ROLE OF DAY 4 AND DAY 7 B-HCG AS AN EARLY PREDICTOR OF SUCCESS AFTER METHOTREXATE THERAPY FOR TUBAL ECTOPIC PREGNANCIES

By

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ABSTRACT

Background: Tubal ectopic pregnancy is potentially life-threatening with an estimated incidence of 1% to 2% of all pregnancies with the wide availability of transvaginal ultrasound and quantitative serum beta human chorionic gonadotropin (β-hCG) assay; ectopic pregnancies can be diagnosed early, leading to successful management without resort to surgery.

Objective: Evaluation of β-hCG levels between days 4 and 7 as a predictor of methotrexate therapy success for ectopic pregnancy.

Patients and Methods: 50 cases, diagnosed of ectopic pregnancy, This study was carried out on Al-Hussein Hospital during July 2018 and August 2019 All cases were subjected to full history taking, complete clinical examination, ultrasongraphy and Laboratory investigations as Complete blood count, Liver profile (ALT and AST), Serum creatinine, and Serum β-hCG levels on day1, 4, and7 after methotrexate therapy.

Results: The mean age was 28 ± 5 years, ranging between 20 and 40 years. The average gestational age was 5 weeks, while the average parity was 1. Of 50 cases, 36 patients (72%) succeeded and 14 failed. The ROC curve for the hCG index identified an hCG index value of 0.192 (19% decrease of hCG value between day 1 and day 4) as the best predictor for ectopic pregnancy treated successfully with a single dose of methotrexate. Sensitivity for the test was 80% and accuracy was 75%.

Conclusion: Early serum β-hCG decline is associated with a very high probability of treatment success. However, given that we found an 80% success rate, not 100%, we suggest it is prudent to continue the serial monitoring of serum β-hCG until the complete resolution of the ectopic pregnancy.

Keywords: β-HCG; Methotrexate; Ectopic Pregnancy.

INTRODUCTION

Ectopic pregnancy is potentially life-threatening with an estimated incidence of 1% to 2% of all pregnancies with the wide availability of transvaginal ultrasound and quantitative serum beta–human chorionic gonadotropin (β-hCG) assay, ectopic pregnancies can be diagnosed early, leading to successful management without resort to surgery *(Panelli et al., 2015)*.

Medical treatment with methotrexate was established in the late 1980s it is an alternative to surgery and has been proven to be safe and effective *(Bachman, et al., 2012)*. Methotrexate is a folic acid antagonist that interferes with DNA synthesis and cell proliferation. Tissues

with a rapid cellular turnover, such as trophoblasts, are most susceptible to its action *(Skubisz and Tong, 2012)*. Methotrexate is commonly given as a single intramuscular injection at a dose of 50 mg/m2 body surface area according to the single-dose protocol, Successful treatment in this protocol is defined by a ≥15% decrease in hCG level between day 4 and day 7 after methotrexate administration. A prospective study has found that a 15% decrease in hCG level between day 4 and 7 was a good indicator of success with positive predictive value (PPV) up to 93%5 *(Girija et al., 2017)*.

Appropriate patient selection is important for methotrexate treatment success. Success rates have been reported to range from 63% to 97.6%, Although associated with the initial hCG level, there is no consensus on the threshold hCG above which methotrexate is contraindicated A systematic review of several observational studies reported a failure rate of ≥14.3% with single-dose methotrexate when pretreatment hCG level was >5000 IU/L, compared with a 3.7% failure rate for hCG level of <5000 IU/L7 *(Pulatoglu et al., 2018)*.

The purpose of this study was to evaluate beta human chorionic gonadotropin (β-hCG) levels between days 4 and 7 as a predictor of methotrexate therapy success for ectopic pregnancy.

PATIENTS AND METHODS

This study was carried out on AL-Hussein University Hospital and Benha Teaching Hospital from July 2018 to August 2019 on women diagnosed as ectopic pregnancies and treated with intramuscular dose of methotrexate (50 mg/m2). The definitive diagnosis of an ectopic pregnancy was done when cases had positive β hCG titers and associated with visualization of gestational sac outside of the uterus by TV/US.

A presumptive diagnosis of ectopic pregnancy was in cases have β-hCG levels above the discriminatory zone (1500-2000 IU/l) with the absence of an intrauterine pregnancy by TVUS or abnormally rising plateauing β-hCG titers below the discriminatory zone that is associated with TV/US findings that are suggestive of ectopic pregnancy (complex adnexal mass and/or free fluid in peritoneal cavity).

Approval of the study protocol by the ethical scientific committee of Faculty of Medicine, Al-Azhar University, and its Hospitals was obtained. Informed consent was obtained from every patient.

Exclusion criteria:

- Intrauterine pregnancy.

- Hemodynamic ally unstable.

- Signs of impending or ongoing ectopic mass rupture (i.e. severe or persistent abdominal pain) or > 300 ml of free peritoneal fluid outside the pelvic cavity.

- Quantitative B-hCG concentration > 10,000 mIU/ml.

- Hypersensitivity to methotrexate.

- Coexistent viable intrauterine pregnancy.

- Breastfeeding.

- Laboratory evidence of immunodeficiency.

- Alcoholism or chronic liver disease.

- The concomitant use of non-steroidal anti-inflammatory drugs.

- Blood dyspraxia such as leukopenia, thrombocytopenia, or severe anemia.

- Active pulmonary disease.

- Hepatic, renal, or hematological dysfunction.

- Adnexal mass $\geq$ 3.5 cm.

- Presence of fetal cardiac motion.

- Active major psychiatric disorder such as major depression, bipolar disease, psychotic disorder, or drug addiction.

- Subjects unable or unwilling to comply with study procedures or illiterate.

All cases were subjected to full history taking, complete clinical examination, ultrasongraphy and laboratory investigations complete blood count, liver profile (ALT and AST), serum creatinine, and serum β-hCG levels on day1, 4, and7 after methotrexate therapy.

The calculation was from the formula of DuBois and DuBois *(Brady et al.,*

2016): BSA = (w0.425 x H0.725) x 0.007184, where the weight was in kilograms and the height was in centimeters. Patients were advised to avoid vitamin containing folic acid, non-steroidal anti-inflammatory drugs and sexual intercourse.

Statistical analysis:

Data were collected, coded and entered by the statistical package SPSS version 22. Data were described statistically as mean, standard deviation, for quantitative data and frequencies and percentages for qualitative data. For comparing categorical data, Chi square (X^2) test was used. ANOVA was performed to compare quantitative variables between the three groups. Receiver operator characteristic curves, (ROC) curves were derived and area-under-the curve (AUC) analysis performed to get the best cutoff values for detecting CRC cases. A probability value (P value) less than 0.05 was considered statistically significant.

RESULTS

This study included 50 patients; the mean age was 28 ± 5 years, ranging between 20 and 40 years. The average gestational age was 5 weeks, while the average parity was 1. In most of the cases (68%), ectopic pregnancies were found on right site, while 32% of them were on the left. The dermatological features and laboratory investigation (**Table 1**).

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Table (1): Dermatological feature and laboratory investigations in the studied group

Variables	Mean ±SD	Range
Age	28 ± 5	20-40
Weight	70.5 ± 10	55-100
Height	160 ± 7.5	140-175
BMI	27.5 ± 3.5	20-40
Gestational age	5 ± 1.5	5-10
Parity	1 ± 0.5	0-5
HB	11 ± 1.5	8.5-15
HCT	31.5 ± 5	20-40
Cr	0.6 ± 0.2	0.5-1
ALT	15.5 ± 5	10-40
AST	15 ± 5	10-35

Of 50 cases, 36 patients (72%) succeeded and 14 failed (12 became disturbed before day 7 and were excluded from the medical records, and 2 cases received 2nd dose of methotrexate).

The median hCG level of day 1 was 1275 and dropped to 620 on day 4, percentage of change was 51.4% **(Table 2)**.

Table (2): Comparison between hCG from day of treatment (day1) till (day 4) after treatment

Time / Variables	Day 1	Day 4	% of change	Z	*P*
Median (IQR)	1275 (640-2615)	620 (315-1120)	51.4%	5	<0.001 HS

To determine whether there was a value of the difference variable that could predict outcome with a high degree of certainty, a receiver operating curve was used in an attempt to identify a cut-off point for the difference variable, The ROC curve for the hCG index identified an hCG index value of 0.192 (19% decrease of hCG value between day 1 and day 4) as the best predictor for ectopic pregnancy treated successfully with a single dose of methotrexate. Sensitivity for the test was 80% and accuracy was 75% **(Figure 1)**.
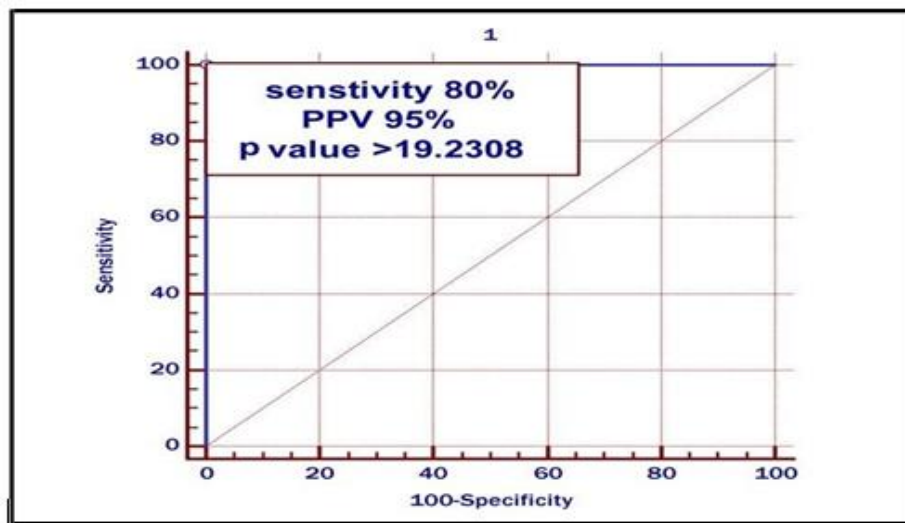
Figure (1): Sensitivity and accuracy of the 4th day hCG

The overall success rate of treatment in our entire study group was 80.6%. A decline between day 1 and day 4 was associated with an 80.6% probability of success, without the need of a further dose of methotrexate or surgery. Thus, a decline in serum hCG by day 4 after methotrexate appears to be highly reassuring with a PPV of 95% and accuracy of 75%. Our indicator has a high positive predictive value (95%) **(Table 3)**.

Table (3): Validity of βhCG index for prediction of success of methotrexate

Variables	%
Sensitivity	80%
Positive predictive value	95%
Accuracy	75%

There was no statistically significant difference between success rates versus age and BMI, although history of previous surgery demonstrated strong trends, they failed to reach statistical significance **(Table 4)**.

Table (4): Comparison between success and failure regarding age and BMI

Variables	Success	Failure	T	P
Age	25 ± 5	30 ± 4.5	0.1	>0.05 NS
BMI	27.5 ± 5	25 ± 4.5	0.1	>0.05 NS

DISCUSSION

In this study, the mean age was 28 ± 5 years, ranging between 20 and 40 years, while in *Mirbolouk et al. (2015)*, The Mean age of women was 29.34±5.57 years old (range 17-48).

In this study, the average gestational age was 5 weeks, while the average parity was 1, while in *Mirbolouk et al. (2015)*, the average gestational age was 7 weeks and the average parity was 1.

The most of the cases of ectopic pregnancy (68%) in this study were found

on right side, while 32% of them were on the left. Of 50 cases, 36 patients treatment (72%) succeeded and 14 failed (12 became disturbed before day 7 and were excluded from the medical records and 2 cases received 2nd dose of methotrexate). *Shaamash et al. (2015)* demonstrated that success rate of single-dose MTX treatment in EP was 77.5%., while the success with the multiple dose regimen was 92.7%. *Ghelichkhani et al. (2016)* stated that Overall treatment success rate of methotrexate was 84- 95% confidence interval (CI).

The ROC curve for the hCG index identified an hCG index value of 0.192 (19% decrease of hCG value between day 1 and day 4) as the best predictor for ectopic pregnancy treated successfully with a single dose of methotrexate. Sensitivity for the test was 80% and accuracy was 75%.

Skubisz (2011) demonstrated that Q B-hCG of 2000 mIU/ml is an optimum cut off value for selecting potential cases for medical failure using the single dose approach as cases with initial Q B-hCG value of > 2000 mIU/ml and/or in embryonic sac of > 3.4 cm should be closely monitored for treatment failure.

Girija et al. (2017) stated that 10% decline in hCG levels between days 1 and 4 during methotrexate treatment has a positive predictive value of 97%. hCG index value of 0.2 was the best predictor for ectopic pregnancy treated successfully with a single dose of methotrexate sensitivity, 92% of cases required surgery or repeated injection had an hCG index <0.2 and 97% of those with an hCG index > 0.2 were successfully treated with a single injection of methotrexate.

Nguyen et al. (2010) evaluated post treatment β hCG level in ectopic pregnancy with single-dose methotrexate therapy reported the novel observation that women whose serum hCG fell between days 1 and 4after a single dose of methotrexate for an ectopic pregnancy had a remarkable 100% treatment success rate, without need for any further treatment. Their study suggests highly reliable prognostic information. There was no need to add extra tests to current protocols. If verified, it could be used clinically, providing early prognostic information for cases and clinicians. Unfortunately, they did not have an adequate cut-off point for the difference variable for this study.

Skubisz (2012) stated that a fall in hCG between days 1 and 4 after treatment with methotrexate for ectopic pregnancy predicts a high likelihood of treatment success.

Atkinson et al. (2014) found that 73% of those who avoided surgery were predicted by a good bhCG fall (sensitivity 73%) while 86% of those who underwent surgery were predicted by a suboptimal bhCG fall (specificity 86%).

CONCLUSION

Early serum hCG decline was associated with a very high probability of eventual treatment success.

Author contribution: Authors contributed equally in the study.

Conflicts of interest: No conflicts of interest.

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دور هرمون الغدد التناسلية المشيمية في اليوم الرابع واليوم السابع في التنبوء المبكر في نجاح الحقن بعقار الميثوتريكسات في حالات الحمل الأنبوبي الهاجر

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خلفيـــة البحـــث: أدي التوسـع الكبيــر فـي إسـتخدام الموجـات فـوق الصـوتية عبـر المهبـل وقيـاس هرمـون الغـدد التناسـليه المشـيميه، إلـي امكانيـة تشـخيص حـالات الحمـل خـارج الــرحم فـي وقـت مبكــر، ممـا يـؤدي إلـى نجـاح العـلاج الـدوائي دون اللجـوء إلـى الجراحة.

الهـدف مـن البحـث: تقيـيم مسـتويات هرمـون الغـدد التناسـلية المشـيمية البشـرية بـين الأيام 4 و7 كمؤشر لنجاح العلاج بالميثوتريكسات في الحمل خارج الرحم.

المريضـات وطـرق البحـث: تـم إختيـار خمسـين حالـة تعـانى مـن الحمـل خـارج الـرحم مــن مستشــفي بنهــا التعليمــي ومستشــفي الحسـين الجـامعي وجمـيعهم تلقـوا ميثوتريكسـيت فـي جرعـة 50 مجـم / م 2. عـن طريـق الحقـن العضـلي .وقـد تـم تأكيـد جميـع الحــالات كحمـل خـارج الـرحم عـن طريـق الموجـات فـوق الصـوتيه وتحديـد كيس الحمل ب4 سم.

نتـائج البحـث: كـان متوسـط عمـر المريضـات 28 ± 5 سـنوات، وتتـراوح بـين 20 و40 سـنة. كـان متوسـط عمـر الحمـل 5 أسـابيع، فـي حـين كـان متوسـط مـرات الـولاده مـرة واحـده. ومـن 50 حالـة أكملـت سـجلها الطبـي، هـذا وقـد تمـت الدراسـة فـى الفتـرة مـابين يوليـو 2018 واغسـطس 2019 وكـان متوسـط هرمـون الغـدد التناسـليه المشـيميه فـي أول يـوم مـن العـلاج 1275 والـذي انخفـض إلـى 620 ثـم 275 فـي اليـوم 4 واليـوم 7 علـى التـوالي بعـد إسـتخدام جرعـة واحـده مـن الميثوتريكسـات، وكـان التغييربالنسـبه المئويـة فـي هرمـون الغـدد التناسـليه المشـيميه 56 ٪. وقـد نجـح العـلاج الـدوائي فـي 94.7 ٪ مـن الحـالات التـي تمـت دراسـتها، فـي حـين فشـل 5.3 ٪ فيمـا يتعلق اليوم الرابع والسابع من أيام العلاج.

الاستنتاج: كــان معــدل النجــاح العــام للعــلاج فــي للحــالات فــي هــذه الدراســة 80.6٪.وقــد إرتــبط التراجــع بــين اليــوم الأول واليــوم الرابــع باحتمــال النجــاح بنســبة 80.6٪، دون الحاجــة إلــى جرعــة أخــرى مــن الميثوتريكســيت أو الجراحــة. وبالتــالي، يبــدو أن الإنخفــاض فــي هرمــون الغــدد التناســليه المشــيميه فــي اليــوم الرابــع بعــد الميثوتريكســيت مطمــئن للغايــة، حيــث بلغــت القيمــه التنبؤيــه الايجابيــه 95٪ ودقــة 75٪. وكان مؤشر الدراسة ذو قيمه تنبؤية إيجابية عالية (95 ٪).