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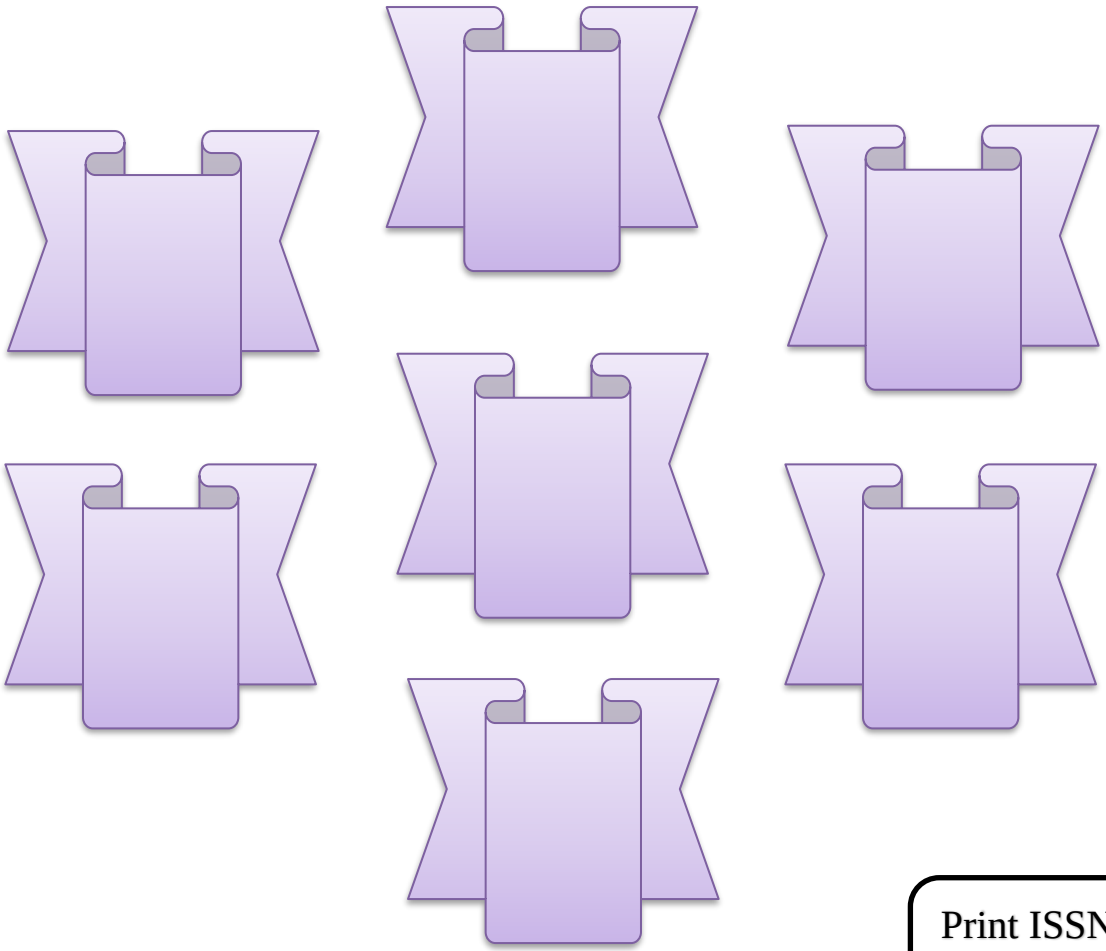

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Original Article

Predictive Role of Beta hCG for The Outcome of The Tubal and Cesarean Scar Ectopic Pregnancy: A Retrospective Study

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ABSTRACT

Background: Ectopic pregnancy is associated with higher maternal morbidity and mortality. Early diagnosis and outcome predictors represented a crucial option to reduce such morbidity and mortality.

Aim of the work: To evaluate the value of serum β-hCG for clinical outcome prediction in tubal and cesarean scar ectopic pregnancy.

Patients and Methods: This retrospective study of 192 ectopic pregnancies [tubal and cesarean section scar]. The collected data included patient demographics, obstetric and past history. Data of clinical examination were also recorded. Serum concentration of β-hCG at admission and after 48 hours were documented. The ultrasound examination was performed to define of the site of ectopic and to ensure empty uterine cavity. All patients were followed-up for their outcome of ectopic pregnancy and for 2 months after discharge.

Results: The outcome was significantly different between both groups [group II managed mainly by surgical wedge resection [96.9%] compared to none in group I. The highest β-hCG values were recorded for surgical wedge resection. 55.4% of those with doubling had no surgical wedge resection compared to 44.9% of those without doubling. The response to medical treatment was significantly associated with non-doubling of β-hCG [33.9% vs 12.3%]. β-hCG in tubal and cesarean scar ectopic pregnancy showed good predictive power [AUC > 0.75] with 100.0% sensitivity.

Conclusion: High β-hCG at admission and after 48 hours and specifically doubling of values are significantly associated with low response to medical treatment in tubal ectopic pregnancy.

Keywords: Ectopic Pregnancy; Cesarean Scar; Tubal; β-hCG

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INTRODUCTION

Ectopic pregnancy is a leading direct cause of maternal morbidity and mortality. Its incidence is approximately 2% of all pregnancies and the fallopian tube is the commonly affected [>90.0%] [1-3]. Tubal ectopic pregnancy usually occurs in the ampullary portion [70.0% of all ectopic pregnancies], followed by isthmus [10.0%], the fimbria [10.0%] and about 2.0% for the uterine cornu or interstitium [4]. However, the incidence of non-tubal ectopic pregnancies accounts for 7-10.0% [5,6]. Non-tubal ectopic pregnancy refers to the implantation of an embryo outside the uterine cavity or fallopian tubes. The common sites are a caesarean scar, the cornua uteri, the ovary, the cervix, and the abdomen. There is an increasing trend of non-tubal ectopic pregnancies, particularly caesarean scar pregnancy [CSP] [7].

In about 30.0% of ectopic pregnancies, normal levels of β-hCG were reported at the time of pregnancy, with lacking of daily doubling [8, 9]. An abnormal β-HCG pattern is highly suspicious for ectopic gestation [10]. The characteristic discriminately level and daily doubling of serum β-hCG has been used for diagnosis and treatment of extra-uterine ectopic pregnancies. However, the use of an hCG discriminatory level in diagnosis of non-tubal ectopic pregnancies is still unclear [11].

Ultrasound is the standard imaging modality of an intrauterine pregnancy as early as the fifth week of pregnancy with high level of confidence. The confirmation of an intrauterine pregnancy rules out ectopic pregnancy, except in a rare condition of heterotopic pregnancy, where ectopic pregnancy coexists with intrauterine pregnancy [12]. Moreover, the Royal College of Obstetrics and Gynecology [RCOG] guidelines emphasize that the β-hCG value is useful for management planning of ectopic pregnancy [13, 14]. Surgery is the standard treatment option. However, however, it is association with higher risk of mutilation. Thus, clinical treatment with methotrexate has become an important therapeutic alternative [15, 16].

Predictors of management outcome are of utmost importance. B-hCG could be a useful predictor in such regard. The aim of the current work was to evaluate the value of serum β-hCG titer for clinical outcome prediction in patients with tubal and cesarean scar ectopic pregnancy.

PATIENTS AND METHODS

The study had been conducted at the obstetrics and Gynecology Departments, Al-Azhar University Hospitals. We conducted a retrospective analysis of data of 192 pregnant women with ectopic pregnancy [96 of them had tubal ectopic pregnancy and they represented the first group and the other 96 had cesarean scar ectopic pregnancy and they represented the second group]. The administrative consents were obtained from the authorized managers and data collection, analysis and interpretation, were performed between January 2020 and June 2022.

Inclusion criteria were clinical and radiological [by ultrasound] confirmation of the singleton ectopic pregnancy in a hemo-dynamically stable patient with definite known gestational age from the date of the last menstrual period. On the other side, exclusion criteria included heteroectopic pregnancy, hemodynamic instability, disturbed or other types of ectopic pregnancies.

For all patients, the data collection included that of patient demographics, data of obstetric history [e.g., gravidity, parity, etc..], data of menstruation, associated chronic medical diseases and medications, past medical and surgical history. In addition, all available data about general, abdominal and local examinations were collected. The data of laboratory investigation included complete blood count, renal and liver function tests, coagulation profile and serum concentration of β-hCG values at admission and values after 48 hours. The ultrasound examination [GE voluson P8 BT 16 GE Ultrasound Korea, Ltd.9] directed to the detection of the site of ectopic pregnancy, ensure empty uterine cavity and absence of internal hematoma or hemorrhage. Finally, to exclude heteroectopic pregnancy. All patients were followed up for their outcome of ectopic pregnancy and provided management were documented.

In the first group, women received single dose of methotrexate according specific criteria [hemodynamic stability, adnexal mass ≤ 4 cm, absent fetal cardiac activity, hemoperitoneum < 100 ml]. Patients who developed complications or clinical disturbance were treated according to their clinical situation either by laparoscopic or surgical exploration. In the second group [CS scar ectopic pregnancy [figure 1]], at termination of pregnancy, the received systemic metho-

trexate and followed up till the final outcome. The outcome recorded as response to medical treatment, submission to wedge resection [figure 2] of the CS scar ectopic or need for suction and hemostatic measures. Data of clinical outcome and any complications were recorded and compared between groups.

Figure [1]: Cesarean scar ectopic pregnancy by transvaginal ultrasound shows the gestational sac implanted in the region of the cesarean scar, clearly outside the endometrial canal

Figure [2]: Cesarean scar ectopic pregnancy intraoperative and gestational sac was removed by wedge resection operation

The primary outcome was the successful induction by methotrexate treatment which was considered as the success. Otherwise, any surgical interference considered as failure. Patients were followed up for two months after discharge by ultrasound and measurement of β-hCG unit.

Data analysis: The collected data organized, coded and analyzed by the statistical package for social science [SPSS] version 16 [SPSS Inc. USA]. Numerical variables presented by their mean and standard deviations. Two means were compared by independent samples [t] test or its equivalents according to normality of data. However, more than two means were compared by one-way analysis of variance [ANOVA] test. Otherwise, the categorical data were presented by relative frequencies and percentages, and groups compared by Chi square test or its equivalents. P value < 0.05 was considered statistically significant.

RESULTS

Both groups of tubal and CS ectopic pregnancies were comparable regarding patient's age, gravidity and previous abortions. However, previous CS were significantly higher among group II than group I [table 1].

Regarding β-hCG at admission and after 48 hours, there was a statistically significant increase in group II than group I. In addition, doubling was significantly increased in group II than group I [40.6% vs 27.1%, respectively]. The outcome was significantly difference between both groups, as group II managed mainly by surgical wedge resection [96.9%] compared to none in group I. However, the hospital stay duration did not significantly differ between both groups [table 2].

Values of β-hCG at admission and after 48 hours showed a statistically significant variability between different outcomes. The highest values recorded for surgical wedge resection [table 3]. In addition, doubling of β-hCG was significantly associated with outcome, as 55.4% of those with doubling had surgical wedge resection compared to 44.9% of those without doubling. In addition, the response to medical treatment was significantly associated with non-doubling of β-hCG [33.9% of no doubling compared to 12.3% with doubling] [table 4].

Receiver operating characteristic [ROC] analysis was performed to determine predictive Value of β-hCG in tubal and cesarean scar ectopic pregnancy showed good predictive power of both values at admission and after 48 hours of admission. The area under the curve was 0.833 and 0.904, for initial values and for that after 48 hours at values <4560 and < 5300 respectively. The test accuracy increased after 48 hours [table 5, figures 3 and 4].

No significant complication was recorded in both groups, and Values of β-hCG reach values between 2-10 Units within 6 weeks after discharge. In addition, other laboratory data were in normal values and did not differ significantly between both groups.

Table [1]: Comparison between the two groups as regards age

		Group I [tubal ectopic] [No.= 96]	Group II [CS ectopic] [No.= 96]	Test	P-value
Age [years]	Mean± SD	26.56±2.42; 20-35	27.01±2.23; 24-36	1.33	0.18
Gravidity	G2	46[47.9%]	43 [44.8%]	2.17	0.53
	G3	41 [42.7%]	47 [49.0%]		
	G4	8 [8.3%]	4 [4.2%]		
	G5	1 [1.0%]	2 [2.1%]		
Previous abortions	None	78 [81.3%]	77 [80.2%]	1.51	0.68
	Once	11 [11.5%]	13 [13.5%]		
	Twice	7 [7.3%]	5 [5.2%]		
	Thrice	0 [0.0%]	1 [1.0%]		
Previous CS	None	51 [53.1%]	0 [0.0%]	72.64	**<0.001***
	Once	37 [38.5%]	64 [66.7%]		
	Twice	7 [7.3%]	27 [28.1%]		
	Thrice	1 [1.0%]	5 [5.2%]		

Table [2]: Comparison between the two groups as regards age

		Group I [tubal ectopic] [No.= 96]	Group II [CS ectopic] [No.= 96]	Test	P-value
β-hCG	At admission	2232.60±1085.47	11823.58±3774.57	23.92	**<0.001***
	After 48 hours	3421.06±1325.15	18771.56±3653.27	38.70	**<0.001***
	Doubling [n, %]	26 [27.1%]	39 [40.6%]	3.93	**0.033***
Outcome	Salpingectomy	40[41.7%]	NA	192.0	**<0.001***
	Response to Medical treatment	51 [53.1%]	0 [0.0%]		
	Spontaneous tubal abortion	5 [5.2%]	NA		
	Suction plus hemostatic measures	NA	3 [3.1%]		
	Surgical wedge resection	NA	93 [96.9%]		
Hospital stay [days]		7.68±1.75; 4-12	7.42±1.07; 5-9	1.24	0.21

NA: not applicable

Table [3]: Association between outcome and β-hCG

B-hCG		Mean	SD	F	p
At admission	Salpingectomy	2138.87	991.84	152.9	<0.001*
	Response to Medical treatment	2229.82	1100.45		
	Spontaneous tubal abortion	3010.80	1552.31		
	Suction plus hemostatic measures	6570.00	3534.92		
	Surgical wedge resection	11993.05	3675.78		
48 hours' after admission	Salpingectomy	3631.00	1323.70	373.5	<0.001*
	Response to Medical treatment	3202.98	1270.50		
	Spontaneous tubal abortion	3966.00	1739.73		
	Suction plus hemostatic measures	16853.33	9076.48		
	Surgical wedge resection	18833.4409	3444.82961		

Table [4]: Relation between β-hCG doubling after 48 hours and outcome

		Doubling				Test	P value
		No doubling [127]		Doubling [65]			
		No.	%	No.	%		
Outcome	Salpingectomy	23	18.1%	17	26.2%	16.12	**0.003***
	Response to Medical treatment	43	33.9%	8	12.3%		
	Spontaneous tubal abortion	4	3.1%	1	1.5%		
	Suction plus hemostatic measures	0	0.0%	3	4.6%		
	Surgical wedge resection	57	44.9%	36	55.4%		

Table [5]: Sensitivity and specificity of β-hCG for prediction of successful methotrexate treatment among studied patients

	β-hCG at admission	β-hCG after 48 hours
AUC	0.833	0.904
St. error	0.028	0.021
95% CI	0.773 to 0.883	0.853 to 0.941
Associated criterion	< 4560	<5300
Specificity	65.2.0%	72.0%
Sensitivity	100.0%	100.0%

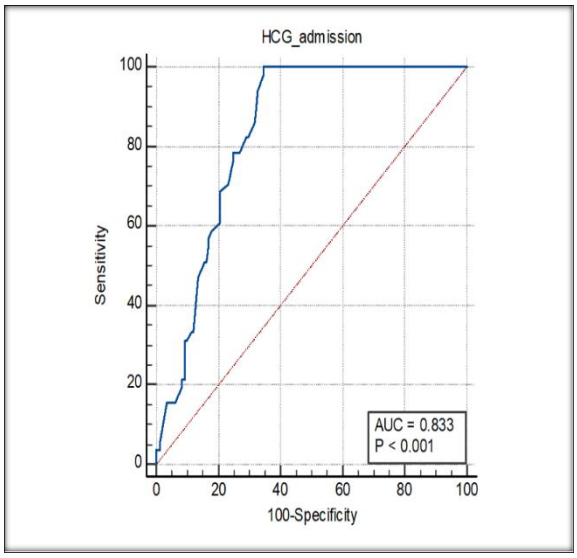

Figure [3]: ROC curve of initial [at admission] values of β-hCG for prediction of successful outcome

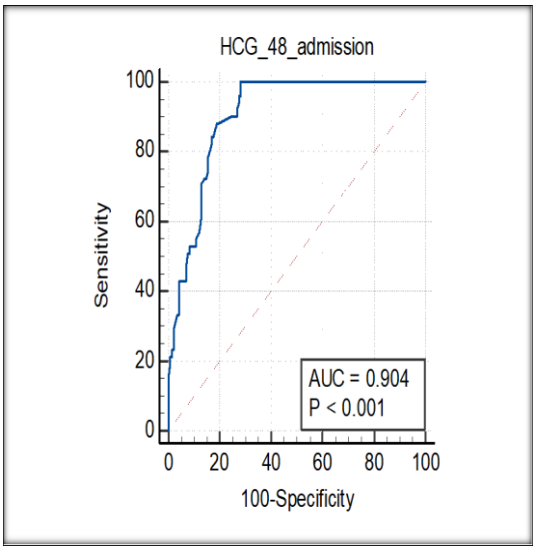

Figure [4]: ROC curve of values of β-hCG after 48 hours of admission for prediction of outcome

DISCUSSION

β-hCG is secreted by syncytiotrophoblasts and the increase of serum hCG level indicates the presence of viable uterine pregnancies: β-hCG doubles every 1.5 days up to 5 weeks after the last menstrual period, and then every 3.5 days from the 7th week [or when β-hCG is >10000 IU/L]. However, it did not follow the same pattern in ectopic pregnancy. But it was used as an accurate indicator of trophoblastic viability and used for diagnosis and follow-up in ectopic pregnancy. It was proposed as an indicator of tubal rupture or response to treatment in ectopic pregnancy. Yet, the results are heterogonous [17-19].

The main aim of this study was to evaluate the role of serum β-hCG titer in predicting the clinical outcome in patients with tubal and cesarean scar ectopic pregnancy. In short, results showed homogeneity of both groups regarding patient's age, gravidity and previous abortions. But previous cesarean deliveries were significantly higher among the group of CS ectopic pregnancy. The total duration of hospital stay did not significantly differ between both groups. However, the group of CS ectopic had significantly higher values of basal [at admission] and values after 48 hours of admission of β-hCG unit than the group of tubal ectopic pregnancy. The different outcomes also vary significantly regarding these values. Doubling of β-hCG was also associated with surgical intervention. The test was predictor of outcome [as area under the curve was above 0.75 for values at admission and after 48 hours]. The sensitivity was 100%, while specificity was 65.2% and 71.6% [at admission and after 48 hours] for detection of response to methotrexate therapy. **Gui *et al.*** [20] reported comparable demographic and obstetric history data when he included 40 patients with CS ectopic pregnancy and 80 controls. Furthermore, **Younes *et al.*** [21] included women with a mean age of 34.3 years [higher than the current], 26 [65%] had one previous scar, 13 patients [32.5%] had two previous scars, and 1 [2.5%] had three previous scars. However, **Faraji Darkhaneh *et al.*** [22] reported that age is a significant factor to discriminate between ruptured and unruptured tubal ectopic pregnancies.

Preliminary diagnosis of pregnancy of unknown location [PUL] was defined as a positive serum β-hCG in the absence of ultra-sound indicators of intrauterine or extrauterine pregnancy. Approximately 30 % of patients with PUL will develop an ongoing intrauterine pregnancy [IUP], while the majority will be diagnosed with failing pregnancies, either mis-carriages or ectopic pregnancies. In the stable patient, the measurement of β-hCG is crucial to clarify pregnancy location and prognosis [23].

Morse *et al.* [24], reported that a single measure of β-hCG is insufficient to clarify prognosis of pregnancy prognosis, and serial measurements are usually used to monitor early pregnancies. The recommendations for β-hCG trends in early pregnancy suggest the minimum β-hCG rise of 35% in 2 days, with an overall accuracy of 80.2 % in predicting EP [25].

Furthermore, **Faraji Darkhaneh *et al.*** [22], shown that patients with β-hCG levels >1750 IU/ml were considerably more likely to undergo rupture. **Downey *et al.*** [26] showed that a serum β-hCG level of 1500 IU/l is associated with a higher rate of tubal rupture than a β-hCG level of <1500 IU/l [values lower than the current one]. **Goksedef *et al.*** [27] also showed patients with ruptured EP are more frequently to have β-hCG levels of 1501-5000 IU/ml and >5000 IU/ml compared with 0-1500 IU/ml [44.3%, 53.3% and 11.3%, respectively [the values near the current results]. On the extreme side, there have been sporadic reports of women with ruptured ectopic pregnancies associated with low and declining levels of β-hCG [28-30]. These reports showed that there is no safe β-hCG titer for ruptured tubal ectopic pregnancy and the range of serum β-hCG level was broad for both ruptured and unruptured groups. Trophoblast degeneration with cessation of hormone production, an extremely small mass of chorionic villi [producing little if any hormone] or defective β-hCG biosynthesis have been supposed as theoretical mechanism to explain unexpectedly low or absent β-hCG in these patients.

Several studies have attempted to ascertain indicators of success after medical treatment of EP. Different markers and features of EP have been studied to predict the outcome of treatment approaches. Yet, the best predictive marker of medical treatment success for EP has not yet identified. A meta-analysis held by **Dilbaz *et al.*** [31] suggested that the initial β-hCG level is the most important predictor of MTX treatment success in EP. Although it did not reach a statistically significant level, the median initial β-hCG concentration was correlated with the treatment success rate. Undoubtedly, women

with a declining trend in the β-hCG level benefited from methotrexate treatment for EP. Other studies reported similar results [32, 33]. Another study conducted by **Sagiv *et al.*** [34] including 238 patients also found that the initial β-hCG value is the most important predictor of the outcome of treatment. Our results also confirm the results of **Skubisz *et al.*** [35], who found that an early decline in serum β-hCG value between days 0 and 4 was associated with a high rate of treatment success [88%]. However, in the success group, 66.2% of patients had an initial β-hCG value below 2000 mIU/mL, and these cases would have undergone spontaneous resolution if they had been treated with expectant management.

In the study of **Faraji Darkhaneh *et al.*** [22], one hundred and ninety-seven [79.8%] were cases with unruptured EP and 50 patients [20.2%] were cases with ruptured EP. The mean level of beta-hCG was significantly higher in patients with ruptured EP compared to patients with unruptured EP [p=0.03]. They revealed that higher β-hCG levels at the time of admission were important risk factors for tubal rupture. However, no significant associations between parity, gravidity, the number of previous normal pregnancies, past history of PID, previous EP, abortion, IUD use and risk of tubal rupture were found.

In short, higher levels of β-HCG at admission and after 48 hours and specifically doubling of values are significantly associated with low response to medical treatment in tubal ectopic pregnancy. Otherwise, it significantly increases in cases needed wedge resection. However, due to retrospective nature of the study [a limitation of the study], the results of the current work should be treated cautiously and could not be globalized. Future prospective and controlled studies are highly recommended.

Conflict of Interest and Financial Disclosure: None.

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