgery was in 66% of surgical cases suspected internal bleeding together with discomforting side effects and in the rest 44% insufficient decrease in S-β-hCG levels was the indication. In total 8 of 27 women (30%) did not report any side effects at all. Of those 19 (70%) women who did report side effects the two most common side effects reported were vaginal bleeding and abdominal pain. In the double dose group all women reported side effects whereas in the single dose group side effect rate was 62%.

In our study the methotrexate treatment success rate over all with up to two doses was 68% which is a lower rate compared to the study made by Lipscomb and colleagues 2005 based on 643 methotrexate treated women for ectopic pregnancy where the success rate overall was 90%. [37] According to Örebro University Hospital’s PM and Lipscomb’s study from 1998, 81% of patients included in the single dose protocol group required only one dose of methotrexate for successful treatment and in our study this rate was almost the same; 79%. Thereby the rate of patients requiring a second dose to succeed is also almost the same as in Lipscomb’s study made 1998. [32] But the small study population in this study makes these results uncertain.

In our study 21 of 27 women (78%) had S-β-hCG <5000 IU/l and 76 % of these 21 succeeded to be treated either with a single or double dose of methotrexate. This is a lower success rate if comparing with the study that Lipscomb and colleagues made 1999, where the success rate was 92% when initial S-β-hCG <5000 IU/L. [30] The difference in these rates might be due to a big difference in patient number included in both studies, 28 patients in our study versus 350 patients in Lipscomb’s study. According to the same study an initial concentration >15,000 IU/L had a success rate of 68 %, comparing with our result of 50% success rate when
> 15 000 IU/L. This difference might also depend on that the rate of this study is based on only two women > 15 000 IU/L. But in our study a surprising good result was reached when a woman with S-β-hCG of 24 534, no embryo heart activity detected, succeeded to be treated with only one dose of methotrexate. While in the other case with S-β-hCG above 36 000 IU/l and the only one in this study where heart activity was detected, methotrexate treatment failed. In the failure group (surgery group) the patients’ initial value was very widespread between 100 and 36 000IU/l, but 5 of 8, 63 % had initial value <5000 IU/l.

The fact that success rate according to our study is greater in the single dose group than in the double dose group might be due to considerably lower initial S-β-hCG levels in the single dose group. Since 80% in the single dose group were given their dose when initial S-β-hCG – levels were very low, <1000 IU/l, there might be a risk that some of these successful treatments actually were resolving normal or ectopic pregnancies and the methotrexate maybe only helped to resolve and not treat. Because when S-β- hCG levels are below 1000 IU/l an option treatment is expectants, that because of earlier studies regarding low S-β-hCG values and spontaneous resolution/ expectant management are showing that in majority of patients with low initial values the pregnancy resolve spontaneously. According to a study initial values below 200 predict successful spontaneous resolution in 88-96% of cases, while in patients with values over 2000 IU/l resolving success rate was between 20% and 25%. [44,45]. Another study showed that when initial values > 2000 IU/L, even if the levels were declining, spontaneous resolving success rate was only 7%. [46] Fifty two percent of all patients included in my study had S-β-hCG-levels <1000 IU/l, the lowest value was 136. In this group the “methotrexate treatment success rate” was 83%, but some of these pregnancies might have resolved even without treatment as mentioned earlier in this discussion.

Majority of “side effects” reported in our study are abdominal pain and vaginal bleeding. These are actually not side effects of methotrexate itself, they are rather side effects of methotrexate treatment that leads to a resolving pregnancy and separation of the blastocyst from the tube can cause the pain (tubal separation pain). According to a research made by Stovall and colleagues in 1993, about 50% of women experience abdominal pain (tubal separation pain) during the first few days following methotrexate administration. The pain was controlled with mild analgesics. [36] In our study 16 of 27 (59%) women reported abdominal pain, which is 9% higher compared to Stovall’s results. But since the abdominal pain also is a symptom of ectopic pregnancy, the question is if all really were side effects of methotrexate treatment? Some of these reported abdominal pains might be symptoms from
ectopic pregnancy or a resolving pregnancy; tubal separation pain. However 4 severe side effect or real side effect of methotrexate itself, were reported. This means that total methotrexate side effect rate in our study was only 15%, comparing with earlier studies where this same rate was about 30%. [1] This difference might be due to the small study population in our study. This could mean that according to our study if giving methotrexate as recommended in the protocol for treatment of ectopic pregnancy with up to two doses the risk of side effect is small and should not be a reason to refrain from treatment. But it should not be forgotten that in our study side effects in some cases were indication for surgery but together with suspected internal abdominal bleeding. Many patients who received only one dose did not have side effects at all, and the rate of side effects increased when receiving two doses. This is logic due to a higher concentration of methotrexate in the whole body that can interact with more receptors in the body and the time for elimination from the body increases with concentration.

In our study the average time (days) until completed treatment, with up to two doses, was 48 days. If compared with Lipscomb’s study (1998) this average was about 36 days, which is 12 days less than in our study. [32] But this difference might be due to the small study population in our study and the fact that the range was wide; 10-100 days.

5.1 Limitations

The biggest limitation of this study that make it difficult to generalize is, as mentioned earlier in the discussion, the small study population. Limiting data access is another limitation of our study, some data was difficult to find such as the total number of patients with the diagnose ectopic pregnancy and suspect ectopic pregnancy, including these who were treated with surgery priory or expectants because of low S-β-hCG values during 2013 and 2014. Comparison of number of these patients and their initial S-β-hCG with patients in this study would have given more information about the success of treatment with methotrexate at Örebro University hospital during the same period. Since data was collected and entered in excel by human hand and reviewed by human eyes, there might be a risk that some data is incorrect. There is also a risk that all patients treated with methotrexate primary for ectopic pregnancy at Örebro university hospital are not included because their methotrexate was not ordered via the pharmacy and therefore they are missing at the pharmacy register.
6. Conclusion

In this retrospective cohort study we found a considerably lower treatment success rate overall with methotrexate up to two doses and a halved methotrexate side effect rate of what can be found in published studies. The trend between the initial β-hCG values and outcome of treatment seem to cohere with earlier studies but in our study no statistical significance was found regarding this trend. Our study showed also that a second dose was not required when initial S-β-hCG <1000. Not all women experienced side effects when given only one dose but all women experience side effects when given two doses. At Örebro University Hospital expectants could be more commonly used as treatment when S- β-hCG < 1000. The small study population in this study makes the results uncertain.
7. References


27. MD Cherly M J, MDTeotico R A. Conservative managment of ectopic pregnancy; A provincial hospital case series of medically managed ectopic pregnancies. 2011;35.


