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Case Report

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Injection Methotrexate in the Management of Ectopic Pregnancy and Pregnancy of Unknown Location – An Audit of Cases at Princess Alexandra Hospital, UK

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Abstract

Ectopic pregnancy is usually treated with surgery. Injection methotrexate is a treatment option for ectopic pregnancy and for Pregnancy of Unknown Location. Meta–analysis of studies have not shown a statistical difference in the success rate or future pregnancy rate or recurrent ectopic pregnancy rate when comparing injection methotrexate with surgery.

Injection methotrexate is also an option for women in whom surgery is contraindicated or who decline surgery.

The length of hospital stay with methotrexate is less than surgery though the follow up period is longer. A health economy model developed by National Institute for Health and Clinical Excellence, UK showed injection methotrexate to be the cheapest option for treatment of ectopic pregnancy.

Our study was a retrospective audit of cases over a two-year period. Patients were selected according to the Royal College of Obstetricians and Gynaecologists guidelines. The study looked at efficacy of methotrexate, time to resolution of the pregnancy and the need for a second dose.

A review of twenty-one cases over a two-year period showed a hundred percent success rate. None of the patients needed a second dose of methotrexate or laparoscopy for a ruptured ectopic pregnancy. One patient had two hospital admissions for lower abdominal pain and needed pain relief.

The review concluded that injection methotrexate is a safe option for medical management of ectopic pregnancies and pregnancy of unknown location in carefully selected cases. It gives the patient greater choice in management. The follow up period is however much longer compared to surgery.

Keywords

Methotrexate; Ectopic pregnancy; Laparoscopy

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Introduction

The management options for an ectopic pregnancy include surgery, medical or rarely expectant treatment. The most commonly used drug for a medical management of an ectopic pregnancy is methotrexate.

Pregnancy of unknown location is defined as a positive urine pregnancy test with the absence of either an intra uterine or extra uterine pregnancy on ultrasound scan [1]. Most cases of pregnancy of unknown location (PUL) resolve spontaneously over time. A few cases of PUL persist and injection methotrexate is a treatment option in such cases.

Methotrexate is an antimetabolite, which prevents the growth of rapidly dividing cells by interfering with DNA synthesis. For the treatment of ectopic pregnancy methotrexate is commonly given intramuscular as a single dose.

The pre-treatment serum beta human Chorionic Gonadotropin (Serum β-hcg) level is said to be the best predictor of the success of methotrexate treatment. Success rates are over 90% with appropriate patient selection [2]. The tube is conserved with an 80% chance of tubal patency. Subsequent fertility appears to be as good as conservative therapy (>70%) and the risk of recurrent ectopic is about 15%.

Meta analysis comparing surgery with systemic methotrexate show there is no statistical difference in the success rate, future pregnancy rate and recurrent ectopic pregnancy rate [3].

One important advantage of medical therapy is the potential for considerable savings in treatment costs. According to the National Institute for Health and Clinical Excellence, (NICE) Clinical Guidelines [3] injection methotrexate is the cheapest treatment option at £1432 followed by laparoscopic salpingectomy at £1608 and laparoscopic salpingotomy at £2205.

The disadvantages of methotrexate therapy are the risk of toxicity and the need for compliance in follow-up to ensure resolution of pregnancy. Abdominal pain is common in the first week following treatment with methotrexate.

Methotrexate is a known teratogen with an increased risk of skull and limb deformities in the fetus. Pregnancy must be avoided for three months. Patients are advised to take 5 mg folic acid during the pre-conception period and in early pregnancy.

Patients must avoid non steroidal anti inflammatory drugs, trimethoprim and folic acid during treatment.

The resolution time is much longer than in women who opt for surgical management of an ectopic pregnancy. Hence follow up and compliance is vital.

Material and Methods

Case notes of patients who received injection methotrexate for either an ectopic pregnancy or a PUL between November 2010 and October 2012 in the Early Pregnancy Unit (EPU) at The Princess Alexandra Hospital, UK were reviewed.

The Royal College of Obstetricians and Gynecology (RCOG) guidelines on the use of injection methotrexate as outlined in Table 1 are followed in our Early Pregnancy Unit.

We gave a single dose of injection methotrexate intramuscular. The dose was calculated on the basis of the body surface area (height×weight) multiplied by 50 [4].

The injection was given in EPU as an outpatient procedure.

All women were counseled thoroughly. A checklist was used and written consent was taken before giving the injection methotrexate. Table 2 shows the checklist used. A signed copy of the checklist was given to the patient. Special emphasis was given on need for follow up, avoidance of alcohol and certain medication. The need to avoid pregnancy for 3 months was also discussed.

All patients were followed up in EPU as outpatient with weekly monitoring of serum β-hcg levels. They were advised to come to Accident and Emergency if they had acute onset abdominal pain.

Serum β-hcg was measured on days 4, 7 and then weekly. A rise in serum β-hcg is not unusual on day 4 of the treatment. A failure of serum β-hcg to fall by 15% between days 4 and 7 was an indication for a second dose of injection methotrexate.

The women were followed up with weekly serum β-hcg levels till the level fell to below 20 IU/L.

We looked at the need for second dose of injection methotrexate, the need for emergency admission and laparoscopy. We also looked at the resolution time i.e. the time taken for the serum β-hcg level to fall below 20 IU/L. In some patients if the serum β-hcg level fell consistently the monitoring was stopped at slightly higher level.

Results

Of the 21 women who were given injection methotrexate, 11 were for Pregnancy of Unknown Location, 9 were for an ectopic pregnancy and 1 was for a cornual pregnancy.

All women who were diagnosed as an ectopic pregnancy on ultrasound scan had an adnexal mass of less than 35 mm. except one patient whose adnaexal mass measured 45×41×35 mm. She declined laparoscopy and opted for injection methotrexate.

For the patient with the cornual ectopic pregnancy, even though the serum β-hcg level was greater than 3000 IU/L, injection methotrexate was considered to be a safer option than surgery.

In one patient the serum β-hcg was very high at 11653 IU/L, However, she was asymptomatic and having had a previous left salpingectomy for an ectopic pregnancy was very keen to try injection methotrexate.

Table 3 outlines the indication, serum β-hcg levels and ultrasound findings on the day of injection methotrexate.

Time to resolution

The time to resolution of the pregnancy was defined as the time interval between the day injection methotrexate (day 0) was given and the day serum β-hcg level fell below 20IU/L.

The range was between 7 and 56 days with most pregnancies resolving in 14 to 28 days (Table 4).

In one patient, monitoring was stopped at a slightly higher level at the patient's request.

Need for laparoscopy or emergency admission

All patients were managed as outpatient from EPU.

One patient was admitted twice as an in-patient with lower abdominal pain. She was clinically stable and her serum β-hCG levels were dropping. A repeat ultrasound scan did not show any change from her initial scan. She was managed conservatively and sent home with codeine phosphate for pain relief. She was followed up in EPU and the pregnancy resolved in 21 days time.

Efficacy of methotrexate

Of the 21 cases we had over a two-year period, we had a 100% success rate. None of the patients needed emergency surgery. Though the initial serum β-hcg level as very high in one patient, the levels fell consistently and the pregnancy resolved in 56 days.

Need for second dose

A rise in serum β-hcg is not unusual on day 4 of the treatment. A failure of serum β-hcg to fall by 15% between days 4 and 7 was an indication for a second dose of injection methotrexate.

The serum β-hcg rose on day 4 of treatment in 6 patients. But the serum β-hcg fell by 15% or more by day 7 and none of our patients needed a second dose of injection methotrexate.

Table 1: RCOG Guidelines on use of Injection Methotrexate.

Indications for considering medical therapy:	Inclusion Criteria	Exclusion Criteria
Haemodynamically stable patient	Normal full blood count, normal liver and kidney function	Fetal Heart Beat seen in ectopic sac
Adnexal mass < 35 mm	Serum β-hcg ,<=3000 IU/L	Hepatitic dysfunction
No fetal heart movements in ectopic sac.	Compliant and will attend follow up	Thrombocytopenia < 100,00
Serum β-hcg < 3000 IU/L.		White Blood Count < 4000
No hemoperitoneum or hemoperitoneum of less than <100mls.		
Persistent ectopic pregnancy after conservative tubal surgery or failed surgical treatment.		
Absent chorionic villi following ERPC with a rising HCG		
Selected cases of cervical and cornual pregnancy		
Persistent PUL		

Table 2: Checklist for Injection Methotrexate.

NAME	DOB
CHECKLIST TO BE NAME	DOB
CHECKLIST TO BE CONFIRMED WITH PATIENT: GIVE COPY TO PATIENT	
Consent form number 3 signed, copy to patient	
Patient information leaflet given	
Discussed abdominal pain in 4- 5 days -75%	
Not to take aspirin, ibuprofen, mefenamic acid	
Can take paracetamol	
Not to take alcohol till bhCG levels are below 20	
Not to have intercourse till bhCG levels are below 20	
Not to get pregnant for 3 months following treatment	
Some women need a second dose of MTX-15%	
If the ectopic ruptures during treatment, there is need for surgery-7%	
Must attend for blood tests as scheduled below	
Minor side effects include nausea, vomiting, diarrhoea, sensitivity to sunlight, mouth ulcer, reversible hair loss, anemia, conjunctivitis	
Not to take folic acid or trimethoprim during treatment	
Contact numbers 01279827107 or A&E	
bhCG on day 4 :Date_____	
bhCG ,LFT,FBC,USS on day 7:Date_____	
bhCG on day 14:Date_____	
bhCG day 21: Date_____	
Signature of patient	
Date	
Signature of person going through checklist	
Copy given to patient	Yes/No

Table 3: Indication for injection methotrexate.

	Indication	Initial Serum β-hcg level IU/L	Ultrasound findings
1	Unresolving PUL	2110	Endometrial thickness (ET) = 10 mm. Small amount of free fluid in Pouch Of Doughlas (POD)
2	Unresolving PUL	1203	Endometrial thickness = 5 mm No adnaexal mass or free fluid in POD
3	Unresolving PUL	94	Endometrial thickness = 5 mm No adnaexal mass or free fluid in POD
4	Unresolving PUL	266	Endometrial thickness = 14 mm No adnaexal mass or free fluid in POD
5	Unresolving PUL	75	No IUP seen, ectopic pregnancy not seen but 27 mm free fluid seen in POD
6	Ectopic Pregnancy	547	Left ectopic pregnancy 27 x 20 mm, small amount of free fluid in POD
7	Ectopic Pregnancy	11653	Right ectopic pregnancy 27 x 23 mm, No free fluid in POD
8	Ectopic Pregnancy	549	Left ectopic pregnancy 12 x 11 x 8 mm, no free fluid in POD
9	Ectopic Pregnancy	1156	Left ectopic pregnancy 19x 13 x 17 mm, no free fluid in POD
10	Ectopic Pregnancy	2357	Left ectopic pregnancy 45 x 41 x 34 mm. 40 mm free fluid in POD
11	Cornual ectopic	4644	Left cornuel pregnancy , 3 cm x 2 cm ,yolk sac seen
12	Unresolving PUL	3453	Endometrial thickness=8 mm.Small amount of fluid in POD.No adnexal mass seen.
13	Ectopic Pregnancy	927	Right side Ectopic 22 x20x22 mm. Small amount of free fluid (deepest 20 mm) in both adnexae.
14	Ectopic pregnancy	103	Right Side Ectopic 23x19x25 mm. No free fluid in POD.
15	Unresolving PUL	215	Endometrial thickness=18mm.No free fluid in the adnexa or POD.

16	Ectopic Pregnancy	1677	Right side ectopic 23 x12 x16 mm. No free fluid in POD.
17	Ectopic Pregnancy	1638	Left side Ectopic 14 mm. No free fluid in the pelvis.
18	Unresolving PUL	1169	Endometrial Thickness=6.5mm. Left adnexa trace of free fluid.
19	Unresolving PUL	107	Endometrial Thickness = 6 mm. No free fluid in the pelvis.
20	Unresolving PUL	3309	Endometrial Thickness=10 mm. No free fluid in POD.5 mm fluid collection in the left adnexa.
21	Unresolving PUL	2055	Endometrial Thickness=8.7mm. No adnexal mass or free fluid in the POD.

Table 4: Time to Resolution.
All levels of serum β-hcg in IU/L

β-hcg	Day 0	Day 4	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Total time to resolution
1	2110	1307	808	384	132	41					28
2	1203	456	363	99	16						21
3	94	57	33	19							14
4	266	164	30								7
5	75	86	2								14
6	547	392	208	114	21						21
7	11653	11183	7684	1431	336	99	69	58	43	20	56
8	549	838	771	193	68	15					28
9	1156	224	131	9							14
10	2357	978	620	263	109	5					28
11	4644	144	42								7
12	3453	2712	1998	249	18						21
13	927	712	354	137	67						21
14	103	18									4
15	215	206	100	22	12						21
16	1677		3086	2681							
17	1638	1939	215	12							14
18	1169	953	483	97							14
19	107	165	117	85	3						21
20	3309	5689	3743	282	149			24			42
21	2055	3384	2952	541	134	41					28

Conclusion

Injection methotrexate is a safe alternative to surgery for ectopic pregnancy. Sometimes it is the only option for unresolving PUL in carefully selected cases.

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Top

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