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Original Article

A day 1 hCG can differentiate non-viable intrauterine pregnancy and ectopic pregnancy following endometrial curettage

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Abstract

Aim: The aim of the present study was to determine a cutoff level for a decrease in human chorionic gonadotropin (hCG) on postoperative day 1 to confirm intrauterine pregnancy (IUP) in patients who have undergone dilatation and curettage (D/C) with a presumptive diagnosis of nonviable pregnancy of unknown location (PUL).

Material and Methods: This retrospective case–control study included patients who underwent D/C with a presumptive diagnosis of failing PUL between January 2010 and June 2015. Patients with failing PUL or confirmed to have an IUP were placed in Group 1 (n=164) and patients subsequently diagnosed with ectopic pregnancy were placed in Group 2 (n=19).In all patients, serum hCG levels were obtained on the day of D/C and on the following day.

Results: The decline in serum hCG percentage on day 1 after D/C was 54.2% in patients with failing PUL/abortion and 14.3% in patients with ectopic pregnancy (p<0.001). A decrease in hCG of more than 35% was the most sensitive marker, with sensitivity, specificity, and positive and negative predictive values of 90%, 89%, 99%, and 50%, respectively.

Conclusion: Determining post curettage day 1 hCG might aid clinicians in confirming failing IUP and in ruling out an ectopic pregnancy at an earlier date.

Keywords: Dilatation and curettage; ectopic pregnancy; human chorionic gonadotropin

INTRODUCTION

Despite advances in ultrasonography and continued efforts in proposing diagnostic algorithms, ectopic pregnancy (EP) is still an important cause of maternal mortality in the first trimester (1,2). Serial human chorionic gonadotropin (hCG) measurements are the standard approach for screening, particularly in patients with a higher risk of EP (3).In approximately 10% of patients, however, intrauterine pregnancy (IUP) and EP cannot be confirmed by screening (1,4). This issue is called pregnancy of unknown location (PUL) (1,4). While in most cases a reliable diagnosis of IUP or EP can be made during follow up, in some patients, serum hCG levels fall without a provisional diagnosis of pregnancy location, known as failing PUL (5).

Dilatation and curettage (D/C) is recommended in patients with PUL in whom viable IUP is ruled out based on serial hCG measurements (6). D/C is both a diagnostic and a therapeutic approach in these patients. According to a previous, small-scale study, a 50% decrease in hCG on day 1 following D/C is a reliable indicator of IUP (7). In more recent two studies the investigators have found that a decrease of greater than % 15 two days after endometrial vacuum aspiration in patients with failing PUL (8,9).

D/C is not deemed necessary in the surveillance of clinically stable PUL patients by some authors, who contend that the procedure does not add up to diagnostic accuracy in these patients (9). In addition, D/C poses a surgical risk, and in rare cases, viable IUPs can be unintentionally terminated. On the other hand, symptomatic patients who present with pain and bleeding, frequently require D/C (10). A patient who presents with bleeding and or passage of tissue initially falls into the PUL/failing PUL category, provided that an IUP has not previously been documented. IUP can be confirmed by visualization of chorionic villi by saline instillation or by histopathological examination of the frozen specimen. However, it has been reported that these modalities have a relatively low sensitivity (70%) (11). Therefore, these patients require a simple adjunct

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test that can diagnose EP reliably. As stated in previous studies, the fall of hCG can be considered a useful tool in the management of such patients and has a good diagnostic value when combined with histopathological examination of curettage material for the presence of chorionic villi (7,9). But this approach still needs to be validated due to its scarcity in the literature. To the best of our knowledge only two studies have so far investigated serum hCG decrease after D/C as a diagnostic tool in patients with failing PUL.

The aim of the present study was to determine a cutoff level for a decrease in hCG on postoperative day 1 in patients who have undergone D/C for failing PUL. As such, the serum hCG characteristics of patients with IUP and EP were compared, as well as diagnostic performance of hCG to differentiate EP from IUP.

MATERIAL and METHODS

This retrospective observational study was conducted at the Early Pregnancy Unit of Zekai Tahir Burak Women's Health, Research and Training Hospital. The study population consisted of patients admitted to the Early Pregnancy Unit with a presumptive diagnosis of abortion or nonviable PUL. Ward registries were checked to identify eligible patients between January 2010 and June 2015.

The determination of PUL was made in line with previous diagnostic algorithms (10). A patient was considered to have failing or nonviable PUL when an increase of less than 52% was detected in serial hCG measurements and when ultrasonography failed to show a gestational sac (intrauterine or extrauterine). Patients with failing PUL and patients who were confirmed to have IUP were placed in Group 1. Failing PUL was diagnosed in patients with PUL in whom EP or IUP could not been confirmed who had a decrease in serial serum hCG measurements during follow up. PUL patients who were subsequently diagnosed with EP were placed in Group 2. Patients who fell into one of the two specified categories, required D/C during inpatient care, and whose serum hCG levels were obtained on the day of D/C and the following day were included in the study.

Serum hCG obtained within six hours prior to D/C was considered the day 0 sample. Day 1 hCG was obtained within 18–30 hours after the procedure. Patients with a gestational age at or beyond 12 weeks according to the last menstrual period were excluded from the study. Patients who did not have proper day 0 or day 1 hCG measurements were also excluded from the study. Maternal serum was obtained from the antecubital vein for determination of serum hCG levels on the day of admission and thereafter. A commercially available human enzyme-linked immunosorbent assay (ELISA) kit for hCG was used on a single analyzer (Beckman Coulter Inc, USA). The standard procedure for ELISA was followed according to the manufacturer's instructions.

The following clinical and demographic data were obtained by reviewing the patients' medical records: maternal age, body mass index, smoking, reproductive history, presence of comorbidities, and prior surgery.

The study was approved by the local ethics committee of Zekai Tahir Burak Women's Health Education and Research Hospital in 13.02.2017/12, and the universal principles of the Helsinki Declaration were applied. Statistical analysis was performed using SPSS version 17 (Statistical Package for the Social Sciences, Chicago, IL). Student's t test was performed for parametric variables between groups, and a Chi-square test was performed for nonparametric variables between groups. P values <0.05 were considered significant.

Retrospective power analysis was performed by NCSS statistical software (Kaysville, Utah: Number Cruncher Statistical Systems). A sample of 164 from the failing PUL/ abortion group and 19 from the ectopic pregnancy group achieve 99.99% power to detect a difference of 0.34 between the area under the ROC curve (AUC) under the null hypothesis of 0.50 and an AUC under the alternative hypothesis of 0.84 using a two-sided z-test at a significance level of 0.05. The data are continuous responses. The AUC is computed between false positive rates of 0.0 and 1.0. The ratio of the standard deviation of the responses in the ectopic pregnancy group to the standard deviation of the responses in the failing PUL/ abortion group is 1.0.

RESULTS

The demographic and clinical data of the patients in the study population are provided in Table 1. Patients with abortion or failing PUL were of similar age and parity compared with patients with EP (p>0.05 in all comparisons). In addition, rate of smoking and previous EP were similar (p>0.05 in all comparisons) in the two groups, as was gestational age on admission (8.6±3.8 vs. 7.5±2.5 weeks; p=0.102). Patients with abortion or failing PUL had greater endometrial thickness (12.3±4.9 vs. 8.7±2.5 mm; p=0.001) and higher gravidity (p=0.001).

The decline in serum hCG percentage on day 1 after the D/C procedure is shown in Table 2. Overall decline in hCG was 54.2% in patients with abortion or failing PUL, but 14.3% in patients with EP (p<0.001). Three patients (1.8%) with abortion or failing PUL and ten patients (52.6%) with EP had a less than 10% decline in serum hCG (p<0.001). A higher rate of decline was observed in patients with abortion or failing PUL than in patients with EP when these patients were categorized as initial serum hCG<1000 IU/L (47.8±18.4 vs. 12.7±22.0, p=0.001) and initial serum hCG 1000–3500 IU/L (61.9±12.7 vs. 10.1±27.0, p<0.001). In patients with initial serum hCG>3500 IU/L, the decline in serum hCG was similar in both groups (p=0.625).

The rate of chorionic villi detected in endometrial samples is shown in Table 3. Chorionic villi were detected in 20 (41.7%) patients with abortion or failing PUL and in none of the patients with EP when initial serum hCG was <1000 IU/L (p=0.011). Chorionic villi were detected in 28 (63.6%)

Table 1. Clinical and demographic data of the study population

Characteristics	Failing PUL/ abortion (n = 164) (%)	Ectopic pregnancy (n = 19) (%)	p
Age (years)			
< 21	1 (0.6%)	0	1.0
21–34	133 (81.1%)	17 (89.5%)	0.559
> 34	30 (18.3%)	2 (10.5%)	0.599
Gravidity	2 (1–5)	3 (1–5)	0.001
Parity	1 (0–4)	1 (0–3)	0.649
Smoking	17 (10.3%)	3 (15.8%)	0.742
Previous ectopic pregnancy	3 (1.8%)	2 (5.3%)	0.145
Gestational age according to LMP (weeks)	8.6 ± 3.8	7.5 ± 2.5	0.102
Endometrial thickness	12.3 ± 4.9	8.7 ± 2.5	0.001

Data expressed as mean ± standard deviation, median (minimum–maximum), and number.
PUL: Pregnancy of Unknown Location; LMP: Last Menstrual Period. Students' t test and chi square test was employed

Table 2. Comparison of rates of decline in hCG in patients with resolving PUL/abortion vs. ectopic pregnancy

Characteristics	Failing PUL/ abortion (n = 164)	Ectopic pregnancy (n = 19)	p
Overall Fall in hCG (%)	54.2 ± 15.6	14.3 ± 24.9	<0.001
Fall in hCG<10%	3 (1.8%)	10 (52.6%)	<0.001
Serum hCG<1000 IU/L			
Fall in hCG (%)	47.8 ± 18.4	12.7 ± 22.0	0.001
Serum hCG: 1000–3500 IU/L			
Fall in hCG (%)	61.9 ± 12.7	10.1 ± 27.0	<0.001
Serum hCG>3500 IU/L			
Fall in hCG (%)	53.9 ± 13.2	37.3 ± 35.1	0.625

Data expressed as mean ± standard deviation and number. hCG: Human Chorionic Gonadotropin;
PUL: Pregnancy of Unknown Location. Students' t test and chi square test was employed

Table 3. Comparison of histopathological characteristics in patients with resolving PUL/abortion and ectopic pregnancy

Histopathological results	Failing PUL/ abortion (n = 164)	Ectopic pregnancy (n = 19)	p
Serum hCG<1000 IU/L			0.011
Chorionic villi present	20 (41.7%)	0	
Chorionic villi absent	28 (58.3%)	10 (100%)	
Serum hCG: 1000–3500 IU/L			0.002
Chorionic villi present	28 (63.6%)	0	
Chorionic villi absent	16 (36.4%)	7 (100%)	
Serum hCG>3500 IU/L			0.300
Chorionic villi present	61 (84.7%)	1 (50%)	
Chorionic villi absent	11 (15.3%)	1 (50%)	

hCG: Human Chorionic Gonadotropin; PUL: Pregnancy Of Unknown Location. Chi square test was employed

patients with abortion or failing PUL and in none of the patients with EP when initial serum hCG was 1000–3500 IU/L (p=0.002). The rate of positive chorionic villi was observed in 61 (84.7%) patients with abortion or failing PUL and in one (50%) patient with EP (p=0.300).

Receiver operating characteristic (ROC) analysis revealed that a decrease in hCG of 34% or more was the optimal cutoff for discriminating abortion or failing PUL from EP with a sensitivity of 93% and specificity of 89% (Figure 1). The area under the roc curve was 0.84. The diagnostic performances of several clinical parameters in discriminating the patients in Group 1 from the patients in Group 2 are shown in Table 4. Overall, a decrease in hCG of 35% or more on day 1 following D/C had the best diagnostic performance, with a sensitivity and specificity of 90% and 89%, respectively. The presence of chorionic villi in endometrial samples had the highest specificity and positive likelihood ratio, but it had low sensitivity (66%).

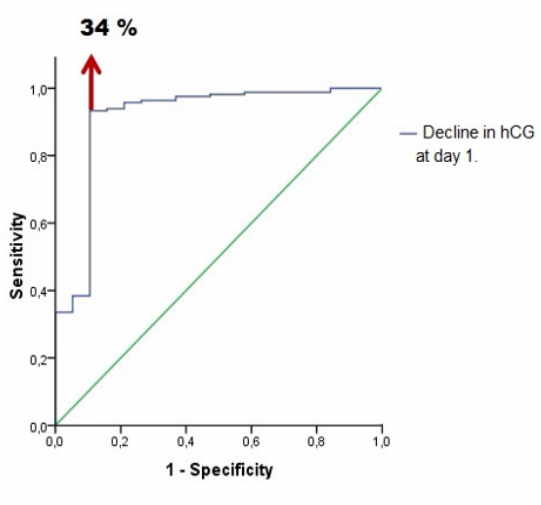

Figure 1. Receiver operating characteristic curve for hCG levels at day 1

DISCUSSION

The findings of the present study show that a decline in serum levels of hCG on postoperative day 1 is of value in discriminating between IUP and EP in patients who have undergone D/C. The mean decrease in the percentage of hCG was 50% in the patients with confirmed IUP, which was significantly higher than that of the patients with EP. The day 0 to day 1 decrease in percentage of hCG was also significantly higher in the patients with failing PUL than in the patients with EP. The optimal cutoff for day 1 decline in hCG was 34% as determined by ROC analysis. Retrospective analysis indicated a power of above 0.8 (0.9999) which indicated a low probability of type 2 error.

hCG levels have previously been shown to be effective for identifying the viability as well as the location of a pregnancy (13,14). In particular, the hCG dynamics of patients might help to distinguish EP from nonviable IUP and avoid unnecessary interventions. In a 2006 study, Cheng et al.(15) reported a decrease in hCG in managed pregnant patients with spontaneous miscarriages. The decline in hCG was altered by the initial values, but there was a consistent decrease of 70% on day 2 (15). The present data is not directly comparable to this study, as all of our patients underwent D/C, and the hCG decline on day 1 was analyzed instead of that of day 2. However, our study agrees with this work, as the decrease in hCG is of discriminatory value. In addition, the day 2 criterion is met earlier, on day 1, possibly due to the impact of the D/C. Similarly, Guha and associates have compared the performance of protocols based on single serum progesterone or repeated serum hCG levels in patients with PUL (16). The authors have compared hCH ratios at hour 0 and hour 48. In FPUL the ratio was 0.38 whereas in EP or IUP this ratio was over 1. Fistouris et al. have classified PUL according to four different hCG-based protocols (17). The authors have observed hCG ratios on admission and after 48 hours and have defined PUL as being high risk or low risk depending on hour 0/hour 48 ratio. In their study, Protocol B defined a hCG decline of 35-50 % and a rise of 53%. PUL cases within this category were classified as high risk and cases out of this range were considered low risk (either failin PUL or EP). This protocol had a sensitivity of 81 % and a specificity of 77 %. The diagnostic value of hCG ratio was lower but comparable to our study. This lower diagnostic yield may be due to no endometrial aspiration was performed in this study.

Table 4. Diagnostic performance of certain parameters to detect intrauterine pregnancy in the study population

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR + (95% CI)	LR - (95% CI)
Presence of chorionic villi	66 (59-73)	95 (74-100)	41 (22-61)	75 (53-90)	12.6 (1.9-85.4)	0.35 (0.28-0.45)
Endometrial thickness ≥9 mm	73 (66-80)	63 (38-83)	94 (89-97)	21 (12-35)	2.0 (1.10-3.63)	0.42 (0.27-0.64)
Decrease in hCG>35%	90 (84-94)	89 (67-99)	99 (95-99)	50 (32-68)	8.5 (2.3-31.6)	0.12 (0.07-0.19)
Decrease in hCG>50%	62 (54-69)	89 (67-99)	99 (93-99)	21 (13-32)	5.9 (1.6-21.9)	0.43 (0.34-0.55)

CI: Confidence Interval; PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR+: Positive Likelihood Ratio; LR-: Negative Likelihood Ratio; hr: Hours; hCG: Human Chorionic Gonadotropin

A decrease in hCG>35% was the most sensitive marker when compared with other markers (Table 4). It had a sensitivity and positive predictive value of 90% and 99%, respectively. In a previous study comprised of 23 patients with PUL, a decrease in hCG>50% within 24 hours after manual vacuum aspiration had a positive predictive value of 100% (7). In a recent work by Brady et al. the authors investigated 45 patients with pregnancy of unknown location (9). The mean percent hCG decline after endometrial sampling was 56.5%. hCG follow up after endometrial sampling had a positive predictive value of 94% when combined with presence of chorionic villi. Our findings are in agreement with both studies, although the optimal threshold differed in our study. Similarly Insogna et al, in their study, have found that in patients with failed intrauterine pregnancy, 100% demonstrated adequate post-sampling beta-human chorionic gonadotropin declines; villi were identified in just 46% (8)

The presence of chorionic villi had an overall sensitivity of 66% and specificity of 95% in the present cohort. Previous studies have reported sensitivities for presence of chorionic villi ranging from 46% -88% (7,9). The significant variance in the sensitivity of chorionic villi can be attributed to gestational age at diagnosis and to the presence of complete abortions in the cohort. In our patients the sensitivity of chorionic villi increased with increasing initial serum hCG. This finding is reasonable, considering that patients with a more advanced gestational age and incomplete miscarriages have a higher rate of trophoblastic tissue in endometrial samples. There was a single case of trophoblastic tissue reported out of 19 patients with EP. We considered it to be a false positive result because it is very unlikely that the patient had a heterotopic pregnancy, as she conceived without assisted reproduction and was free of complications during follow up.

The present study is among the few studies that have investigated the decline in hCG levels on postoperative day 1 in patients with a diagnosis of failing PUL who have undergone curettage for diagnostic and therapeutic purposes. As discussed above, these findings indicate that day 1 hCG is a useful diagnostic tool for the exclusion of EP. A controversy that can be raised regarding the design of the present study is the inclusion of failing PUL and miscarriage in the same category. However, considering that many patients with failing PUL actually have spontaneous miscarriage, it is logical to assign these patients to a single category. Doing so also allowed a ROC analysis that has stronger clinical implications.

The main drawbacks of the present study are its relatively low sample size and those inherent in all retrospective studies. In addition, a separate analysis of patients with failing PUL would have provided additional valuable information. However, such an analysis would have resulted in fewer patients in each group, which might have invited type 1 error.

CONCLUSION

As a result, the implementation of day 1 hCG can confidently aid the clinician to confirm a failing IUP and to rule out an EP in the early stages of pregnancy. This is especially important in busy hospitals, such as ours, where most of these patients are admitted during the night shifts. Obtaining day 1 levels has been shown to be a useful tool at our institution, where most of the patients are admitted during the night and are evaluated by senior residents.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki.

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