Retrospective review of the medical management of ectopic pregnancies with methotrexate at a South African tertiary hospital

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Background. An ectopic pregnancy can be a life-threatening condition. Early diagnosis with ultrasonography and quantitative beta-human chorionic gonadotrophin (β-hCG) measurement has improved early and accurate diagnosis and treatment. Medical management with methotrexate internationally has a success rate of up to 93%, but there is a paucity of data on this treatment option in developing countries.
Objective. To determine the success of methotrexate treatment for ectopic pregnancies at a referral hospital in a developing country. This non-surgical, outpatient treatment seems a good option in hospitals with an ever-rising pressure on bed occupation and long waiting lists for emergency surgery.
Methods. A 5-year retrospective audit was performed on 124 patients treated for ectopic pregnancies with methotrexate at Tygerberg Hospital, Cape Town, South Africa.
Results. With success defined as a β-hCG level of <15 IU/L without requiring surgical intervention, the success rate was 44%. Fifteen per cent of medically managed patients required surgery. The remaining 41% were lost to follow-up. One patient had a major adverse outcome with a ruptured ectopic and required 2 units of blood, resuscitation and emergency laparotomy.
Conclusion. Medical management of ectopic pregnancies is a safe and effective management option, as proven by international data, but at Tygerberg Hospital the safety of this treatment modality cannot be guaranteed because of poor follow-up. Improvement in patient selection with consideration of predictors of success and thorough counselling, as well as full informed consent, is recommended before using this treatment modality. A new follow-up system should be developed at Tygerberg Hospital to guarantee patient safety.

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There has been a global increase in the incidence of ectopic pregnancies.[1] This potentially life-threatening condition is ranked among the top direct obstetric causes of maternal mortality in South Africa (SA). According to the Confidential Enquiry into Maternal Deaths,[2] 1.5% of maternal deaths were caused by ectopic pregnancy in the 2008 - 2010 triennium, which is an increase compared with the 2005 - 2007 triennium. Continual improvement in ultrasonography and quantitative measurement of the beta-unit of human chorionic gonadotropin (β-hCG) have improved early and accurate diagnosis of ectopic pregnancies.[3] In carefully selected patients, medical management with methotrexate has shown a success rate of about 90%.[4] Theoretically this non-surgical, potentially outpatient treatment modality seems a good solution in a hospital with ever-rising pressure on bed occupation and long waiting lists for emergency surgery.

In Europe and North America, the incidence of ectopic pregnancies is 1 - 2% of all pregnancies.[5] Scanty data are available for SA. In 1995, a study at Umtata Hospital, Transkei, quoted an incidence of 11/1 000 reported pregnancies, with a mortality rate of 2%.[6]

The reason for tubal implantation in an ectopic pregnancy is unknown, but retention of the embryo as a result of impaired embryo-tubal transport is a common theory. Causes of fallopian tube pathology include genital tract infection, tubal surgery, and a previous ectopic pregnancy.[7] Other risk factors include pelvic adhesions, conception from assisted reproductive technologies, a pregnancy with current use of an intrauterine contraceptive device, and cigarette smoking.[3]

The use of methotrexate for the medical treatment of ectopic pregnancies was first described in 1982.[8] Methotrexate is a folic acid antagonist that inhibits dihydrofolate reductase, which reduces folic acid to tetrahydrofolate, essential in the synthesis of DNA and RNA. Methotrexate inhibits growth in any rapidly dividing tissue such as trophoblasts and is excreted largely by the kidneys.[9] Side-effects associated with the use of methotrexate for ectopic pregnancies include abdominal pain, possibly caused by tubal abortion or tubal stretching, which usually responds to non-steroidal anti-inflammatory treatment. Approximately half of ectopic masses will increase in size after methotrexate treatment, because of haematoma formation. An asymptomatic increase in size of the ectopic mass should therefore not be interpreted as treatment failure.[10] Methotrexate can be stored in the liver and kidneys, so a delay in conception for a period of at least 12 weeks is recommended.[1] Methotrexate may have a short negative effect on oocyte production, but this improves after 180 days.[11]

There are three main medical treatment regimens. The single-dose methotrexate regimen consists of a dose of 50 mg/m^2 administered intramuscularly or intravenously. The β-hCG level is measured on post-treatment days 4 and 7. If there is a less than 15% decrease in the β-hCG level between these days, a second dose is given. The β-hCG is

then measured weekly until it reaches a non-pregnant level.[7] The other regimens are the two-dose and fixed multidose regimens.

There are no randomised trials comparing the different treatment protocols. In a large meta-analysis comparing data from 26 trials and 1 327 cases, the success of the multidose regimen was 93% and that of the single-dose regimen 88%.[4] The average time to full resolution to a β-hCG level of <15 IU/L is 35 days, but it can take up to 109 days, with 20% of patients requiring more than one treatment cycle.[4] The longest time reported from initial treatment to tubal rupture was 31 days.[4]

The cost of outpatient treatment v. surgery varies widely, but many cost analyses favour medical treatment. Interestingly, in a study conducted in the UK National Health System, the cost of medical v. laparoscopic management showed that medical management was only more cost-effective in patients with an initial β-hCG of <1 500 IU/L. This was due to the increased risk of complications, including emergency surgery, repeated admission and subsequent doses of methotrexate.[12]

Patient compliance with follow-up is a major obstacle in medical management, especially in lower-income areas. A retrospective analysis evaluating compliance of inner-city patients who received methotrexate at Bronx Lebanon Hospital Center in New York found that only 10% of patients were fully compliant with follow-up.[13] Simplified follow-up protocols with fewer visits have been suggested to improve compliance.[13]

There are many studies looking at treatment success of ectopic pregnancies with methotrexate, but none in an SA setting. This treatment modality is used at Tygerberg Hospital, Cape Town, but the objective outcomes are unknown. Our retrospective review set out to answer this question.

Objective

The objective of this study was to determine whether medical management of ectopic pregnancies with methotrexate in selected patients at Tygerberg Hospital was an effective and safe treatment option. The outcomes measured were the number of patients requiring surgical intervention despite methotrexate treatment, how many patients needed repeat doses of methotrexate, the average duration of follow-up, time spent in hospital, complications associated with methotrexate use, and compliance of patients with follow-up.

The current protocol for medical management is the single-dose methotrexate regimen. Recommendations for medical management include a stable patient with a β-hCG of <4 000 IU/L, a mass of <40 mm in diameter, no fetal cardiac activity, and minimal free fluid on ultrasound. β-hCG levels are monitored weekly until the value is <15 IU/L.

Methods

A 5-year retrospective audit was performed. Ethical approval was obtained from the Health Research Ethics Committee of Stellenbosch University (ethics number: S12/08/229). All patients treated for ectopic pregnancies with methotrexate were included. Exclusion criteria included cervical ectopic pregnancies, molar pregnancies, intrauterine pregnancies and pregnancies of unknown location. Patients were identified by obtaining a list from the pharmacy of all patients treated with methotrexate from 23 May 2008 to 23 May 2013. Patient folders were systematically assessed, and information was extracted onto a data capture sheet which was then transferred to a MS Excel data sheet with data cleaning and checking.

Statistical analysis was performed using Statistica version 12 (StatSoft Inc., 2009). Descriptive statistics were used. Frequencies (counts and percentages), measures of location (mean and median) and spread (standard deviations (SDs) and percentiles) were used to describe distribution of the data; 95% confidence intervals (CI) are presented for measures of location, as well as for the relative frequencies (proportions). Student's *t*-test, the Wilcoxon rank sum test and the exact χ^2 test were used to assess differences in the study groups.

Results

A total of 181 patients were identified from pharmacy records; 124 met the inclusion criteria, and 42 were excluded because they had received methotrexate for another indication. Fifteen patient folders could not be found.

The mean age was 24.4 years (SD 5.47, range 17 - 44). Most were multigravidas (85%). Eighteen women (14%) had had one or more previous ectopic pregnancies. Twenty (16%) had documented previous sexually transmitted infections, with one woman having had surgery for acute

Table 1. Presenting complaints

Complaint	*n* (%)
Bleeding	37 (29.8)
Bleeding and pain	58 (46.8)
Pain	17 (13.7)
Ultrasound scan showed ectopic pregnancy	4 (3.2)
None (referred from primary care hospital for medical management, with no complaints)	8 (6.4)
Total	124 (100.0)

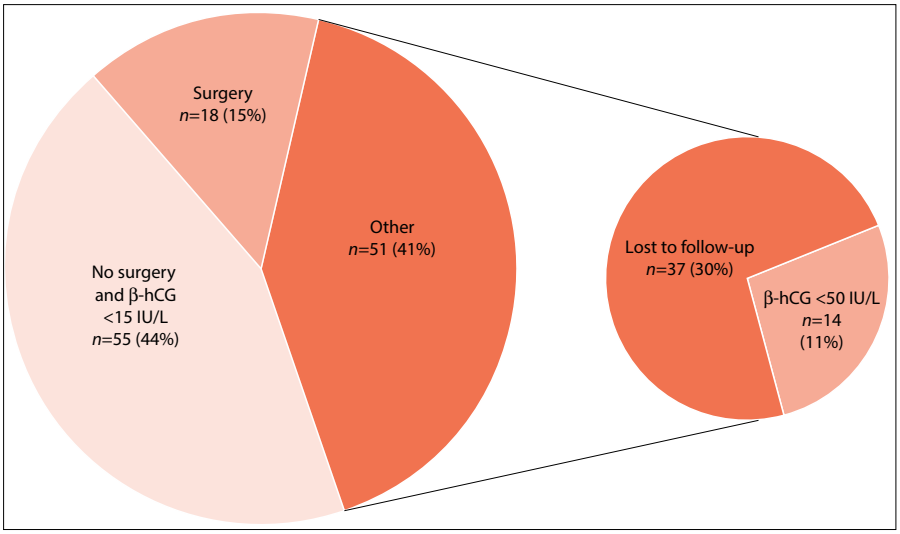

Fig. 1. Outcomes after medical management with methotrexate. (β-hCG = beta-human chorionic gonadotrophin.)

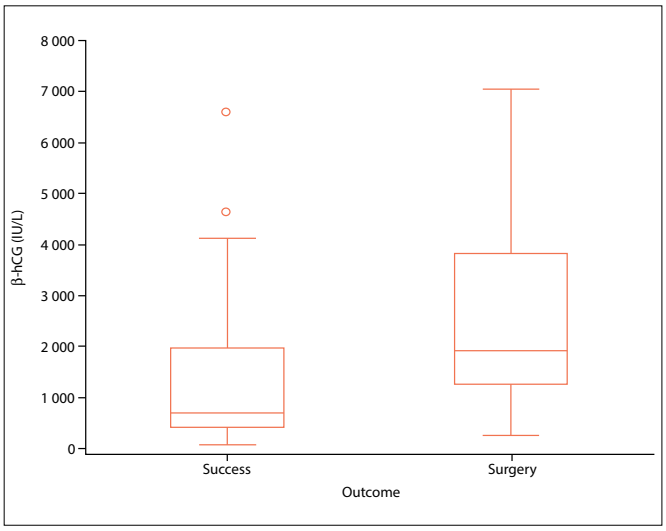

Fig. 2. β-hCG levels of successful methotrexate management v. those requiring surgery. (β-hCG = beta-human chorionic gonadotrophin.)

salpingo-oophoritis. Sixty-nine (48%) were cigarette smokers. None had an intrauterine contraceptive device *in situ*. Ten (8%) had documented fertility problems, and two (2%) had reversals of tubal ligations. Eleven women (9%) were HIV-positive and 50 (40%) HIV-negative, but the majority (*n*=63, 51%) had unknown HIV status.

Over 75% of patients presented with either bleeding or a combination of bleeding and pain (Table 1).

If successful treatment with methotrexate was defined as a patient who was followed up to a β-hCG level of <15 IU/L, without requiring surgical intervention, the success rate was 44% (55/124) (Fig. 1).

Fourteen women were followed up to a β-hCG level of <50 IU/L, and checking the hospital database showed that they were not admitted to our hospital or any district hospital in our drainage area for further treatment. If success was redefined as follow-up to a β-hCG level of <50 IU/L, the success rate of methotrexate treatment would be 56% (59/124).

Repeat doses of methotrexate were required in 17 women (14%); nine were successfully treated and followed up to a β-hCG level of <15 IU/L, four did not complete follow-up, and four required surgery. One of the surgical patients received a third dose of methotrexate, and eventually had a laparoscopic salpingostomy for an unruptured ectopic pregnancy. The indication for surgery was a rising β-hCG level and not worsening clinical symptoms.

Eighteen women (15%) required surgical intervention. Four operations were performed laparoscopically and 14 by open laparotomy. Twelve patients had clinical signs of possible rupture, and this was confirmed in 11 cases. Six operations were performed for increasing β-hCG levels, and none of these cases had ruptured. Potentially five patients could have received a second dose of methotrexate. Of the patients who required surgery, two had large amounts of free fluid at diagnosis, and four had β-hCG levels of >4 000 IU/L.

When comparing the successfully treated group with those who required surgical intervention, a significant difference in β-hCG levels was noted (mean 1 447 v. 2 701 IU/L; p=0.006) (Fig. 2).

Of the 12 patients who were treated with methotrexate with an initial β-hCG level of >4 000 IU/L, four were successfully treated, four required surgery and the remaining four did not complete follow-up.

The size of the ectopic mass at the time of diagnosis was significantly larger in the group who were successfully treated with methotrexate compared with those who required surgical intervention (mean 32.8 v. 23.7 mm; p=0.027). Seventeen patients had an initial ectopic mass size of >40 mm. Of these nine were successfully treated, two had surgery and six did not complete follow-up. Two women with a large amount of free fluid on ultrasound were given methotrexate, and both required surgery. Fourteen patients had a moderate amount of free fluid in the pouch of Douglas, of whom 11 (79%) were successfully treated and three (21%) required surgery. Twenty-three patients had minimal free fluid; 18 (78%) were treated successfully and five (22%) required surgery. Of the patients who had no free fluid, 12 (86%) were treated successfully and two (14%) required surgery. In no patient was fetal heart activity present on ultrasound.

The mean number of follow-up visits for those who were successfully treated was five (range 3 - 13). Of the group that did not complete follow-up, only five were lost after the first visit, and 28 were followed up to four hospital visits or more. Ninety-two patients (74%) required admission to hospital. The high admission rate was mostly due to delay in diagnosis and obtaining methotrexate therapy.

In the successfully treated group, the β-hCG level on day 4 dropped from the initial value in 45 of the 55 patients (mean drop 53%). In the group that required surgery, only one of the 18 patients had a drop in β-hCG levels on day 4.

One patient had a major adverse outcome. She was readmitted 3 days after receiving medical treatment with a ruptured ectopic that required emergency laparotomy and transfusion of 2 units of packed cells. There was one possible minor adverse effect. A patient presented one month after initial medical treatment with lower abdominal pain and was diagnosed with a urinary tract infection. She had elevation of the liver enzymes and marked renal impairment. She was admitted for one day and treated with antibiotics. This patient was HIV-negative. No further follow-up of her renal function was documented, and it is unclear whether there was any relationship to the initial methotrexate treatment.

Advice on the treatment, complications and follow-up was documented in 62% of the folders. Only 45 patients (35%) were discharged with contraception or contraceptive counselling; 19 were on injectable contraceptives, 11 on combined oral contraceptives and one on barrier methods. Twelve patients received counselling or referral to the family planning clinic. In five patients there was evidence of a pregnancy within the same year.

Discussion

In this study of the medical management of ectopic pregnancies with methotrexate, success was defined as follow-up to a β-hCG level of <15 IU/L. Our success rate was 44%, which is much lower than international reports of success rates of 88 - 93%.[10] These rates were achieved in prospective studies where loss to follow-up was not a contributory factor. If we included all patients who were followed up to a β-hCG level of <50 IU/L, the success rate would rise to 55%. The main reason for the low success rate in our study was poor follow-up, as 41% of the patients did not complete surveillance to β-hCG <15 IU/L. Other reasons included incorrect patient selection and incorrect application of the treatment protocol.

Seventeen (14%) of the total group required a repeat dose of methotrexate. This correlates with international rates, where about

20% of women require more than one treatment cycle.[10] In 52% of these cases, the treatment was successful with sufficient follow-up.

Eighteen patients (14%) required surgical intervention. This is higher than the international rates of 7 - 12%.[11] Of these patients, two had large amounts of free fluid on ultrasound and four initially had β-hCG level of >4 000 IU/L, so medical management was less likely to succeed. β-hCG levels were significantly higher in those with failed medical treatment. In five patients a second dose of methotrexate could have been given and surgery could potentially have been avoided. Implementing a standardised protocol, whereby decisions regarding treatment are consistent, is crucial.

No significant differences in the presence of free fluid on ultrasound or the size of the ectopic mass could be shown between the successfully treated patients and those who required surgery. Both patients with large amounts of free fluid on ultrasound who were treated with methotrexate required surgery. A large amount of free fluid is a contraindication to methotrexate therapy, and these patients should not have received medical management.

In our series, as was confirmed in 11 of 12 patients with pain requiring surgery, a presenting sign of pain after treatment with methotrexate was very suggestive of rupture. This is in contrast to the published literature, where most patients presenting with pain did not have a ruptured ectopic.[10] It was thought that the pain was due to tubal stretching in these cases.[10] It is possible that patients in our population group only present to hospital when their pain is very severe.

The size of the mass did not correlate with treatment failure; interestingly, in our series the mass was larger in the patients who were successfully treated with methotrexate. It has also been reported that size is not a good predictor of treatment success.[14] This is possibly because it is difficult to distinguish the surrounding haematoma from the actual ectopic mass.

The day 4 β-hCG level decreased in 42/55 of the successfully treated patients, and increased on day 4 in 12 of the 18 patients who required surgery. This correlates with the literature, where a decline in the day 4 β-hCG level has been associated with a success rate of 88% for single-dose treatment.[15] If the level increases on day 4, the success rate is only 42%.[15]

Study limitations

Our study has limitations, as it is a retrospective review. There was a large loss to follow-up, and the patient notes often had missing information or were not complete. There may have been patients who were lost to follow-up and received surgical management at other private units. We checked the database for all the level 1 and 2 hospitals in our drainage area, and none of the patients who were followed up to a β-hCG level of <50 IU/L had surgery performed in these units. These limitations highlight areas where we would be able to improve our management.

Conclusion

At present the medical management of ectopic pregnancies at our institution is suboptimal. We need to implement a protocol that will enable doctors to correctly select patients who not only meet the criteria for treatment, but are also able and willing to be followed up according to the recommended regimen. Staff training is essential, and doctors and nurses providing this treatment should have sound knowledge of the selection criteria and the follow-up regimen. Patients should be thoroughly counselled. Baseline renal and liver function tests are probably not necessary for single-dose treatment with methotrexate if a good history is taken and clinical examination done. This is important, as it would minimise cost. Access to ultrasound and methotrexate should be improved to avoid unnecessary admission to hospital. There are risks associated with the medical management of ectopic pregnancies. Patients must be informed of these risks, and the benefits of this treatment option and the other treatment options available.

Medical treatment does decrease the number of patients needing surgery, which is very helpful in hospitals with overburdened theatre lists. Medical treatment is a safe option if correct advice, documentation and follow-up are provided. Currently this is not the case at our institution.

We recommend that a follow-up programme is developed where patients are contacted if they do not attend. Patients should be advised that they may need to return for follow-up on average five times, with the possibility of up to ten visits. They must be informed that a second dose of methotrexate is required in up to 20% of cases, and that there may still be a need for surgery. They should be advised to delay conception for at least 12 weeks after treatment, they should be tested for HIV infection, and contraceptive counselling should be offered. Detailed documentation is essential.

We intend to design a patient-kept card providing information about medical treatment with methotrexate, the risks and benefits, warning signs, contact telephone numbers, follow-up dates and β-hCG values. It will also include advice about contraception. The card will enable patients to be followed up at their primary care hospital, which would be less costly and time-consuming for them. This should improve compliance with follow-up and the safety of medical treatment with methotrexate for ectopic pregnancies.

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