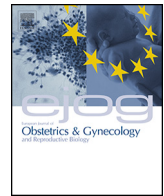




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Methotrexate-treated ectopic pregnancy: beta human chorionic gonadotropin serum changes as a success predictor using a mathematical model validation

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ABSTRACT

Background: Surgical rescue of methotrexate-treated ectopic pregnancy is necessary when tubal rupture or medical therapy failure is detected during post-therapeutic monitoring. It is known that an increased beta human chorionic gonadotropin (β -hCG) concentration is the most important factor associated with treatment failure. Therefore, we suggested that relative changes in serum β -hCG could predict a successful result of medical treatment, leading to facilitation of the decision to forgo the prospect of possible surgical rescue.

Methods: A retrospective observational study of 115 patients with an ectopic pregnancy who were treated with a single dosage protocol of 50 mg/m² of methotrexate injected intramuscularly was performed at Puerta de Hierro University Hospital and Gregorio Marañón University General Hospital. Standard statistical tests were applied in order to evaluate the relative changes in β -hCG concentration between the 1st and the 4th days following methotrexate injection.

Results: Methotrexate treatment has a 95% probability to be successful if the relative change of β -hCG from the 1st to the 4th day of monitoring is within the following interval: [−1.02; 0.15]. Moreover, if the values of β -hCG-relative change from 1st to 4th day of monitoring are within [0.54; 1.2], it assures a negative result of treatment with 95% probability. Therefore, the value 0.15 (15%) of β -hCG relative change can be considered a cut-off value for a positive result to treatment.

Conclusions: Our data support that negative β -hCG relative changes on the 4th day of treatment likely predict a successful result of methotrexate therapy, with a cut-off point of 0.15. Expectant management should be carried out in these cases if no clinical indications of surgery are presented.

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Introduction

According to the United States Centres for Disease Control and Prevention, the incidence of ectopic pregnancy is 1–2% of overall pregnancies and represents 3–4% of pregnancy-related deaths [1]. Early diagnosis leads to a higher possibility that surgery can be avoided. A single-dose methotrexate (MTX) injection was reported by Stovall et al. in 1991 [2] to be an alternative to surgical treatment in patients with an ectopic pregnancy, and this method has also

been investigated by other researchers [3–18]. The advantage of single-dose MTX is that it requires less intensive monitoring, is less expensive, and eliminates the need for surgery in more than 90% of properly selected patients [3,4]. Surgery is usually performed in the case of drug treatment failure. In previous investigations, it was observed that the serum beta human chorionic gonadotropin (β -hCG) increase was lower in women with successful treatment as compared with those with treatment failure [8,9]. However, the initial β -hCG titre was not considered to be a predictor of the necessary number of MTX cycles to achieve a successful outcome [10].

The goal of this study was to determine a cut-off value in β -hCG serum levels, which could be an early predictor of a successful result following MTX therapy.

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Methods

The retrospective study was performed at Puerta de Hierro University Hospital and Gregorio Marañón University General Hospital between June 2010 and March 2012. It included 115 patients with ectopic pregnancy who underwent MTX therapy.

All the patients were treated according to a protocol established by the Spanish Society of Obstetrics and Gynecology [5]: a single dose of 50 mg/m² MTX was injected intramuscularly. The failure of MTX drug treatment led to surgery. The β-hCG serum and leucocyte levels were measured on the 4th and 7th days after treatment, respectively. β-hCG levels were followed in all patients until they fell below 15 mIU/ml.

Patients who experienced a decrease in the β-hCG concentration of more than 15% between the 4th and 7th days were administered a second dose of MTX. A rescue surgery (defined as a failure of the drug treatment) was performed in case of non-response to MTX treatment, impending, or on-going tubal rupture. The diagnosis of tubal rupture was based on hemodynamic instability, increased abdominal pain, or the presence of blood in the abdomen confirmed by ultrasound results. Finally, we could not identify any correlation between pain, bleeding, patient age or gestational age, and successful or failed treatment results, so we did not include them in our report.

The success and failure groups' data included the initial β-hCG level, its relative change on the 4th day, the relative change in leucocytes on the 7th day, and the median number of follow-up visits. We determined the relative change in the β-hCG level by calculating the difference between the β-hCG value on the 4th day and the 1st day and then dividing the result by the 1st day's value. To convert this number to a percentage, it was multiplied by 100. Also, the results of chi-square test association are displayed. p-Values larger than 0.05 were considered insignificant. The mean values of the parameters and the standard errors are shown in Table 1. The serum relative change data for success/failure groups were tested for normality fitting using standard methods. We represented data of the serum relative change for both groups by histograms and fitted normal curves (Fig. 1). The grey columns, which are centered at their mean values, show the standard error of parameter estimate. Statistic Matlab Toolbox framework was used for our data analysis and representation.

Results

The main result of this work is that there was a strong association between the 4th day β-hCG relative change, the mean number of follow-up visits, and the success/failure treatment results (p = 1.211e - 5 and p = 0.005, correspondingly). There was a considerable dependence between the leucocytes' relative change on the 7th day of treatment (p = 0.03) and the treatment results. In Fig. 1, the confidence intervals (95%) for success/failure groups are (-1.02; 0.54) and (0.15; 1.15), respectively. There is an overlap region between them, where the uncertainty about the diagnosis still exists. Therefore, to deduce the cut-off value, we excluded the overlapping interval. The statistical analysis for the means and standard deviations showed that the mean relative change of

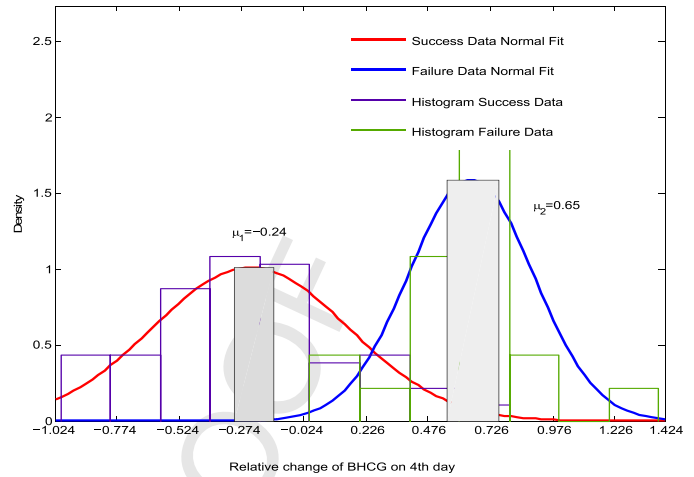


Fig. 1. Histograms and density functions of normal distributions of success and failure groups for relative BHCG change on 4th day. The grey color columns, centered in mean values, show the standard error of parameter estimate.

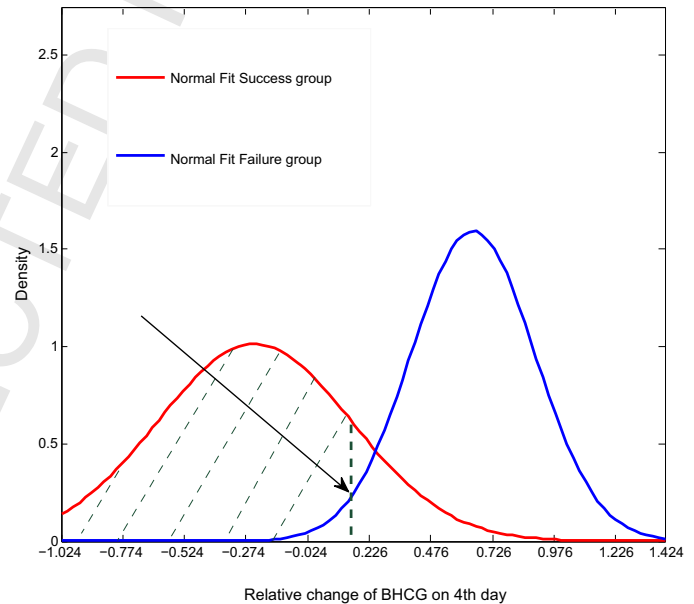


Fig. 2. Fitting normal curves for success/failure groups are presented. The success cutoff value of β-hCG relative change is shown by an arrow. The dashed area is the region of 95% of success.

β-hCG was almost 0.9 units lower in the success group than in the failure group. Fig. 2 shows both fitting curves and the success confidence interval without this overlapping region. Thus, if the relative change of β-hCG is less than 0.15 units, the success of MTX treatment can be provided with 95% confidence. We highlight this area using dashed lines and show its cut-off value with an arrow.

Table 1
Statistical data (NS = not significant, % = percentage).

Patients characteristics	Success group	Failure group	p Value
Serum β-hCG (mIU/mL) at diagnosis	2216.4 ± 2049.6	3005.4 ± 1482.6	NS
Relative change in β-hCG on 4th day of treatment	-0.236 ± 0.275	0.646 ± 0.250	1.211e - 05
Relative change in leucocytes (millions/mm ³) between diagnosis and 7th day of treatment	-0.171 ± 0.214	0.023 ± 0.429	0.030
Median of number of visits for following up	6 (range 3-16)	4 (range 2-10)	0.005

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