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Double versus Single Dose Methotrexate Regimens in Management of Undisturbed Ectopic Pregnancy

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Abstract

Objective: To assess the effectiveness and safety of double-dose methotrexate in comparing to single-dose methotrexate for management of ectopic pregnancy.

Methods: A prospective randomized-controlled trial was conducted on 200 patients with ectopic pregnancy at the Obstetrics and gynecological Departments of Zagazig University, Egypt between June, 2011 to May 2014. Patients were randomized into two groups, (group 1) who received a single dose 50 mg per meters squared surface area methotraxate (50 mg/m^2 IM on day 1) intramuscularly or (group 2), who received double-dose methotrexate regimen (50 mg/m2 intramuscularly on days 0 and 4). The outcomes were; success rate, time duration of fall down of b-hcg to <15 mIU/mL and undesirable effects of methotrexate.

Results: In general, there is significant differences between both groups as regard the success rate and the duration of fall down β-hCG. The success rate was better in group 2 than in group 1 (90% versus 78.75%, P=0.01). The duration of fall down β-hCG until <15 mIU/mL was shorter in group 2 (P=0.01). There was no significant difference between groups in adverse effects.

Conclusion: Double-dose methotrexate as one of regimens of medical management of undisturbed ectopic pregnancy had more effectiveness and success rate than that of single-dose regimen with equivalent safety.

Keywords: Undisturbed ectopic pregnancy; Beta HCG; Medical treatment; Methotrexate

Introduction

Ectopic pregnancy (EP) is the implantation of the blastocyst outside the uterine cavity, also known as extrauterine pregnancy [1].

The incidence is around 1.5-2.0% of all pregnancies. The most common locality for ectopic pregnancy is the uterine tube (96-98%), then the cervix (0.2-0.5%), the ovary (0.2-2.0%) and the abdomen less than 1% [2]. It is a serious medical and surgical condition. It amplifies the incidence of maternal mortality and morbidity in addition to pregnancy loss and the unknown future conception [3]. The clinical judgments can be very unpredictable, ranging from no symptom to the complete photo of acute abdomen [4] until the end of 1980's, the diagnosis of ectopic mostly was retrograde after its rupture and only 20% of ectopic pregnancies could be diagnosed before. Now, transvaginal ultrasounds and serum serum β human chorionic gonadotropin (s-β HCG) levels act as a guide to reach to a perfect diagnosis as early as possible when ectopic is suspected [5]. Early diagnosis allows many ectopic pregnancies pursue somewhat lethargic course with a little probability of sudden haemorrhage. So, this has resulted in increasing interest to use medical therapy for the management of ectopic pregnancy [6]. In 85% of normal early pregnancies the β-hCG level will double every 48 to 72 hours. Abnormal rising in S-β-hCG levels points out an abnormal pregnancy but not its location. Combination of the S-β-hCG concentration and transvaginal ultrasound findings contributes significantly to reach diagnosis. When pregnancy is not seen intra uterine at S-β-hCG levels above the discriminative value, the suspicion of an abnormal pregnancy will be high [7]. The most common agent as medical management therapy of ectopic pregnancy is methotrexate. It is an antimetabolite, that avoids the growth of rapidly dividing cells by impedeing with DNA synthesis. There is different route for administration; locally guided by transvaginal ultrasound or through laparoscopy, or systemically [8]. The systemic way may be as a single dose regimen with success rate of 88%–90% or a multiple dose regimen with success rate 86%-95% [9]. It was found that, the outcome of either regimen depends on a lots of factors like initial human chorionic gonadotropin (β-hCG) levels and gestational mass size [10]. As regard as the Clinical Guidelines of National Institute for Health and Clinical Excellence, (NICE); there are many significant advantages of medical therapy as the ability to conserve the tube with about 80% patency chance and good Subsequent fertility also considerable savings the costs of treatment [11]. The aim of this study was to evaluate the efficacy and safety of a

double-dose methotrexate regimen in comparison with single dose for the management of ectopic pregnancy.

A prospective randomized-controlled trial trial was conducted on 200 patients with ectopic pregnancy at the Obstetrics and gynecological Departments of Zagazig University hospital, Egypt, which is tertiary one has about 120 beds and manages around 13.000 cases/year between June, 2011 to May, 2014. The participants were diagnosed to have tubal (EP) enrolled in the study after rewarding the inclusion and keeping in mind the exclusion criteria; 40 women were excluded then a written informed consent was taken from eligible patient after giving full discussion and informations about nature of the study. The study protocol was approved by the ethics committee of Zagazig University hospitals. Ectopic pregnancy (EP) was diagnosed by using quantitative serum b-hCG measurement and transvaginal ultrasound.

The inclusion criteria of women who were eligible for entering into the study were having; a gestational adnexal mass ≤ 4 cm, serum β-hCG level of ≤6000 mIU/mL; stable hemodynamically, no cardiac activity in gestational sac, no haemoperitoneum or minimal (less than 300 mL) on transvaginal ultrasound assessment. Fulfillment of Patient for regular follow ups must be accessible [12].

Exclusion criteria were: vitally unstable, clinical suspected ruptur of ectopic, uncertain diagnosis, if serum b-hCG concentration was falling, cervical, cornual, ovarian or heterotopic pregnancy was diagnosed by ultrasonic examination, any abnormal laboratory tests confirming probable injurious effects of methotrexate on organ functions like thrombocytopaenia, leukopaenia, elevated serum creatinine or liver enzymes, breast feeding, immunodeficiency or concomitant use of corticosteroids and known hypersensitivity to methotrexate [13].

Patients who gave verbal and written informed consent were randomised to receive either single dose or double doses methotrexate regimen intramuscular after calculating the patient body surface area from her height and weight.

Complete obstetrical and gynecological history was taken. Clinical examination was done for presence of any vaginal bleeding, adnexal mass, tenderness, and an enlarged soft uterus. B-hCG samples were assayed in the same laboratory. The sensitivity of assay was 20 mIU/ml. Randomized patients were grouped into (group 1) who received a single dose 50 mg per meters squared surface area methotraxate (50 mg/m^2 IM on day 1) intramuscularly or (group 2), who received double-dose methotrexate regimen (50 mg/m^2 intramuscularly on days 1 and 4) [14].

A computer programme was used for randomization and distribution details were enclosed in sequentially numbered opaque envelopes sealed by a third person. Envelopes were unlocked in the attendance of the patients who were entering the study.

The both groups were monitored clinically and laboratory. Informations were given to the patients about the possibility of pelvic pains which are frequent in the week follow methotrexate injection and its side effects like (nausea, diarrhea and stomatitis). Laboratory monitoring includes; checking blood group, hemoglobin platelet count, liver and renal functions in day 1 and re-evaluated on day 7. Checking Serum B-hCG Day 1, 4 and 7; and weekly until become negative value (15 mIU/mL) or for 6 weeks. Admission of all patients to the hospital during the first week of management and then were followed as outpatients. The outcomes were success rate which was defined as 15% or more drop in serum β-hCG level between day 4 and day 7 with a sustained fall to less than 15 mIU/mL within 6 weeks without surgical interference or a repeat dose, time duration of fall down of b-hcg<15 mIU/mL.

Information was given to the patients to avoid vaginal intercourse, pelvic exams, sun exposure and non-steroidal anti-inflammatory drugs during treatment period. Paracetamol with or without codeine was given as pain relief [15].

Failed treatment was considered in both groups if; level of β-hCG had get higher or fallen by less than 15% at day 7, persisted at elevated levels for more than 6 weeks, or surgical interference was needed for any patient (elective or emergency).

Elective surgical interference was done for patients with failed treatment in group 2 but, in group 1, some patients underwent surgical intervention and had a repeat methotrexate dosage after counseling and full information was given to them.

Statistical analysis of all outcomes using; Unpaired Student t test which was used to compare mean values with 95% confidence intervals or medians with a range; χ2 or Fisher exact test was used to compare percentages, and the Mann-Whitney U test was used for comparisons of ordinal and continuous data.

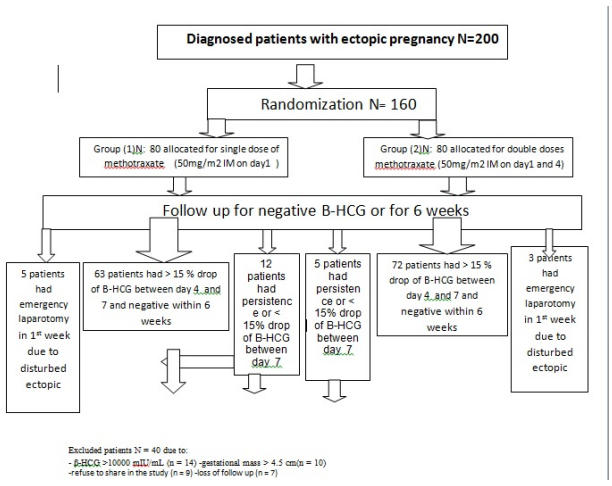

Figure 1 Study profile of patient.

Results

200 women were diagnosed with an ectopic pregnancy and registered in this study, 160 women completed it to the end while 40 participants were excluded. The design and issue track through the study is illustrated in **Figure 1**. **Table 1** shows no statistically significant difference between the two studied groups in baseline characters.

Management by using single dose of methotrexate (group 1) did not success for 17 cases (21%); 5 patients (6.25%) needed to emergency laparotomy during the first week due to tubal rupture while in group 2; using double doses of methotrexate 8 patients (10%) showed failed management 3 (3.75%) required emergency laparotomy (**Figure 1)**.

Table 1 Baseline characteristics of the two studied groups.

Baseline criteria	Group 1 (single dose) N= 80	Group 2 (double doses) N=80	P value
Patient age, years	21.3 ± 5.4 (18-34)	23.3 ± 3.8 (17-36)	0.4
Parity 0-1 2-5 >5	36% 39% 25%	32 % 46% 22%	0.5 0.7 0.6
BMI	26.5 ± 7.3 (21-38)	27.1 ± 6.9 (20-37)	0.7
History of ectopic	25 %	28 %	0.9
History of assisted reproductive	6%	8 %	0.3
Presented by vaginal bleeding	23 %	25 %	0.8
Presented by abdominal pain	15 %	13 %	0.7
Values are given as N (%), mean [SD] or median [range]. P-value<0.05 is significant			

Table 2 Outcome of adverse effects.

Adverse effects	Group 1 (single dose)		Group 2 (double doses)		P value
	N	%	N	%	
	20/80	25	28/80	35	
Abdominal pain (new onset)	7	8.75	8	10	0.7
Gastrointestinal symptoms	6	7.5	7	8.75	-
Mucositis	3	3.75	5	6.25	-
Elevated liver enzymes	2	2.5	4	5	-
Loss of hair	2	2.5	2	2.5	-
Thrombocytopenia/	0	0	1	1.25	-
leucopenia	0	0	1	1.25	-
Values are given as N (%) P-value<0.05 is significant					

Those patients who were done laparetomy had increasing level of, the β-hCG on day 4 more than 20% up to 50% of the premethotraxate level plus complaining of abdominal pain made the sugestion of ruptur of ectopic pregnancy.

The remaining 5 with failed treatment in group 2, 5/12 treatment in had elective laparoscopy with no signs or symptoms of tubal rupture but persistence of <15% drop of β-hCG level. The success rate in group 1 was 63/80 (78.8%) and in group 2 was 72/80 (90%).

Table 2 showed adverse effects in both groups clinically and laboratory; in (group 1), four women had an elevated aspartate transaminase level versus two in (group 2), one woman had mild thrombocytopenia and one woman had mild neutropaenia subsequent a second dose of methotrexate. These haematological deviations came back to normal within ten days.

Clinically, few patients of both groups had abdominal pain, gastrointestinal manifestations in the form of nausea and vomiting or loss of hair with no significant differences.

The mean time for b-hCG levels to drop to less than15 IU/L was 13 days (range 10-30) in group 1 and 24 days (range 19-41) in group 2 with P value 0.01 (**Table 3)**.

Table 3 Time duration of fall down of B-HCG and success rate.

p-value	Group 2 (double doses)	Group 1 (single dose)	Outcome
0.01	72/80 90%	63/80 78.75%	Overall success rate
0.01	13.4 ± 3.6(14-31)	24.2 ± 3.9 (19–41)	Time duration of fall down of B-HCG to <15 mIU/mL

Values are given as mean ±SD (range) or number (percentage). Time duration of treatment and follow up until β-hCG 15 mIU/mL. Student test was used to compare means; χ^2 or Fisher exact test was used to compare percentages.

Table 4 Success rate in relation to basic diameters (B-hCG and diameter of ectopic mass).

p-value	Group 2 (double doses) 72/80	Group 1 (single dose) 63/80	Success rate in relation to baseline parameters
0.7 0.001	49/50 98% 23/30 76.6%	94.4% 51/54 12/26 46.1%	β-hCG, mIU/ml** <3000 mIU/mL ● ● 3000-6000 mIU/mL
0.5 0.01	49/52 94.2 % 23/28 82.1%	48/52 92.3% 15/28 53.5%	** Ectopic mass in diameter (cm) <3 cm ● ● 3-4 cm
P value<0.05 was significant Values were given as number (N) or percentage (%)			

There was no significant difference between the 2 groups when any of regimens was used while the basic β-hCG level<3000 mIU/mL and a gestational mass diameter<3 cm. The double regimen showed highly significant difference in patients

with β-hCG levels between 3000 and 6000 mIU/mL (P=0.001) and significant difference if size of ectopic mass 3-4 cm (0.01) (**Table 4)**.

Discussion

Methotrexate was primary initiated as a flourishing dealing option for EP in the 1980's by Tanaka et al. [16].

Many studies published different rates of success for medical management of EP either by single or multidose regimens; ranging from 85% to 95% to 100% by Nguyen et al. and Skubisz et al. [17]. Feras et al. found the cure rate of ectopic pregnancy by management with methotrexate was 72%. It shows to be comparatively lower than international rates, an average of 90% [18]. In this study we anticipated to prove that using double doses of methotraxate as a medical management of selected cases of ectopic pregnancies has promising success rate than single dose. Our results revealed overall success rate 90% for the double- and 78.75% for the single-dose methotrexate regimens. The success rate for the double-dose regimen (90%) was higher than that of Barnhart, et al. [14] who first depicted this regimen, accounting a rate of 76% in a study that contained 101 patients of different ethnicities. The single-dose treatment had overall success rate of (78.75%) which is analogous to other descriptions (65%-96%) [9]. The Royal College of Obstetricians and Gynecologists express merely the single-dose regimen in its recommendations for the medical treatment of EP [19]; this recommendation is standed on numerous studies representing that only 15%-25% of women will need more than one dose. But those patients cannot be exactly predicted and therefore cannot be counseled for repeating this single dose again [20]. Definitely, the expression "single-dose protocol" is not sure because it includes the opportunity of repeating the dose at weekly intervals in poor responders. Repeating doses are related to longer treatment and follow up extent, more unpleasant effects, and less fulfillment. One of the advantages of the double-dose protocol is the closeness of the second to the first dose which improves outcome of the drug with high trophoblastic-cell load [8]. In study of Hamed, et al. revealed a comparable overall success rate for the double- and the single-dose methotrexate regimens (88% versus 82%) [21]. This result was higher than that of Barnhart, et al. [11] (76%) but near to our result (90%). About single dose, the overall success rate for Barnhart, et al. was (82%) which was comparable to other reports (65%-96%) of Bixby, et al. and Alleyassin, et al. Also our result was similar to their results about using of single dose regimen [22].

If the success rate would be subscribed according to basic parameters (basic B-hcg and size of ectopic mass; there was no significant difference between the 2 groups when any of regimens was used while the basic β-hCG level<3000 mIU/mL and a gestational mass diameter<3 cm. The double regimen showed highly significant difference in patients with β-hCG levels between 3000 and 6000 mIU/mL (P=0.001) and significant difference if size of ectopic mass 3-4 cm (0.01) our results were comparable to that of Hamed, et al. [21] they found; no significant difference between the 2 protocols in with an primary β-hCG level of <3600 mIU/mL and diameter of ectopic mass<2.7 cm. But double doses protocol had better results with statistical significance (P=0.03) in patients with with β-hCG levels between 3600-5500 mIU/mL. As regard diameter of ectopic mass, they found success rate was more for the double-dose regimen with imminent significance (P=0.055 between 2.7-3.5 cm. This may be based on the concept of more large the size of ectopic mass, more production of β-hCG and the more methotrexate dose required to manage active trophoblasts [23]. In current study, the types and frequency of adverse effects were analogous in both groups (25% versus 35%) and similar to other reports (25%-32%) [24].

Pelvic pain was the most frequent undesirable effect (8.78% versus 8%), which is generally caused by declaration of ectopic pregnancy relatively than methotrexate itself. The current rates of pain were lesser than that of earlier studies which was 27% for the double-dose in study of Barnhart, et al. [11] and 20% for the single-dose regiemens [25].

Conclusion

Double-dose methotrexate as a one of regimens of medical management of undisturbed ectopic pregnancy had more effectiveness and success rate than that of single-dose regimen with equivalent safety.

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