



The impact of maternal electrolyte and albumin levels on the efficacy of single-dose methotrexate treatment for ectopic pregnancies

Ektopik gebeliklerde tek doz metotreksat tedavisi başarısına maternal elektrolit ve albümin düzeylerinin etkisi

Yusuf Başkiran¹, Kazım Uçkan¹, Talip Karaçor², İzzet Çeleğen³, Züat Acar⁴

¹Van Yüzüncü Yıl University Faculty of Medicine, Department of Obstetrics and Gynecology, Van, Turkey

²Adıyaman University Faculty of Medicine, Department of Obstetrics and Gynecology, Adıyaman, Turkey

³Van Yüzüncü Yıl University Faculty of Medicine, Department of Public Health, Van, Turkey

⁴Istanbul Tema Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey

Abstract

Objective: This study aims to investigate the impact of maternal albumin and serum electrolyte levels on the efficacy of single-dose methotrexate (SD-Mtx) therapy for ectopic pregnancies. Building on previous research, recommendations are provided to enhance the success of SD-Mtx therapy in the management of ectopic pregnancy.

Materials and Methods: Conducted at a tertiary center gynecology clinic, the study included 353 patients diagnosed with ectopic pregnancy and treated with SD-Mtx from 2012 to 2023. Patients who responded positively to SD-Mtx treatment comprised Group 1 (n=313), while those requiring surgical intervention due to failed SD-Mtx therapy constituted Group 2 (n=40). Through the hospital's digital database, patient data including complete blood count, biochemistry, and hormone test results were retrospectively examined.

Results: The mean β -hCG value was 1996 IU/mL for Group 1 in contrast to 2058 IU/mL for Group 2. There was no statistically significant difference in β -hCG levels between the two groups. Notably, Group 1 patients exhibited lower serum magnesium levels but higher potassium levels compared to Group 2 patients, with statistically significant differences. Furthermore, Group 1 patients had higher albumin levels than those in Group 2, with a statistically significant difference.

Conclusion: Successful SD-Mtx treatment was associated with lower maternal serum magnesium levels and higher potassium and albumin levels. Considering electrolyte levels before administering SD-Mtx and addressing any imbalances could potentially enhance treatment success. Additionally, restoring low albumin levels might improve the efficacy of SD-Mtx treatment for ectopic pregnancies. While this study suggests these trends, further extensive studies with a larger sample size are necessary to establish more definitive evidence.

Keywords: Ectopic pregnancy, methotrexate, inflammation, β -hcg, serum electrolytes, albumin

Öz

Amaç: Bu çalışmanın amacı maternal albümin ve serum elektrolit düzeylerinin, ektopik gebelik tedavisinde tek doz metotreksat (TD-Mtx) tedavisi üzerine etkisini incelemektir. Daha önce yapılan araştırmalar eşliğinde ektopik gebelik tedavisinde TD-Mtx tedavisinin başarısını artıracak önerilerde bulunmaktadır.

PRECIS: Continuous studies have been made to make medical treatment more successful in treating ectopic pregnancy, but sufficient results have not been obtained. In our research, we think that the levels of magnesium and potassium from maternal electrolytes and the plasma protein albumin level may help predict the success of medical treatment in the treatment of ectopic pregnancy in addition to β -hCG, which is the most used parameter in the literature. In addition, we believe that correcting blood electrolyte and albumin values and adjusting them to reference values will increase the success of TD-Mtx treatment in ectopic pregnancy treatment.

Address for Correspondence/Yazışma Adresi: Yusuf Başkiran MD,

Van Yüzüncü Yıl University Faculty of Medicine, Department of Obstetrics and Gynecology, Van, Turkey

Phone: +90 541 952 34 68 **E-mail:** yusufbaskiran1@gmail.com **ORCID ID:** orcid.org/0000-0003-1123-6062

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Gereç ve Yöntemler: Çalışma tersiyer merkez olan kadın doğum kliniğinde yapıldı. Çalışmaya 2012-2023 yılları arasında ektopik gebelik tanısı almış ve TD-Mtx tedavisi uygulanmış 353 hasta dahil edildi. TD-Mtx tedavisine yanıt vermiş hastalar Grup 1 (n=313) ve TD-Mtx tedavisi başarısız olup cerrahi tedavi uygulanan hastalar Grup 2 (n=40) olarak belirlendi. Hastaların tam kan, biokimya ve hormon tetkik sonuçları hastane dijital veri tabanı üzerinden retrospektif olarak incelendi.

Bulgular: Grup 1'e dahil edilen hastaların β -hCG ortalama değeri 1996 IU/mL idi. Grup 2'ye dahil edilen hastaların β -hCG ortalama değeri 2058 IU/mL idi. İki grup arasında β -hCG düzeyleri açısından istatistiki olarak anlamlı fark yoktu. Grup 1 hastalarının serum magnezyum değerleri, Grup 2 hastaların serum magnezyum değerlerinden bariz düşük, potasyum değerleri ise daha yüksek bulundu. İki grup arasındaki magnezyum ve potasyum değerlerinin farkı istatistiki olarak da anlamlı idi. Ayrıca albümin değerleri Grup 1 hastalarda, Grup 2 hastalara göre daha yüksek ve aradaki fark istatistiki olarak anlamlı idi.

Sonuç: TD-Mtx tedavisi başarılı olan grupta maternal serum M seviyesi düşük, K ve albümin seviyesi ise yüksek bulundu. TD-Mtx tedavisi öncesi kan elektrolit değerlerinin değerlendirilmesi ve var olan düzensizliğin düzeltilmesi, TD-Mtx tedavisinde başarıyı artırabilecek bir yaklaşım olabilir. Ayrıca düşük albümin değerlerinin de düzeltilmesi ektopik gebelik tedavisinde TD-Mtx tedavi başarısını artırabilir. Bu konu ile ilgili daha net kanıtlar elde edebilmek için daha geniş olgu sayıları ile daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Ektopik gebelik, metotreksat, enflamasyon, β -hCG, serum elektrolitleri, albümin

Introduction

An ectopic pregnancy arises when a fertilized ovum implants itself outside the uterus, typically within the fallopian tubes, often in the ampulla⁽¹⁾. Risk factors encompass a history of tubal surgery or ectopic pregnancy, pelvic inflammatory diseases, smoking, and specific assisted reproductive techniques⁽²⁾. The combined utilization of transvaginal ultrasonography and β -hCG levels aids in the prompt diagnosis⁽³⁾, facilitating the selection of an appropriate treatment strategy to enhance outcomes and mitigate associated mortality and morbidity⁽⁴⁾. One prominent approach for managing unruptured ectopic pregnancies involves single-dose methotrexate (SD-Mtx) therapy⁽⁵⁾. This regimen involves administering a solitary intramuscular dose of 50 mg/m² SD-Mtx. In cases where β -hCG levels do not exhibit a decrease of less than 15% between the 4th and 7th days, a second dose is administered, a course of action necessitated in approximately 14-20% of cases⁽⁶⁾. Generally, the success rates of SD-Mtx treatment vary between 64-80%⁽⁷⁾. The achievement of success hinges on attaining β -hCG values below 5.000 IU/mL and the absence of fetal cardiac activity⁽⁸⁾. However, the risk of tubal rupture persists, underscoring the importance of identifying predictive factors for the success of medical treatment^(2,8,9).

Methotrexate, acting as a folic acid antagonist, competitively inhibits the enzyme dihydrofolate reductase, thereby impeding cellular proliferation⁽⁸⁾. Much like other enzymes, specific co-enzymes or co-factors can influence this effect. A range of reductants and oxidants partake in these redox-type reactions. Electropositive alkali metals such as lithium, sodium, magnesium, iron, zinc, and aluminum function as potent reductive agents. Given their impact on numerous bodily enzymes, any fluctuations in electrolyte levels can reverberate across the system, maintaining overall bodily balance⁽¹⁰⁾.

Substances such as drugs and hormones are primarily transported within the body through plasma proteins, with albumin being a prominent carrier^(11,12). When substances are bound to albumin, they remain inactive in the plasma. This suggests that the efficacy and duration of drug action could be

influenced by fluctuations in plasma carrier proteins, notably albumin levels⁽¹³⁻¹⁵⁾. The presence of albumin's dual metal ion binding sites enables it to bind with a range of ions, including zinc, copper, cadmium, mercury, gold, silver, and nickel. Additionally, albumin interacts with calcium and magnesium, thereby exerting an impact on their concentrations within the blood^(11,15). Notably, these variations in electrolyte levels can also lead to alterations in enzyme activity, potentially resulting in individualized changes in methotrexate effectiveness.

The aim of our study is to conduct a comparative analysis of maternal serum electrolyte and albumin levels between patients who demonstrated successful response to TD-Mtx therapy and those who experienced treatment failure, requiring surgical intervention. Through this investigation, we aim to ascertain whether these serum levels have a discernible influence on the success of TD-Mtx treatment.

Materials and Methods

The study was conducted within the Department of Obstetrics and Gynecology at the Van Regional Training and Research Hospital, a tertiary center, spanning from 2012 to 2023. Approval for this non-interventional study was obtained from the local ethics committee (Van Training and Research Hospital Clinical Research Ethics Committee), under the reference number 2023/03-03. The study involved a total of 353 patients who presented at our clinic with ectopic pregnancy and subsequently underwent TD-Mtx treatment.

Ectopic pregnancy diagnosis was established through a combination of transvaginal ultrasound examination, clinical manifestations, and irregularly elevated β -hCG levels. Among the patients diagnosed with ectopic pregnancy, individuals with β -hCG levels surpassing 5.000, those with detectable fetal heartbeats, and those with a gestational sac measuring 2 cm or more were directed towards surgical intervention and were consequently excluded from our study. The participants were categorized into two groups: Group 1 comprised those who responded favorably to TD-Mtx treatment, while Group 2 consisted of individuals for whom TD-Mtx treatment proved ineffective, leading to subsequent surgical intervention.

Participants who underwent emergency surgery due to ectopic rupture, those who declined Mtx treatment, and individuals with pre-existing conditions such as diabetes, chronic kidney failure, and chronic heart disease were not included in the study. Furthermore, patients below 18 years of age or above 40 years were also excluded. The demographic information, clinical assessments, and laboratory results of the patients were acquired from the hospital's digital database and archival records. Throughout the study, the researchers diligently adhered to the guidelines stipulated by the Declaration of Helsinki pertaining to medical research involving human subjects.

Statistical Analysis

The statistical analysis was conducted utilizing the licensed SPSS 22.0 software. To compare two distinct independent groups with a normal distribution, the independent t-test was employed. The level of statistical significance was set at $p < 0.05$.

Results

A total of 353 patients who underwent TD-Mtx treatment were enrolled in the study. Among these, 40 patients did not exhibit a favorable response to medical treatment and necessitated surgical intervention. The patients who demonstrated a positive response to TD-Mtx treatment were categorized as Group 1, while those who did not respond were labeled as Group 2. The mean age of the patients in Group 1 was 31.26 years, whereas Group 2 patients had a mean age of 30.58 years. No statistically significant difference in age was observed between the two groups of pregnant women.

The mean β -hCG level in Group 1 was recorded as 1996 IU/mL, while Group 2 exhibited a mean value of 2058 IU/mL. In terms of β -hCG levels, no statistically significant difference was identified between the two groups.

Table 1. Distribution of groups according to maternal characteristics

	Methotrexate (n=313)		Surgical (n=40)		p
	Mean	SD	Mean	SD	
Age	31.26	4.80	30.58	5.75	0.11
Gravida	2.83	1.45	2.85	1.69	0.24
Parity	1.16	1.16	1.23	1.23	0.22
Abortion	0.73	0.79	0.78	1.20	0.38
EG	0.074	0.32	0.06	0.32	0.36
Height (cm)	162.85	6.67	162.50	7.20	0.13
Weight (kg)	67.70	10.34	68.5	8.4	0.17
BMI (kg/m ²)	25.87	4.05	25.38	3.13	0.16
Gestational week	6.62	0.64	6.47	0.97	0.23

SD: Standard deviation, BMI: Body mass index. Values in bold represent statistically significant results

Table 1 presents the distribution of the groups by maternal characteristics. No significant distinctions were observed between the groups concerning factors such as age, parity, gravidity, abortion history, body mass index, gestational week, prior ectopic pregnancy occurrences, weight, and height.

The distribution of the groups by complete blood count and coagulation parameters is detailed in Table 2. No discernible differences were noted between the groups in terms of pre-treatment hemoglobin and hematocrit values. Similarly, there were no significant differences between the groups regarding platelet count (PLT), activated partial thromboplastin time (aPTT), prothrombin time, and fibrinogen values.

Table 3 outlines the distribution of groups based on hormone and electrolyte levels. There were no significant differences in thyroid hormone values between the groups. However, notable differences emerged in terms of albumin and creatinine levels. Group 1 patients exhibited higher albumin and creatinine values in comparison to those in Group 2.

The analysis of electrolyte values revealed no statistically significant difference between the two groups concerning sodium and calcium values, while a statistically significant difference surfaced in terms of potassium and magnesium values. More specifically, potassium values were elevated in Group 1 patients, whereas magnesium values were notably higher in Group 2 patients.

Discussion

Ectopic pregnancy represents a significant gynecological concern with implications for maternal mortality and morbidity^(16,17). Methotrexate (MTX) typically serves as the primary treatment option for stable cases of unruptured ectopic pregnancies. MTX can effectively address ectopic pregnancies

Table 2. Distribution of groups according to hemogram and coagulation parameters

	Methotrexate (n=313)		Surgical (n=40)		p
	Mean	SD	Mean	SD	
WBC (10 ⁹ /L)	8.27	2.06	9.10	3.20	0.002
HGB (g/dL)	12.92	1.31	12.87	1.7	0.092
HCT (%)	38.75	3.53	37.09	5.83	0.093
APTT (sec)	29.03	3.92	28.15	3.63	0.076
PT (sec)	14.10	1.25	13.55	1.16	0.086
PTZ%	1.00	0.00	1.00	0.00	cannot be computed
INR	94.25	12.26	95.18	13.07	0.092
Fibrinogen	326.48	72.63	332.82	74.64	0.42

SD: Standard deviation, WBC: White blood cell, Hb: Hemoglobin, HCT: Hematocrit, MON: Monocyte ratio, MCV: Mean corpuscular volume, PLT: Platelet count, MPV: Mean platelet volume, aPTT: Activated partial thromboplastin time, values in bold represent statistically significant results

Table 3. Distribution of groups according to hormone and electrolyte values

	Methotrexate (n=313)		Surgical (n=40)		p
	Mean	SD	Mean	SD	
TSH (U/L)	2.33	1.83	2.59	1.73	0.18
ft3 (pmol/L)	3.27	0.43	3.23	0.73	0.44
ft4 (pmol/L)	1.11	0.29	1.04	0.21	0.64
BUN (mg/dL)	10.81	3.11	10.37	2.26	0.16
CRE (mg/dL)	0.68	0.42	0.56	0.51	0.001
Albumin (g/dL)	46.20	2.99	38.08	3.10	0.001
AST (IU/L)	21.12	5.62	21.91	9.33	0.29
ALT (IU/L)	20.05	8.25	19.95	11.24	0.92
LDH (IU/L)	195.55	40.97	209.09	40.40	0.02
Na (mg/L)	139.20	2.27	139.18	1.78	0.93
Ca (mg/L)	9.51	0.66	9.45	0.58	0.36
K (mg/L)	4.32	0.16	4.03	0.13	0.026
Mg (mg/L)	1.89	0.16	2.13	0.07	0.025
Bhcg	1996	287	2058	327	0.07

SD: Standard deviation, TSH: Thyroid stimulating hormone, ft4: Free T4, ft3: Free T3, BUN: Blood urea nitrogen, CRE: Creatinine, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, values in bold represent statistically significant results

situated in various locations such as the cervix and cornual region, while preserving the patient's ovarian reserve and future fertility prospects⁽¹⁸⁾. Global studies have reported MTX success rates ranging from 65% to 95%⁽¹⁹⁾. In our investigation, the success rate of MTX treatment reached 88.7%.

Numerous studies in the existing literature have explored factors influencing the efficacy of systemic methotrexate (TD-Mtx) treatment, aiming to curtail maternal mortality and morbidity associated with ectopic pregnancies. Among these, β -hCG levels have emerged as pivotal prognostic indicators for predicting and assessing the effectiveness of Mtx treatment. While a definitive consensus on the ideal threshold value for predicting the success or failure of β -hCG is lacking, a substantial body of data employs 5.000 IU/mL as a threshold indicative of higher failure rates⁽¹⁸⁾. Within our present study, the mean β -hCG values for both patient groups remained below 5.000 IU/mL. Specifically, in the successfully treated TD-Mtx group, the mean β -hCG level was noted as 1.996 IU/mL, while the unsuccessful group exhibited a mean value of 2.058 IU/mL, with no significant difference between the two groups.

Certain studies in the literature have delved into the relationship between the success and failure of TD-Mtx treatment for ectopic pregnancy and various factors, including inflammation markers, white blood cell (WBC) count, and PLT, among others. Nonetheless, it is recognized that employing inflammation markers, WBC, and PLT values as predictors of the success of

medical ectopic pregnancy treatment might prove challenging. Changes in these inflammation-related values are influenced by a multitude of factors and lack specificity for ectopic pregnancy. As a result, ongoing research seeks to identify alternative factors that can enhance the efficacy of Mtx treatment^(20,21).

Another study in the literature explored the combination of methotrexate with mifepristone and found no discernible difference. Moreover, this study recommended avoiding the concurrent use of potassium chloride with methotrexate⁽²²⁾. In our current study, Group 1 patients displayed lower serum magnesium values but higher potassium levels. Our results indicate that the success of TD-Mtx treatment was more prevalent among patients with elevated pre-treatment serum potassium and albumin levels, along with lower magnesium levels. This suggests that fine-tuning electrolyte and albumin levels in patients undergoing treatment for ectopic pregnancies could potentially boost treatment success rates.

Our study investigated whether changes in maternal electrolyte levels influenced the activity and inhibition of the dihydrofolate reductase enzyme, a key player in the mechanism of methotrexate action. We also explored whether the success of TD-Mtx treatment was impacted by these electrolyte levels and associated parameters.

In the existing literature, no studies have investigated the influence of electrolytes on methotrexate's effects. In this study, we aimed to explore the potential impact of maternal electrolyte levels on methotrexate's mechanism of action, with the goal of enhancing the success of medical treatment. Our results showed that within the context of the mechanism of methotrexate, magnesium levels negatively affected the success of TD-Mtx treatment, while potassium levels had a positive influence. Nonetheless, we did not identify any specific electrolyte directly affecting methotrexate's actions.

Another crucial aspect we examined in our study was albumin. As a primary plasma protein, albumin plays a pivotal role in facilitating the transport of various hormones, drugs, and substances within the bloodstream. Additionally, albumin can act as a reservoir for the drugs it carries, thereby influencing their pharmacokinetic profiles. This pertains to albumin's involvement in the distribution and metabolism of many drugs, including methotrexate. While methotrexate has a half-life of 2-3 hours, albumin's half-life extends to 18-19 days. Elevated albumin levels can potentially lead to an increased distribution volume of methotrexate, potentially augmenting its therapeutic response^(14,15). Consequently, monitoring albumin levels in methotrexate-treated patients could offer valuable insights into optimizing therapeutic outcomes in ectopic pregnancy management. This could involve minimizing adverse reactions, reducing free radicals (as in various diseases), and potentially enhancing the body's responsiveness. Moreover, heightened albumin levels might extend methotrexate's half-life in the body, thereby prolonging its therapeutic effects and potentially contributing to more favorable outcomes in ectopic pregnancies.

As such, we propose that maintaining albumin levels within the normal range could potentially amplify the efficacy of methotrexate and lead to improved outcomes in the treatment of ectopic pregnancies.

Study Limitations

Nevertheless, our study does have certain limitations, including its retrospective nature, a limited number of patients, and the utilization of patient records from the healthcare system. On the positive side, our study sheds light on the previously unexplored relationship between TD-Mtx and albumin. It represents one of the few studies revealing a relationship between TD-Mtx and electrolyte values.

Conclusion

We hold the perspective that maternal electrolyte levels, particularly magnesium, and potassium, along with the plasma protein albumin, could emerge as valuable indicators for predicting the success of medical treatment in the context of ectopic pregnancy management, complementing the role of β -hCG. Additionally, we posit that the optimization of blood electrolyte and albumin values, aligning them with established reference ranges, might significantly enhance the efficacy of TD-Mtx in the management of ectopic pregnancy.

The results of our study are anticipated to serve as a foundational resource and reference for subsequent research endeavors focused on this subject matter. We believe that more extensive and comprehensive studies are warranted to yield more nuanced and well-defined data, thus contributing to a deeper understanding of this relationship.

Ethics

Ethics Committee Approval: Approval for the non-interventional study was obtained from the Van Training and Research Hospital Clinical Research Ethics Committee with approval number 2023/03-03, date: 01.02.2023.

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: Y.B., K.U., T.K., İ.Ç., Z.A., Concept: Y.B., K.U., T.K., İ.Ç., Z.A., Design: Y.B., K.U., T.K., İ.Ç., Z.A., Data Collection or Processing: Y.B., K.U., T.K., İ.Ç., Z.A., Analysis or Interpretation: Y.B., K.U., T.K., İ.Ç., Z.A., Literature Search: Y.B., K.U., T.K., İ.Ç., Z.A., Writing: Y.B., K.U., T.K., İ.Ç., Z.A.

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