β-Human chorionic gonadotropin in prediction of tubal rupture. Is it enough in the diagnosis?

**Cihan Kaya,
Huseyin Cengiz,
Murat Ekin,
Hakan
Guraslan,
Sema Karakas,
Levent Yasar**

*Department of Obstetrics
and Gynecology,
Bakirkoy Dr Sadi Konuk
Teaching and Research
Hospital,
Istanbul (Turkey)*

*Correspondence:
Dr. Cihan Kaya
e-mail: drcihankaya@
gmail.com*

Abstract

Objective. *To evaluate the predictive value of β -Human Chorionic Gonadotropin (β- hCG) and other risk factors in patients with tubal rupture.* ***Methods.*** *The study group was comprised of 188 cases of ectopic pregnancy treated in our gynecology department from January 2007 to March 2011. A chart review was then performed with the use of medical records, ultrasound records and a laboratory database. The study group was divided into two subgroups according to their tubal status, which was diagnosed during surgery.* ***Results.*** *About131 (69.7%) of the patients were classified in the ruptured group and 57 (30.3%) of the patients were in the unruptured group. There was statistical significance in the preoperative hemoglobin (p=0.001) and hematocrit (p=0.0001) levels. There was no statistical significance between the two groups in β- hCG levels.* ***Conclusions.*** *The preoperative β-hCG measurement alone is not sufficient to predict tubal rupture in patients with ectopic pregnancy.*
Keywords: *ectopic pregnancy, hCG-beta, risk factors*

Introduction

Ectopic pregnancy (EP) is any pregnancy in which the fertilized ovum implants outside the uterine cavity[1]. Mortality associated with ectopic pregnancy remains the leading cause of maternal death in the first trimester of pregnancy, with an incidence of 13%[2]. The Centers for Disease Control and Prevention reported a rate of 19.7 ectopic pregnancies per 1,000 reported pregnancies[3]. Therefore, there has been a marked increase in the rate of EP in the past two decades. The reasons for this increase could be the increased rate of sexually transmitted diseases, unsuccessful tubal sterilizations, and induced abortion followed by infection, increased use of assisted reproductive techniques, tubal surgery.

Tubal rupture is defined as any loss of integrity of the tubal serosa which is noted in the operative report[4]. The incidence of tubal rupture is reported from 18% to 35% of the cases with EP[5]. Earlier diagnosis is possible for EP with sensitive assays for β human chorionic gonadotropin (β- hCG) and by performing transvaginal ultrasound (TVUS), but not for diagnosing tubal rupture[6]. The diagnosis of tubal rupture is obvious in a woman with hemodynamic instability. However, the clinical symptoms of tubal rupture are more subtle. In most cases, careful history-taking, the characteristics of acute pelvic pain and finally diagnostic laparoscopy can be used for ruling out tubal rupture[7].

β- hCG is reported to be a predictive marker in patients with tubal rupture in previous studies[5,8]. It is secreted by syncytiotrophoblasts and doubles every 2 days in early, normal intrauterine pregnancies. In the present study we aimed to evaluate whether β-hCG measurement alone is sufficient to diagnose a tubal rupture in patients with EP.

Methods

Before the onset of data collection, approval was obtained from the institutional review board to perform a chart review of 188 patients who had undergone an operation for EP in our Obstetrics and Gynecology Department between January 2007 and March 2011. The Bakirkoy Dr. Sadi Konuk Teaching and Research Hospital is a tertiary referral center serving mainly the indigent, low socio-economic population. A retrospective chart review was then performed with the use of medical records, ultrasound records and the laboratory database. Basic parameters, such as age, gravidity, parity, educational level, smoking habits, pelvic inflammatory disease (PID), previous tubal and abdominal surgery, a history of menstrual delay, and laboratory parameters were analyzed. Laboratory parameters included: mean size of ectopic mass in the TVUS. Further parameters included sonographic blood accumulation in the pouche of Douglas (PoD), pre-operative β- hCG values (which are divided into subgroups: <1500, 1501-5000, 5001-10000, and >10000 to clearly identify the correlation between the elevated rates and a possible tubal rupture). Hemoglobin (Hb) and hematocrit (Htc) values were also analyzed. Clinical parameters, such as presenting symptoms, physical examination findings (including peritoneal irritation signs and vital signs

with a measure of arterial blood pressure), were also analyzed. The β- hCG levels were measured by using an Architect C16000 integrated systems (Abbott Laboratories, Abbott Park, IL, USA) and the TVUS was performed by using a 6.5 MHz transvaginal probe of Logiq 200 PRO Series ultrasound (General Electric Medical Systems, Milwaukee, USA).

The statistical analysis was performed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) among the two groups, ruptured and unruptured EPs. Statistical analysis included the Student's t test, and the Mann-Whitney rank. A p value <0.05 was considered to be statistically significant.

Results

About 188 patients were diagnosed with EP during the time period reviewed. About 131 (69.7%) of the patients were classified in the ruptured group, and 57 (30.3%) of the patients were classified in the unruptured group. The mean age was 31.69±6.31 in patients with ruptured EP, and 32.07±5.66 in patients with unruptured. The characteristics of the patients are listed in Table 1. There was no significant difference between the two groups with respect to maternal age, gravidity, parity, educational level, smoking habits, PID, and previous tubal or abdominal surgery. There was statistical significance in preoperative Hb (p=0.001) and Htc (p=0.0001) levels, with lower levels (9.8±1.68 vs. 30.07±4.64) seen in the ruptured group. The mean size of the ectopic mass seen in the TVUS was 37.21±16.26 mm in the ruptured group and 38.79±18.56 mm in the unruptured group. There was no statistical significance between the two groups. The preoperative β- hCG levels were ranged (min. 76 mIU/ml-max. 60075 mIU/ml, mean

Table 1   Demographic characteristics of the patients with possible risk factors for EP

		Unruptured group	%	Ruptured group	%	p-value
Age		32.07±5.66		31.69±6.31		0.700
Gravidity		2.61±2.31		2.75±2.04		0.691
Parity		1.54±1.24		1.62±1.64		0.759
Smoking		23	40.40	50	38.20	0.778
PID*		17	29.80	35	26.70	0.662
Curettage		17	29.80	49	37.40	0.317
Previous abdominal surgery		19	33.33	41	31.30	0.916
Infertility		8	14.00	10	7.60	0.170
Abortion		12	21.10	28	21.40	0.961
Tubal surgery		9	15.80	14	10.70	0.326
Type of delivery	Nulliparous	13	22.80	25	19.10	0.513
	VB**	28	49.10	71	54.20	
	C/S ***	10	17.50	28	21.40	
	VB+C/S	6	10.50	7	5.30	
Educational status	Non educated	8	14.00	11	8.40	0.600
	Primary school	40	70.20	103	78.70	
	High school	6	10.50	10	7.60	
	University	3	5.30	7	5.30	

*PID= pelvic inflammation disease; **VB=Vaginal Birth; ***C/S=Cesarean Section*

Table 2 Laboratory and ultrasound findings of the patients with EP

	Unruptured group	**Ruptured group**	**p-value**
Sonographic blood accumulation in the PoD*(mm)	28.23±19.42	46.09±21.22	0.0001
Hb** g/dl	10.67±1.57	9.8±1.68	0.001
Htc*** %	32.75±4.99	30.07±4.64	0.0001
Systol mmHg	100.7±11.32	99.31±14.1	0.512
HR**** per min.	78.25±4.78	84.54±8.67	0.0001
Mean size of the ectopic mass (mm)	38.79±18.56	37.21±16.26	0.558

*PoD= pouche of Douglas; **Hb= hemoglobin; ***Htc= hematocrit; ****HR=heart rate*

Table 3 β-hCG values of the patients with EP

β-hCG* value mIU/ml	Ruptured group		Unruptured group		P value
	n	%	n	%	
<1 500	12	21.10	37	28.20	
1 501-5 000	25	43.90	59	45.00	0.492
5 001-10 000	7	12.30	16	12.20	
>10 000	13	22.80	19	14.50	

* β-hCG= β -Human Chorionic Gonadotropin

5065.24±7197.63 mIU/ml) in the ruptured group, and (min. 100 mIU/ml - max. 54261 mIU/ml mean 6997,53±9620.48 mIU/ml) in unruptured group (p value 0.130). The β- hCG levels were categorized as <1500, 1501-5000, 5001-10000, >10000, and the results are shown in Table 2. There was no statistical significance between the two groups according to β- hCG levels. The sonographic blood accumulation in the PoD was 46.09±21.22 mm in the ruptured group and 28.23±19.42 in the unruptured group, which was significantly higher in the ruptured group (p= 0.0001) (Table 3). There was no significance in blood pressure, abdominal pain, vaginal bleeding, history of menstrual delay, nausea and/or vomiting between the two groups. The heart rate (HR) was 78.25±4.78 in the unruptured group, and 84.54±8.67 in the ruptured group, and that was statistically significant with a p=0.0001. There was also statistical significance in adnexal tenderness in the ruptured EP group when compared to the unruptured EP group, with a p=0.0001.

Discussion

EP is still a major concern as a cause of maternal deaths due to acute hemorrhage. The occurrence of tubal rupture in EP ranges from 18.0% to 64.5%, as reported in previous large population-based studies[9-11]. In our study, the incidence of tubal rupture was 69.7%, which is a higher than the previous studies. The high rupture rates may be explained secondarily by the indigenous population that we served, and as a result of difficulties in reaching health care provider.

In this century, as a result of developing technologies, there are a major improvements in laboratory and imaging studies. However, there are still difficulties in reaching these technologies in developing countries. β-hCG, which is secreted by syncytiotrophoblasts, is a useful marker in the diagnosis of EP. There are conflicting results concerning the correlation between serum β-hCG levels and tubal rupture in the literature. Some of these studies reported a positive correlation between serum β-hCG levels and tubal rupture[5,8,12]. Goksedef and contributors reported a finding that β-hCG levels greater than 5000 are associated with tubal rupture[8]. In another study, Job-Spira et al. reported findings that suggested a high level of β-hCG (at least 10000 IU/L) is associated with tubal rupture[5]. However, in our study we stratified the β- hCG levels into four groups between <1500 and >10000 in order to identify the correlation between the elevated rates and tubal rupture.

We found no statistical significance between tubal rupture and the β- hCG subgroups. Other authors reported similar results, concluding that serum β-hCG levels do not predict tubal rupture[13,14].

In other studies, serum β-hCG levels were associated with the dimensions of the tubal pregnancy and gestational age[8,15-17]. Mol and contributors reported a positive correlation between the dimension of EP and gestational age with tubal status (tubal rupture, abortus or intact tubes)[18]. They also reported a risk of tubal rupture or an increase in active bleeding when gestational age is ≥7 weeks, ectopic mass is ≥ 24 mm and serum β- hCG levels ≥1300 IU/L[18]. In our study, the mean measure of ectopic mass in the ruptured group was 37.21±16.26 mm, and in contrast with the previous studies, there was no statistical significance between the ruptured and unruptured groups. Despite the results of the other studies[8,15-18], we believe that tubal rupture is not only associated with the dimension of EP measured in the TVUS, but also depends on the implantation site of EP in the tube. Detailed data about the size and placement of the ectopic pregnancy (ampullary, isthmic, fimbrial, ovarian, and so on) was not available in our study as a result of the retrospective collection of the cases.

In our study, there was statistical significance in preoperative Hb (p= 0.001) and Htc (p-value 0.0001) levels, which were lower than those seen in the ruptured group, and these results were similar with other studies[18,19]. This undoubtedly depends on the blood leakage from the ruptured part of the tube into the abdominal cavity.

As a first-line basic examination parameter, HR may be helpful in predicting ruptured EP. In our study, HR increased in the ruptured group when compared with the unruptured group. This can be explained by reference to a decrease in the circulation of the blood volume and an increase in the left ventricular stroke work. HR's application to the detection of ruptured EP has been reported before and we found HR can be useful in the prediction of ruptured EP[20, 21].

Presenting symptoms like abdominal pain, vaginal bleeding, and missing periods has a high sensitivity in the diagnosis of EP. Mol and contributors showed that the presence of abdominal pain and fluid accumulation in the PoD increases the possibility of tubal rupture in 19% and 13% of cases, respectively[18]. In our study, the presenting symptoms of abdominal pain, vaginal bleeding and missing periods were found to be at the rate of 96.20%, 46.60% and 64.10%. However, there was no statistical significance between the ruptured and unruptured groups. The sonographic fluid accumulation in the PoD was greater in the ruptured group, with a mean measure of 46.09±21.22 and 28.23±19.42 in the unruptured group, and this difference was statistically significant when comparing both of the groups.

Conclusions

By using anamnesis and basic clinical and laboratory findings to predict tubal rupture is almost possible. We ascertained that a serum β-hCG level alone is not helpful in this evaluation. Our study showed that lower Hb and Htc levels, sonographic fluid accumulation in the PoD, increased HR and adnexal tenderness are associated with an increased risk of tubal rupture. Physicians should be aware of the possibility of a ruptured EP in a reproductive aged woman who presents these symptoms, and should prompt ask further investigation. ■

References

1. Phillips RS, Tuomala RE, Feldblum PJ, Schachter J, Rosenberg MJ, Aronson MD. The effect of cigarette smoking Chlamydia trachomatis infection, and vaginal douching on ectopic pregnancy. Obstet Gynecol 1992; 79:85–90.
2. Barnhart K, Esposito M, Coutifaris C. An update on the medical treatment of ectopic pregnancy. Obstet Gynecol Clin North Am 2000; 27: 653–67.
3. Centers for Disease Control and Prevention: Ectopic pregnancy, United States, 1990–1992. JAMA 1995; 273: 533.
4. Berlingieri P, Bogdanskiene G, Grudzinskas JG. Rupture of tubal pregnancy in the Vilnius population. Eur J Obstet Gynecol Reprod Biol 2007; 131:85–8.
5. Job-Spira N, Fernandez H, Bouyer J, Pouly JL, Germain E, Coste J. Ruptured tubal ectopic pregnancy: risk factors and reproductive outcome results of a population-based study in France. Am J Obstet Gynecol 1999;180: 938–44.
6. Dündar O, tütüncü L, Müngen E, Muhcu M, Yergök YZ. Heterotopic pregnancy: Tubal ectopic pregnancy and monochorionic monoamniotic twin pregnancy: A case report. Perinatal Journal. 2006;14:96–100.
7. Huchon C, Panel P, Kayem G, Bassot A, Nguyen T, Falissard B et al. Is a standardized questionnaire useful for tubal rupture screening in patients with ectopic pregnancy? Acad Emerg Med 2012; 19:24–30.
8. Goksedef BPC, Kef S, Akca A, Bayik RNE, Cetin A. Risk factors for rupture in tubal ectopic pregnancy: definition of the clinical findings. Eur J Obstet Gynecol Reprod Biol 2011; 154: 96–9.
9. Bickell NA, Bodian C, Anderson RM, Kase N. Time and the risk of ruptured tubal pregnancy. Obstet Gynecol 2004; 104: 789–879.
10. Falcone T, Mascha EJ, Goldberg JM, Falconi LL, Mohla G, Attaran M. A study of risk factors for ruptured tubal ectopic pregnancy. J Womens Health 1998; 7: 459–63.
11. Saxon D, Falcone T, Mascha EJ, Marino T, Yao M, Tulandi T. A study of ruptured tubal ectopic pregnancy. Obstet Gynecol 1997; 90: 46–9.
12. Ackerman R, Deutsch S, Krunholz B. Levels of human chorionic gonadotropin in unruptured and ruptured ectopic pregnancy. Obstet Gynecol 1982; 60:13-4.
13. Roussos D, Panidis D, Matalliotakis I, Mavromatidis G, Neonaki M, Mamopoulos M et al. Factors that may predispose to rupture of tubal ectopic pregnancy. Eur J Obstet Gynecol Reprod Biol 2000; 89(1):15-7.
14. Galstyan K, Kurzel RB. Serum beta-hCG titers do not predict ruptured ectopic pregnancy. Int J Fertil Womens Med 2006; 51:14–6.
15. Latchaw G, Takacs P, Gaitan L, Geren S, Burzawa J. Risk factors associated with the rupture of tubal ectopic pregnancy. Gynecol Obstet Invest 2005; 60:177–80.
16. Laibl V, Takacs P, Kang J. Previous ectopic pregnancy as a predictor of methotrexate failure. Int J Gynaecol Obstet 2004; 85: 177–8.
17. Sindos M, Togia A, Sergentanis TN, Kabagiannis A, Malamas F, Farfaras A et al. Ruptured ectopic pregnancy: risk factors for a life-threatening condition. Arch Gynecol Obstet 2009; 279(5):621–3.
18. Mol BW, Hajenius PJ, Engelsbel S, Ankum WM, van der Veen F, Hemrika DJ, et al. Can noninvasive diagnostic tools predict tubal rupture or active bleeding in patients with tubal pregnancy? Fertil Steril 1999; 71:167-73.
19. Birkhahn RH, Gaeta TJ, Van Deusen SK, Tloczkowski J. The ability of traditional vital signs and shock index to identify ruptured ectopic pregnancy. Am J Obstet Gynecol 2003; 189:1293-6.
20. Birkhahn RH, Gaeta TJ, Bel R, Bove JJ. Shock index in the first trimester of pregnancy and its relationship to ruptured ectopic pregnancy. Acad Emerg Med 2002;9 :115–9.
21. Onah HE, Oguanuo TC, Mgbor SO. An evaluation of the shock index in predicting ruptured ectopic pregnancy. J Obstet Gynaecol 2006; 26(5): 445 – 7.