Association between response to the medical treatment and predicting factors in ectopic pregnancy

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Abstract

Original Article

BACKGROUND: Ectopic pregnancy (EP) is the leading cause of maternal death in the first trimester of pregnancy. There are many variables which can predispose EP. The aim of this study was to evaluate the possible association between individual's response to given medical treatment and predicting factors of ectopic pregnancy among pregnant women.

METHODS: In this cross-sectional study, 277 patients with ectopic pregnancy who were admitted to obstetrics and gynecology ward of Besat hospital, Sanandaj, Iran, were evaluated. The necessary information was obtained from all women diagnosed with EP during 2008 to 2013. Patients who received any medication before study or those who could not use methotrexate (MTX) were excluded from study.

RESULTS: In this study, 205 (74.1%) patients responded to the medical therapy. There was a significant association between successful response to the treatment and beta human chorionic gonadotropin (β-hCG) serum level less than 5000 mIU/ml, pregnancy sac size less than 4 cm and lack of fetal heart rate (FHR) in transvaginal sonography (TVS).

CONCLUSION: In conclusion, it was found that β-hCG serum level, pregnancy sac size and presence of FHR play a key role in predicting the response to the medical treatment in women with ectopic pregnancy, and might be helpful in selecting appropriate therapeutic scheme.

KEYWORDS: Ectopic Pregnancy, Pregnant Women, Methotrexate

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Introduction

Ectopic pregnancy (EP) is a major health problem for women in child-bearing age. It states the pregnancy occurring outside the uterine cavity that constitutes 1.2–1.4% of all reported pregnancies.[1] In this phenomenon blastocyst implants outside the uterine cavity endometrium, mostly (95.5%) in the fallopian tube.[2,3] The other most common implantation sites are ovarian (3.2%) and abdominal (1.3%) sites.[4]

Treatment for EP includes surgical or medical treatment which is usually systemic or through local route, or by expectant treatment.[5] According to the American College of Obstetricians and Gynecologists (ACOG) guideline, when beta human chorionic gonadotropin (β-hCG) level is < 200 mIU/ml, which is further in decline phase, expectant management may play a role.[6]

The favourable prognostic signs of ectopic pregnancy for successful expectant management

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are absent or there are minimal clinical symptoms with no evidence of haemodynamic and low initial β-hCG serum level.[7]

Previously, it has been reported that the medical treatment is quite less expensive than surgery.[8] Different medications have been tried to treat ectopic pregnancies, including systemic or local methotrexate (MTX), local potassium chloride, hyperosmolar glucose, prostaglandins, danazol, etoposide, and mifepristone.[9,10] Today, therapies mainly focus on MTX treatment. This agent was first used for supporting the surgical removal of the placenta from its abdominal implantation sites in second and third trimester cases.[11] MTX treatment causes severe abdominal pain and side effects; therefore, patient should be monitored closely. In addition, the serum β-hCG concentration should be assayed every week. In 15–20% of patients the serum β-hCG concentration has not declined by at least 25% in first week after drug use, and the next dose should be administered.[12] Regarding MTX treatment, there are two regimens: multi-dose (MTX 1.0 mg/kg intramuscularly (IM) daily; days 0, 2, 4, and 6 alternated with folinic acid 0.1 mg/kg orally on days 1, 3, 5, 7) and single dose (MTX 0.4 to 1.0 mg/kg or 50 mg/m^2 IM without folinic acid).[11] Researchers compared both regimens and concluded that the multi-dose regimen was more effective than the single-dose regimen.[13] According to the above information, this study was aimed to verify the possible association between response to the medical treatment and predicting factors in ectopic pregnancy among pregnant women referred to the Besat hospital, Sanandaj, Iran, during 2008–2013.

Materials and Methods

In a cross-sectional study, all women admitted to the obstetrics and gynecology ward of Besat hospital, Sanandaj City, during 2008 to 2013, who were diagnosed with EP, were included. Patients who received any medication before study or those who could not use MTX were excluded from study. The data were collected from patients' dossiers.

A logistic regression model was used to associate the contribution of underlying factors in predicting the serum level of β-hCG after the medical intervention. The outcome was defined on the basis of β-hCG levels. The absolute value of the β-hCG was not of great importance; rather, β-hCG level less than 2000 mIU/ml indicated a high chance for ectopic pregnancy. Thus, the nature of the medical outcome is dichotomous: either β-hCG falls below 2000 mIU/ml threshold or it is above this cut-off point. If the probability of changing the serum level of β-hCG follows a logistic function, then its probability can be estimated by:

$$p(y = 1|X) = \frac{1}{1+e^{-X\beta}}$$

Where X is the list of predictors and β is their corresponding coefficients to be estimated.

Results

In this retrospective study, 277 patients with ectopic pregnancy were evaluated. 197 (71.1%) patients were younger than 35 years, and 205 (74.1%) patients were successfully treated with medical treatment with MTX, while 72 (25.9%) patients required surgery. For each participant, several variables which were believed to influence the outcome of MTX treatment were recorded. The complete list of predictors is shown in table 1.

The question of interest was whether there is any association between the probability of β-hCG serum level less than 2000 mIU/ml with absence or presence of predictors. If there is not any association, then the determination of β-hCG would not be useful for prediction. To account for this, the significance of the fitted logistic regression with full list of predictors (full model) was tested against a model without predictors (null model).

Table 1. List of predictors included in logistic regression model

Predictor	Meaning	Nature of predictor
Response		
β-hCG	1 - β-hCG over 2000 mIU/ml; 0 – less than 2000 mIU/ml	Dichotomous
Predictor		
EP	1 - History of EP present; 0- no history of EP	Design
PLSUR	1 - History of pelvic surgery; 0 – no history of pelvic surgery	Design
PID	1 - History of pelvic inflammatory disease; 0 – no History of pelvic inflammatory disease	Design
INFER	1 – Infertility problem present; 0 – no infertility problem	Design
IVF	1 - In vitro fertilization; 0 - no in vitro fertilization	Design
INTCRS	1 - First intercourse before 18; 0 – no intercourse before 18	Design
ABORTION	1 - History of abortion; 0 – no history of abortion	Design
CS	1 – Birth by caesarean surgery; 0 – normal delivery	Design
Age	Age of subject	Continuous
Sac4	1 - Pregnancy sac over 4cm; 0 – pregnancy less than 4cm	Design
FHR	1 - Fetal heart rate present; 0 – no fetal heart rate	Design
β-hCG 5000	1 - β-hCG level over 5000 mIU/ml; 0 – β-hCG under 5000 mIU/ml	Design

EP: Ectopic pregnancy; PLSUR: Pelvic surgery; PID: Pelvic inflammatory disease; INFER: Infertility; IVF: In vitro fertilization; INTCRS: Intercourse; CS: Caesarean surgery; FHR: Fetal heart rate; β-hCG: Beta human chorionic gonadotropin

The result was highly significant, showing that there was a significant difference between the full model and the null model ($\chi^2 = 152.53$, degree of freedom (df) = 2, $P < 0.00001$), which indicates the good prediction power of predictors.

The results of fitting multiple logistic regression model showed that at $\alpha = 0.05$ level, the pregnancy sac larger than 4 cm (Sac 4), fetal heart rate (FHR), and β-hCG level over 5000 mIU/ml are statistically significant, infertility problem and individual's age are marginally significant, and other variables do not influence the level of β-hCG. To evaluate the goodness-of-fit of the logistic model, McFadden's pseudo R-square was used.[14] For a good fit, this index should be between 0.2 and 0.4.[15] For multiple logistic regression model, McFadden's pseudo R-square was obtained 0.46 which indicates a good fit. Table 2 represents the coefficients and odds ratios of the logistic regression model containing all predictors.

Table 2. Estimated coefficients and odds ratios for the logistic regression model containing all predictors

Predictor	Coefficient	Standard Error	Odds ratio	Wald Statistics	P
EP	0.062	0.061	1.064	0.993	0.321
PLSUR	-0.102	0.062	0.903	-1.624	0.105
PID	0.052	0.054	1.054	0.970	0.332
INFER	0.032	0.061	1.032	0.522	0.602
IVF	-0.206	0.113	0.813	-1.823	0.067[*]
INTCRS	-0.039	0.049	0.962	-0.791	0.429
ABORTION	0.082	0.051	1.085	1.614	0.108
CS	0.058	0.053	1.060	1.115	0.266
Age35	-0.090	0.047	0.913	-1.905	0.058[*]
Sac4	-0.211	0.051	0.809	-4.119	< 0.001
FHR	-0.316	0.085	0.728	-3.719	< 0.001
β-hCG 5000	-0.423	0.053	0.655	-7.950	< 0.001

EP: Ectopic pregnancy; PLSUR: Pelvic surgery; PID: Pelvic inflammatory disease; INFER: Infertility; IVF: In vitro fertilization; INTCRS: Intercourse; CS: Caesarean surgery; FHR: Fetal heart rate; β-hCG: Beta human chorionic gonadotropin
[*]$P < 0.100$ based on Wald test

Table 3. Estimated coefficients and odds ratios for the logistic regression model containing three predictors

Predictor	Coefficient	Standard Error	Odds ratio	Wald Statistics	P
Sac 4	-0.208	0.051	0.812	-4.037	< 0.001
FHR	-0.306	0.085	0.736	-3.606	< 0.001
β-hCG 5000	-0.441	0.053	0.643	-7.374	< 0.001

FHR: Fetal heart rate; β-hCG: Beta human chorionic gonadotropin

For ease of interpretation and practical use, it is recommended to construct a reduced model with fewer predictors as possible. Thus, to eliminate the less significant variables form the full model (Table 2), the top-down strategy of Diggle was followed.[16] Starting with the full model, the least significant covariate was determined based on Wald statistics and was dropped from the model. Likelihood ratio test (LRT) was applied to compare the initial and reduced model. The procedure proceeded until the LRT showed significant p-value, indicating no need for further reduction. The procedures led to excluding all marginal and non-significant design variables and ended up with a model including only the pregnancy sac larger than 4 cm (SAC 4), FHR, and β-hCG level over 5000 mIU/ml. For this model, McFadden's pseudo R-square reduced to 0.42 but still indicated a good fit. Table 3 represents the coefficients and odds ratios of the reduced logistic regression model.

Interaction and confounding effects: The interaction effects of three variables (i.e. Sac 4, FHR, and β-hCG 5000) were added to the final model to investigate whether there was any improvement in predicting the probability of increasing β-hCG level after medical intervention or not. In the same manner as discussed above, the LRT was used to discriminate between succeeding models. The process began with three significant predictors and their interactions. Top-down strategy found no significant interactions; as well as no confounding effects.

Model interpretation: Increasing the β-hCG level due to medical intervention tends to be linked with pregnancy sac larger than 4 cm (Sac 4). The estimated odds ratio is 0.812 or 1/1.231 (95% CI: 0.05-0.78) which is less than 1.0, indicating that the probability of increasing the level of β-hCG for a women with pregnancy sac larger than 4 cm is less than the probability of increasing the level of β-hCG for a women with pregnancy sac less than 4 cm. Specifically, the odds ratio of β-hCG growth would decrease by 0.231 for a woman with a sac less than 4 cm. The logistic regression model also suggests that the absence of FHR increases the level of β-hCG. The odds ratio of 0.736 (or 1/1.358) indicates that the probability of increase in the β-hCG is 1.358 times more than the probability of increasing the β-hCG if FHR is detected. Furthermore, the baseline β-hCG also affects the β-hCG level after medical treatment in similar manner. The odds ratio of 0.643 (or 1/1.555) indicates that the probability of increasing the level of β-hCG for a treated women with baseline β-hCG over 5000 mIU/ml is 1.555 times more than that of for a treated women with baseline β-hCG less than 5000 mIU/ml.

Discussion

The findings of this study showed that there was an association between the pregnancy sac ≥ 4 cm and failure to the treatment. In this regard, Kimiaei et al. reported that pregnancy sac ≥ 3.5 cm is the most important predicting factor in response to the treatment.[17]

In addition, according to the results it was found that the primary β-hCG serum level ≥ 5000 mIU/ml may be a predicting factor for treatment failure. This finding was in agreement with Saadati et al., who reported that in patients with higher serum level of β-HCG, the successful treatment increased by using double dose of MTX method. They showed that using double dose also could

decrease the necessity of operation, re-administration of MTX, and duration of hospitalization.[18] In another study, serum level of β-hCG ≥ 6000 mIU/ml was the only predicting factor of treatment failure.[19]

In agreement with the findings of the present study, Potter et al. reported that the median primary β-hCG serum level was lower in women with successful treatment compared to those women with treatment failure.[20]

Another finding was the rate of successful treatment with MTX. In this study, 72 (25.9%) patients required surgery. In accordance with these results, Mirbolouk et al. reported that among 370 patients, 285 (77.1%) patients were successfully treated with MTX and 85 (22.9%) patients required surgery.[21]

Furthermore, comparing to the present findings, compelling evidence suggests that there was no significant difference between groups regarding the age of patients, history of EP, infertility, abortion and location of ectopic mass; therefore, none of these factors could predict the success of drug treatment in this population.[13,21,22]

In addition, in the present study, it was revealed that presence of FHR in patients was associated with reduced rate of successful medical treatment, which was in line with the findings of Lipscomb et al., who indicated that FHR in sonography is a predictor of treatment failure.[22]

Conclusion

Taking together, the results of this study suggest that there is a significant association between successful response to the treatment and β-hCG serum level, pregnancy sac size or presence of FHR; while age, history of infertility, number of abortion, history of EP, history of pelvic infection or surgery, nulliparity, history of smoking, and caesarean were not predictors of treatment failure.

Conflict of Interests

Authors have no conflict of interests.

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