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MATERNAL-FETAL MEDICINE

Can early βhCG change and baseline progesterone level predict treatment outcome in patients receiving single dose Methotrexate protocol for tubal ectopic pregnancy?

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Abstract

Introduction We aimed to assess the prognostic significance of early βhCG change and baseline progesterone level on treatment outcome among women receiving single dose Methotrexate protocol for tubal ectopic pregnancy (EP).

Material and methods Retrospective study involving all consecutive patients diagnosed with EP and receiving Methotrexate therapy form January 2015 to December 2016. Patients were stratified into 2 groups according to treatment outcome: success group ($n=66$) involved women who displayed complete resolution of serum βhCG levels following a single course of Methotrexate; failure group ($n=55$) included patients who required repeated Methotrexate administration and/or surgical management. Predictive performances of baseline progesterone and ratio"βhCG level on day 4/ βhCG level on day 1" (d_4/d_1) on treatment outcome were assessed using Receiving Operating Characteristics curves.

Results The ratio d_4/d_1 displayed good performances in predicting treatment outcome (AUC = 0.826). A ratio ≤ 0.7 was associated with a success rate of 94% after 1 course of Methotrexate and 100% after 2 courses. In contrast, a ratio >1.7 was associated with a failure rate of 100%. Conversely, baseline progesterone showed poor performances (AUC = 0.611).

Conclusions Patients with extreme βhCG changes ($n=33$) on day 4 might benefit from a more personalized approach: simplified monitoring in those with a decline ≥30%, anticipated second course of treatment in those with an increase > 70%.

Keywords Tubal ectopic pregnancy · Methotrexate · Early βhCG change · Baseline progesterone · Prognosis

Introduction

The single dose Methotrexate (MTX) protocol for medical management of ectopic pregnancy (EP) was first developed in 1991 by Stovall et al [1, 2]. Due to high success rate (ranging from 65 to 96%) and tolerance, it is still used worldwide [3–8]. The change in serum βhCG measurement between day 4 and day 7 following MTX administration is the key prognostic factor for treatment outcome. Indeed, a drop of βhCG levels ≥15% defines initial treatment success and allows for serial biological follow up.

The main drawback of this protocol is the need for 7 days and repeated visits to assess treatment effectiveness, that exposes to lost to follow up. An earlier recognition of treatment success could thus enhance protocol observance and reduce psychological stress, medical visits and global health expenses. Several studies have focused on early changes in serum βhCG between day 1 and day 4, with conflicting results [9–14]. Hence, no standard has been raised in the day 4 βhCG trend, particularly in patients with an increase in serum measurement. Initial progesterone measurement has also been evaluated as a risk factor of treatment failure but most studies failed to demonstrate its prognostic significance [15, 16].

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Herein we investigated the prognostic significance of early kinetics in βhCG levels among women receiving single dose MTX for EP. We also aimed to determine whether initial progesterone measurement could improve the prognostic value of early βhCG changes.

Material and methods

Study design

From January 2015 to December 2016, all patients diagnosed with tubal EP and receiving single dose MTX protocol were enrolled in this retrospective study. All women were managed in the department of Obstetrics and Gynecology at Purpan University Hospital, Toulouse, France. They all received information regarding the potential use of their medical records for clinical research purpose and gave their consent for participation. The study was approved by local IRB (Comité d'éthique regional).

Inclusion criteria comprised: asymptomatic and hemodynamically stable patient, confirmed EP on ultrasound examination, βhCG level <5000 UI/l.

Exclusion criteria comprised: medical contraindication to MTX treatment, history of previous ipsilateral EP, extrapelvic hemoperitoneum, embryo heart beat.

Medical management

Baseline workup comprised clinical evaluation, abdominal and transvaginal ultrasound examination and serum measurement of βhCG and progesterone, complete blood count and biological assessment of liver and renal functions.

In the absence of contraindication, patients received intramuscular administration of MTX (1mg/kg) and were scheduled for further visits on day 4 and day 7 following treatment, including clinical examination and serum βhCG measurement.

Subsequent management was based on the changes in βhCG levels between day 4 and day 7. A drop of ≥15% defined treatment success and patients were scheduled weekly for βhCG level screening until resolution. Patients with a drop <15% or an increase in βhCG levels received a second course of MTX, in the absence of contraindication. Treatment failure was defined as the requirement for surgery.

Objectives

Our principal objective was to assess the effectiveness of early βhCG kinetics in the prediction of MTX treatment outcomes.

Our secondary objective was to determine if initial progesterone level could improve the predictive value of early βhCG kinetics.

Study groups definition

Our study population was stratified according to treatment outcome. Success group included all patients who displayed a complete resolution of serum βhCG levels following a single course of MTX. Failure group included patients who required repeated MTX administration or surgical management.

Statistical analyzes

All data were collected from medical records. They were anonymized and de identified prior analysis. Statistical analysis was performed using Stata® software (Stata Corp., College Station, Texas, USA). For quantitative variables, we performed average comparison (Student's *t* test) or rank tests (Mann–Whitney) according to the normality of the variable. We used the Chi statistical test or Fisher's exact test for the comparison of qualitative variables.

Predictive performances of baseline progesterone and early βhCG kinetics on treatment outcome were assessed with eceiving perating haracteristics (ROC) curves. A p value <0.05 was considered significant.

The ratio d_4/d_1 corresponded to the ratio "βhCG level on day 4/ βhCG level on day 1″. It was computed to reflect early βhCG change.

Results

From January 2015 to December 2016, 121 patients received MTX treatment for EP. Main symptoms were mild to moderate pelvic pain (89.3%) and vaginal bleeding (80%).

Treatment outcome

In our study population, MTX treatment led to complete resolution of serum βhCG measurement in 99 patients (Table 1). Among them, 33 required 2 courses of MTX. Overall success rate of MTX protocol was thus 81.8%. In contrast, success rate of single dose MTX treatment was 54.5%. Surgery was performed in 21 cases: 11 within the week following the first course of MTX and 10 after a second course of treatment. Indications for surgery included: hemoperitoneum following tubal rupture ($n=12$), acute pain ($n=4$), de novo embryo heart beat on screening ultrasound ($n=3$), absence of drop in βhCG levels after 2 courses of treatment ($n=2$). One patient was lost to follow-up after first

Table 1 Comparative demographics according to treatment outcomes

	Whole population $N=121$	Success group $N=66$	Failure group $N=55$	p value
Age, median	30 (17–41)	30 (17–41)	30 (19–40)	0.84
Gestity, median	2 (0–7)	2 (0–7)	2 (0–5)	0.68
Parity, median	1 (0–4)	1 (0–4)	1 (0–3)	0.21
Weight (kg), mean	63.6 ± 12.8	64.2 ± 13.8	62.8 ± 11.5	0.39
Size (mm), mean	19.3 ± 7.7	19.8 ± 8.9	18.6 ± 6.3	0.46
Volume of Douglas pouch effusion				0.9
Absent or mild	113 (93.4%)	62 (93.9%)	51 (92.7%)	
Moderate	8 (6.6%)	4 (6.1%)	4 (7.3%)	
Progesterone level (ng/ml), median	6.6 ± 5.9	5.7 ± 5.6	7.7 ± 6.2	0.10
βhCG level (UI/l) day 1, mean	1426.8 ± 1416.7	937.2 ± 986.4	2025.3 ± 1942.6	0.0001
βhCG level (UI/l) day 4, mean	1792.3 ± 2555.6	867.7 ± 1955.5	2922.3 ± 3289.3	$< 10^{-4}$

mild effusion = effusion restricted to the Douglas pouch, moderate effusion = effusion exceeding the Douglas pouch but restricted to the pelvic area

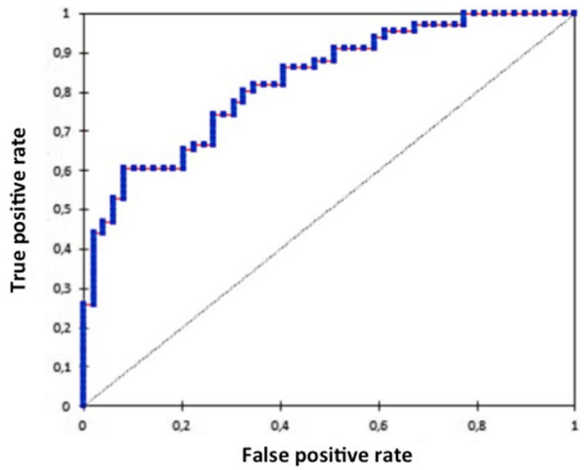

Fig. 1 Receiving Operating Characteristics curve evaluating performance of early βhCG changes in treatment outcome prediction (AUC = 0.832)

course of treatment. Noteworthy, no severe adverse events related to MTX occurred during the study period.

We did not observe any difference in patients parameters according to treatment outcome except serum βhCG level at baseline that was significantly higher in the failure group (2025 versus 937, respectively; $p = 0.0037$).

Prognostic significance of early changes in βhCG level

On day 4, serum βhCG level increased in 53 patients and decreased in 67. Overall the ratio d_4/d_1 displayed good performances in predicting treatment outcome, with a AUC = 0.826 [CI: (0.75–0.90)] (Fig. 1). A ratio $d_4/d_1 > 1$ was associated with successful single dose treatment in 32.1% of cases (17/53). This rate reached 79.1% in patients with a ratio $d_4/d_1 \leq 1$ (53/67). Noteworthy, when the ratio was ≤ 0.7, success rate was 94% after 1 dose of MTX and 100% after 2 courses. In contrast, a ratio>1.7 was associated with a failure rate of 100%. Such finding suggests that patients with extreme βhCG change between day 1 and day 4 might benefit from simplified monitoring. In our study population, serum βhCG measurement on day 7 could thus have been avoided in 27.2% of women.

Based on our data, the optimal cut-off in the ratio d_4/d_1 was 1.15. Corresponding sensitivity, specificity, predictive positive value and negative predictive value were 80%, 67%, 77% and 72%, respectively.

Prognostic significance of progesterone level at baseline

Progesterone level at baseline was available in 91 patients. Among them, 51 belonged to the success group and 40 to the failure group. No difference in progesterone level was observed between groups (Table 1). Furthermore, ROC curve showed poor performances in predicting treatment outcome, with a AUC = 0.611 (Fig. 2). Similarly, pooling progesterone level with ratio d_4/d_1 did not show any superiority in outcome prediction compared to ratio alone.

Discussion

In our study, early change in serum βhCG level was predictive of treatment outcome in patients receiving single dose Methotrexate (MTX) therapy for tubal ectopic pregnancy (EP). Optimal cut-off of the ratio d_4/d_1 was 1.15. Progesterone level at baseline was not an independent prognostic factor and did not improve early βhCG kinetics predictive value.

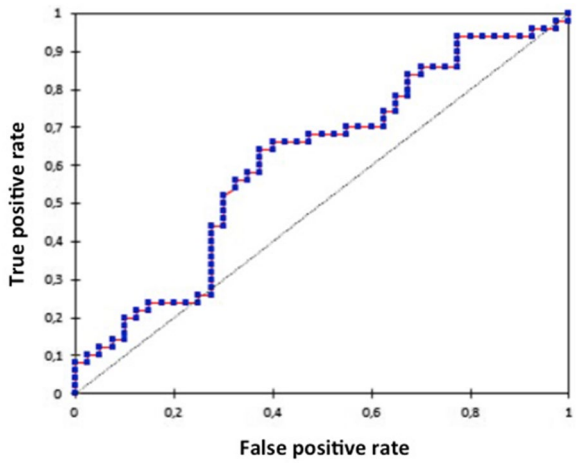

Fig. 2 Receiving Operating Characteristics curve evaluating baseline progesterone level in treatment outcome prediction (AUC = 0.611)

Single dose MTX protocol has been first described in 1991 and is still routinely used [1, 2]. Our success rate following first course of treatment was relatively low, in comparison with previous published data [9]. We have no further explanation for such finding since all patients had received intra-muscular administration of 1mg/kg MTX. Noteworthy, overall treatment efficacy was 81.8% regardless of the number of MTX courses, consistently with other studies [17].

Among parameters we analyzed at baseline, initial serum βhCG measurement was the only significant prognostic factor for MTX efficacy. Conversely, ultrasound criteria such as size of EP and volume of Douglas pouch effusion did not impact treatment outcome. Most studies have drawn similar conclusions [12, 17–20]. In contrast, Helmy et al observed a trend toward a greater EP volume in patients with failed MTX therapy (15.24 ml versus 5.11 ml in the success group) but the difference was not significant [19, 21].

The main objective of our study was to determine whether early βhCG kinetics could predict treatment outcome. In a retrospective study involving 83 patients, Gabbur et al investigated the prognostic value of serum βhCG levels on days 1, 4 and 7 following single dose MTX protocol [11]. AUC were 0.45, 0.59 and 0.74, respectively. Supporting that serum βhCG measurement on day 4 could not predict treatment outcome. Nevertheless, the authors only considered crude βhCG levels with no dynamic approach. In contrast, data addressing the prognostic significance of early βhCG level change provided better results, particularly in the setting of a decline in βhCG measurement on day 4: treatment success rate ranged from 88 to 100% [9, 10, 12]. Similarly, Bottin et al observed a 100% success rate in patients displaying a decrease in βhCG level on day 4 ≥ 20% [13]. The authors proposed a simplified monitoring for these patients with a single followup visit 1 month following MTX injection. In our study, a ratio $d_4/d_1 < 1$ was associated with a success rate of 79%. When the ratio was ≤ 0.7, this rate increased to 94%, and up to 100% in case of a repeated course of treatment. Suggesting that these women might benefit from simplified surveillance.

The prognostic value of early βhCG kinetics was more controversial when βhCG levels increased on day 4. Indeed, Skubisz et al and Nguyen et al. reported success rates of 42% and 61% respectively, and could not provide an ideal cut-off [9, 12]. In our study, a ratio $d_4/d_1 > 1$ was associated with a success rate of 32.2%. Optimal cut-off was 1.15, with good performances (AUC = 0.826). However, its prognostic value seemed too low to impact on subsequent followup (sensitivity = 80% and specificity = 67%). Noteworthy, all women with a ratio $d_4/d_1 > 1.7$ required a second MTX course. Hence βhCG measurement on day 7 might be avoided in such patients and MTX administration repeated as early as on day 4.

In conclusion, our results indicate that in most patients receiving MTX therapy for EP ($n = 88$) early βhCG kinetics does not adequately predict treatment outcome and cannot impact subsequent followup. Conversely, women displaying extreme βhCG changes ($n = 33$) on day 4 might benefit from a more personalized approach: simplified monitoring in those with a decline ≥ 30%, anticipated second course of treatment in those with an increase > 70%. In 27.2% of patients, serum βhCG measurement on day 7 could thus have been avoided. Prospective data are required before definitive implementation in routine clinical practice.

Author contribution JB manuscript writing, statistical analysis. PG data collection, project development. CC data collection, project development. AY data collection. MB data collection, clinical management. OP manuscript reviewing. CV manuscript reviewing. CV manuscript reviewing. EC data collection, project development. FV manuscript writing, statistical analysis, project development.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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