



Correlation between hCG Kinetics and the Effectiveness of Methotrexate in the Management of Ectopic Pregnancies

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Abstract

Purpose: To evaluate a therapeutic monitoring strategy for ectopic pregnancies treated with methotrexate (MTX) injection based on hCG level kinetics, in order to identify patients at low risk of treatment failure. **Materials and Methods:** This series of 14 cases allowed us to evaluate the success rate of therapeutic management with a single injection of methotrexate (MTX), based on the kinetics of hCG levels. The protocol stipulated that if the decrease was greater than 20% between days 1 and 4, follow-up was limited to an hCG measurement one month later. **Results:** Among the 14 patients treated, the overall success rate of MTX treatment was 85.71%. **Conclusion:** Our protocol allows us to select patients at low risk of failure of single-dose MTX treatment, and to offer them less restrictive monitoring.

Subject Areas

Gynecology & Obstetrics

Keywords

Methotrexate, Ectopic Pregnancy, hCG

1. Introduction

The incidence of ectopic pregnancies (EPs) has doubled or tripled in the last two decades in industrialized countries. Depending on the country, the estimated incidence is 12 to 14 per 1000 pregnancies [1]. EPs are often diagnosed at a paucisymptomatic stage through hCG testing and transvaginal ultrasound [1], thus

avoiding surgery in many cases. Medical treatment of EP with methotrexate (MTX) has success rates of 78% to 96% [2] [3]. The risk of failure persists until the serum hCG level becomes negative [4]. For this reason, it is necessary for patients to be regularly monitored until the serum hCG level becomes negative. However, given the high success rate, a large number of patients will have to undergo this monitoring unnecessarily. Several studies have evaluated the predictive value of different markers for early prediction of the success of MTX treatment [5]-[11]. However, none of these studies has allowed for adjustments to post-MTX treatment monitoring based on the risk of failure. In a retrospective study, we demonstrated that when the drop in hCG levels between days 1 and 4 of MTX injection was greater than 20%, the probability of success was 97% [12]. It therefore seemed worthwhile to evaluate this marker in clinical practice by adapting clinical monitoring accordingly.

The aim of our study was to evaluate a therapeutic monitoring strategy for ectopic pregnancies treated with methotrexate injection based on hCG level kinetics between day 1 and day 4 in order to select patients who will require secondary surgical treatment or multiple MTX injections.

2. Materials and Methods

2.1. Type of Study

This study describes a series of 14 patients treated at the specialized mother and child hospital in Sidi Bel Abbes over a period from 01/01/2024 to 31/07/2025.

This is a retrospective descriptive study whose objective was to evaluate the correlation between serum hcg kinetics and the effectiveness of medical treatment with methotrexate (MTX).

2.2. Population

Patients diagnosed with an unruptured ectopic pregnancy and eligible for medical treatment.

2.3. Inclusion Criteria

The inclusion criteria for medical treatment were a minimally symptomatic ectopic pregnancy with stable hemodynamic status, the absence of hemoperitoneum beyond the pelvis or embryonic cardiac activity, and the patient's informed consent. The diagnosis of ectopic pregnancy was made in the presence of direct ultrasound signs of ectopic pregnancy (gestational sac with or without an embryo or heterogeneous adnexal mass) associated with an empty uterus and a positive hCG level, or in the case of clinical signs associated with an hCG level greater than 2000 IU/L and the presence of an empty uterus on ultrasound.

2.4. Exclusion Criteria

The exclusion criteria for medical treatment were contraindications to MTX treatment (hepatic insufficiency, renal insufficiency, thrombocytopenia and/or severe

anemia), ovarian or interstitial localization, a desire for surgical treatment as a first-line approach, hemodynamic instability, poor compliance with regular follow-up, or poor understanding by the patient.

2.5. Treatment Protocol

MTX treatment was administered intramuscularly at a dosage of 1 mg/kg as a single dose.

2.6. Clinical and Biological Monitoring

There was no pre-treatment hCG threshold. Treatment success was determined by a negative serum hCG level (less than 10 mIU/mL) after one or more MTX injections without the need for surgery.

By convention, day 1 was the day of the first dose of MTX injection.

If hCG levels dropped by more than 20% between days 1 and 4, the patient was scheduled for a follow-up appointment at 1 month for a serum hCG test. The patient was considered cured if the hCG level was negative at one month. If hCG remained positive at one month, the level was assessed by requiring a minimum weekly decrease of 15% compared to the hCG level at day 1. If this was the case, the patient was scheduled for another follow-up appointment at one month for an hCG test. If the decrease was insufficient, the patient was then monitored according to the standard protocol of Lipscombs *et al.* [5] [6].

In the event of an urgent interim consultation before the scheduled date, after clinical examination, hCG measurement and ultrasound, a second injection of MTX was offered in the event of insufficient decrease in hCG (hCG decrease was assessed as less than 15% weekly decrease compared to the hCG level on day 1), or surgical treatment was carried out in the event of suspected tubal rupture, refusal of a second injection of MTX or refusal to continue monitoring.

3. Results

During the study period, 14 patients with ectopic pregnancy were included in the study and were able to benefit from treatment with MTX.

Twelve patients experienced a decrease in hCG levels greater than 20% between days 1 and 4 with a follow-up at one month, and two patients experienced a decrease of less than 20% between days 1 and 4 with a follow-up at day 7 and standard monitoring by Lipscomb *et al.* The mean hCG levels on day 1 were 1183.13 IU/L.

All 12 patients remained asymptomatic with negative hCG levels at one month. No patient required an interim consultation, a second MTX injection, or surgical treatment. The success rate with a single MTX injection was 100%.

The two remaining patients underwent surgical treatment. Surgical intervention was required during an interim consultation (suspected tubal rupture) after two injections in both cases. There were no further interim consultations. No patient required surgical treatment due to hCG level stagnation, a decrease of less

than 15%, or refusal of additional injections (See **Table 1** & **Table 2**).

Table 1. Cohort characteristics and clinical outcome

Characteristic/Result	Total Cohort (N = 14)	Group Decline hCG ≥ 20% (N = 12)	Group Decline hCG < 20% (N = 2)
Clinical outcome			
Success (hCG negative at 1 month)	12 (85.7%)	12	0
Failure (Surgery required)	2 (14.3%)	0	2
Follow-up performed			
One-month check-up	12	Yes	No
Lipscomb <i>et al.</i> follow-up	2	No	Yes

Table 2. Predictive performance of hCG kinetics (20% decay threshold days 1 - 4).

Performance Measurement	Observed Value
Sensitivity	100%
Specificity	100%
Positive Predictive Value (PPV)	100%
Negative Predictive Value (NPV)	100%

4. Discussion

Medical treatment of ectopic pregnancies allows a significant number of cases to avoid surgery as a first-line treatment. The relative simplicity of the medical treatment protocol should not lead to a neglect of close monitoring of these patients. This demanding monitoring can sometimes result in poor adherence [13]. In our series, the overall success rate of medical treatment for ectopic pregnancies with methotrexate (MTX) was 85.71%. According to studies, the success rate of medical treatment varies from 78% to 96% [2] [3]. Many authors have attempted to identify predictive factors for the success of medical treatment in order to select patients who would require a second injection of MTX or even surgical treatment, or conversely, to reduce monitoring in patients at low risk of failure. Many risk factors for failure have been studied, biological (hCG levels and kinetics, progesterone levels, CPK levels) or ultrasound (size of gestational sac or hematosalpinx, cardiac activity, hemoperitoneum) [5]-[11].

The initial serum hCG level before MTX injection is classically cited as the main predictor of successful medical treatment for ectopic pregnancy. In practice, the hCG threshold predictive of treatment success varies considerably across studies, from 1000 to 5000 IU/L [14]-[17]. However, more recent studies converge in favor of a lower hCG threshold [14] than in the initial studies. The initial serum hCG level remains an essential tool for choosing between medical and surgical treatment. However, it is difficult to use it to tailor patient monitoring.

The kinetics of hCG before and after MTX injection appear to have greater predictive value. According to the Stovall and Lipscomb monitoring protocol [5] [6], a 15% decrease in hCG between days 4 and 7 suggests successful medical treatment but implies weekly monitoring. Dudley *et al.* had demonstrated a greater increase in hCG before the diagnosis of ectopic pregnancy and a smaller decrease in hCG after MTX in cases of tubal rupture [8]. A decrease in serum hCG levels between days 1 and 4 after MTX injection had already been found as a prognostic factor for the success of MTX treatment [12] [15] [17]. In a retrospective study of 101 patients, Thurman *et al.* They found that if hCG levels decreased by less than 50% between days 1 and 7, a second injection of methotrexate (MTX) was necessary, particularly if hCG levels were greater than 2000 IU/L [18]. The authors suggested discontinuing monitoring patients on day 4. However, with this protocol, twice as many patients would have received a second MTX injection, sometimes unnecessarily, exposing themselves to more side effects.

In a preliminary retrospective study, a 20% decrease in hCG between days 1 and 4 was shown to have a positive predictive value of 97% for treatment success. The sensitivity of this test was 0.6 and its specificity was 0.92 [12]. We decided to implement this monitoring protocol in daily practice. Our goal was to avoid overly burdensome monitoring for patients at lower risk of treatment failure, while closely monitoring others to prevent tubal rupture. Patients benefited from a one-month serum hCG test, resulting in reduced healthcare costs and less demanding follow-up, with a 100% negative predictive value for treatment success. The practitioner can reassure them that the risk of needing surgery or further injections is very low in this case.

The main limitation of this study lies in the small sample size ($n = 14$ patients). Although the observed sensitivity and specificity reached 100%, these results must be interpreted with extreme caution, as this major methodological constraint has direct implications for the robustness and generalizability of our conclusions. These high percentages likely reflect a statistical artifact rather than true perfect diagnostic accuracy. Our results are borderline statistically significant due to the small sample size. It would be worthwhile to continue this work with a larger number of cases.

5. Conclusions

Methotrexate is part of the therapeutic arsenal for managing ectopic pregnancies. Conservative medical treatment has proven its effectiveness. This technique is reproducible and easy for anyone to use when the rules for inclusion, dosage, and monitoring are followed. This is a major advantage of medical treatment.

Our preliminary results suggest a strong and clinically relevant correlation between early β -hCG kinetics and the success of medical treatment with methotrexate for ectopic pregnancies (EP).

In our cohort of 14 patients, biological indicators demonstrated apparently perfect diagnostic performance (100% sensitivity and specificity) in predicting treat-

ment outcome, highlighting the potential of hCG kinetics as a clinical decision support tool.

However, the small sample size ($n = 14$) and the limited number of events ($n = 2$ failures) necessitate a cautious interpretation of these perfect measurements, which are probably a reflection of a statistical artifact rather than real and robust diagnostic accuracy.

In perspective, these data justify the need for larger-scale validation studies (multicenter, prospective) to confirm these results, establish robust confidence intervals, and define an optimal and generalizable hCG threshold for the management of ectopic pregnancies with methotrexate.

Conflicts of Interest

The authors declare no conflicts of interest.

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