Research Article

Ultrasonic and Laboratory Predictors of Pregnancy Loss in Patients with Threatened Miscarriage: A Three-Year Observational Study

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Abstract

Objectives: The aim of this study was to assess the relation between different abnormalities of the yolk sac, serum level of Cancer Antigen 125 (CA-125) and serum level of Beta Human Chorionic Gonadotropin (β –HCG) as early predictors of first trimester pregnancy loss in patients with threatened miscarriage.

Methods: This prospective observational study was conducted on 292 pregnant women between six to 13 weeks of gestation who were suffered threatened miscarriage. Visualization of yolk sac and diameter were recorded by transvaginal ultrasound . Maternal serum CA-125 and β HCG were also measured. Pregnancy outcome was the main outcome measure. Data was collected and tabulated.

Results: There was highly Significant relation between YS size and pregnancy outcome (P<0.001). CA-125 and β-HCG were good predictors of miscarriage with accuracy 88%and 81.5% respectively.

Conclusions: Yolk sac size and maternal serum CA-125 and β-HCG are good predictors of pregnancy outcome in first trimester threatened miscarriage.

Keywords: Miscarriage; Cancer Antigen 125 (CA-125); Yolk sac; Beta Human Chorionic Gonadotropin (β-HCG)

1. Introduction

Miscarriage is defined as pregnancy loss before 20 weeks' gestation and remains the most common complication of early pregnancy [1]. The yolk sac appears at the fifth week of gestation and the diameter increases steadily (0.1 mm/d) until the end of the 10th week. The upper limit of a normal yolk sac diameter in pregnancies with a gestational age of 5 to 10 weeks was defined as 5.6 mm [2, 3].Typically, when the 10th or 11th week of gestation is completed; the yolk sac starts to degenerate and rapidly shrinks [4]. Cancer antigen-125 (CA-125) is derived from embryonic coelomic epithelium and was used as a predictive marker for spontaneous abortion or subsequent pregnancy outcome particularly in women with threatened miscarriage [5, 6]. Disruption of the epithelial basement membrane of the fetal membrane or of the decidua could theoretically lead to a rise in the maternal CA-125 level; this increase may be a predictor of subsequent spontaneous miscarriage [6]. Beta subunit human chorionic gonadotropin (β-HCG) is produced during pregnancy. It is made by cells that form the placenta. A low β-HCG level could indicate: miscalculation of pregnancy dating, possible miscarriage, blighted ovum or ectopic pregnancy. A high β-HCG level can indicate miscalculation of pregnancy dating, molar pregnancy or multiple pregnancy [7].

The aim of this study was to assess the relation between different abnormalities of the yolk sac, serum level of Cancer Antigen 125 (CA-125) and serum level of Beta Human Chorionic Gonadotropin (β –HCG) as early predictors of first trimester pregnancy loss in patients with threatened miscarriage.

2. Materials and Methods

This prospective observational study was conducted on 292 women who attended the Antenatal clinic or Emergency room at the Department of Obstetrics and Gynecology, Menoufia University Hospital during the period between the beginnings of August 2016 and August 2019. The study protocol was formally reviewed and approved by the local review board and ethics committee at Menoufia Faculty of Medicine with all patients signed the informed consent for prior to conducting the study. Patients presented with threatened miscarriage after thorough history taking, clinical examination and transvaginal ultrasound were included in the study. Patients with missed miscarriage, multiple pregnancies and with any type of medical disorders as diabetes mellitus and hypertension were excluded from the study.

All enrolled patients underwent the followings:

- Transvaginal ultrasound (Sonata Plus 2009-02, IBE Technology, International Biomedical Engineering Technologies; with vaginal probe multi frequency four to nine MHZ) to measure yolk sac size and diameter in addition to crown rump length. Scanning was done in both coronal and sagittal planes.
- Blood sampling: Maternal venous blood samples were collected in plain blood collection tubes containing EDTA as anticoagulant.β-HCG and CA-125 were measured using immune assay system. The ARCHITECT Total β-HCG and CA-125 assay is a two-step immunoassay to determine the presence of β-HCG and CA-125 in human serum and plasma using Chemiluminescent Microparticle Immunoassay (CMIA) technology with flexible assay protocols, referred to a Chemiflex.

Serial follow up visits of patients (twice weekly) was adopted if patients declined to be admitted to hospital till the 14th week of gestation or pregnancy loss has occurred; whatever earlier.

2.1 Statistical analysis

Results were statistically analyzed by SPSS version 22 (SPSS Inc., Chikago, IL, USA). Non paired t test was used for parametric data. Mann-Whitney test was used for non-parametric data. Chi-Squared (χ^2) and Fisher's exact tests were used for qualitative variables. Receiver operating characteristic (ROC curve) is a graphical plot of the sensitivity, vs. false positive rate (one minus the specificity). P value was considered significant if ≤0.05.

3. Results

Maternal characteristics including age, parity, body mass index and parity were depicted in table [1]. Beta Human Chorionic Gonadotropin was significantly lower in the group (YS size >5 mm) than the group (YS size ≤≤5 mm) (P< 0.001), while CA-125 was significantly higher in the group (YS size >5 mm) than the group (YS size ≤ 5 mm) (P< 0.001). There was highly Significant relation between YS size and pregnancy outcome (P<0.001) as demonstrated in table [2] and figures [1]. Gestational age and HCG were significantly lower in abortion group than complete pregnancy group (P=0.015 and < 0.001 respectively). But YS size, CA-125 and threatened abortion were significantly higher in abortion group than complete pregnancy group (P <0.001, <0.001 and 0.002) respectively as shown in table [3]. Yolk Sac size, CA-125 and β-HCG were a good detector of miscarriage with accuracy 70.6%, 88% and 81.5% respectively as shown in table [4] and figure [2].

General characteristics	**Study group (n=292)**
Age (Years)	
Mean ± SD	25.19 ± 5.64
Range	17.0-42.0
Body mass index (kg/ m²)	
Mean ± SD	29.12 ± 5.34
Range	20.30-45.40
Gestational age (weeks)	
Mean ± SD	7.06 ± 1.22
Range	5.0-10.0

Table 1: Maternal characteristics.

	Yolk sac size		**Mann-Whitney test**	**P value**
	>5mm No.=32	**≤5 mm No.=260**		
	Mean ± SD	**Mean ± SD**		
β HCG	17417.75 ± 6742.75	31098.62 ± 15975.51	3.60	<0.001**
Median	17301.0	28334.50		
Interquartile range	11751.50-21380.0	19178.0-40092.25		
CA 125	43.85 ± 13.87	27.93 ± 10.74	4.23	<0.001**

Median Interquartile range	44.0 33.0-54.77		29.05 19.70-32.80			
	no	**%**	**no**	**%**	**Fisher's exact**	**P value**
Outcome -Abortion -Ongoing pregnancy	 24 8	 75.0 25.0	 18 242	 6.9 93.1	53.61	<0.001**

Table 2: Distribution of the studied yolk sac group regarding β HCG, CA 125 and the pregnancy outcome.

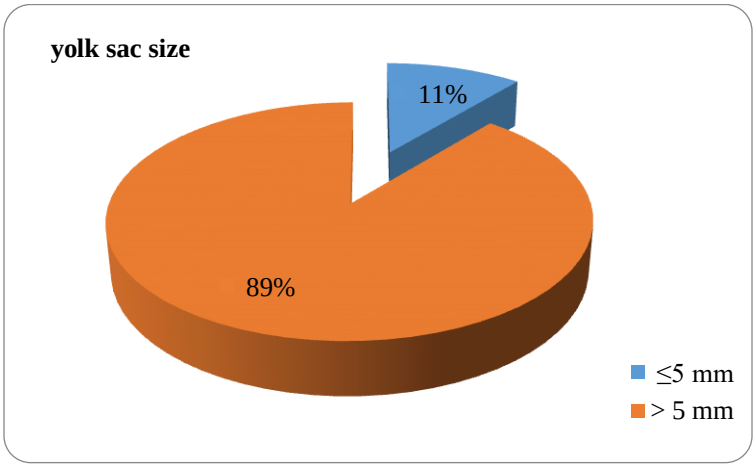

Figure 1: Distribution of the studied group regarding the size of yolk sac.

	Outcome				**Test of sig**	**P value**
	Abortion No.=21		**Complete pregnancy No.=125**			
	Mean ± SD		**Mean ± SD**			
Age (Y)	25.19 ± 6.41		25.20 ± 5.53		t= 0.01	0.994
BMI (kg/ M2)	28.69 ± 4.23		29.19 ± 5.52		t= 0.01	0.995
Gestational age (w)	6.47 ± 0.74		7.16 ± 1.25		Mann-Whitney 2.44	0.015*
Yolk sac size (mm)	0.61 ± 0.30		0.34 ± 0.10		Mann-Whitney 6.36	<0.001**
β HCG (mIU/ml)	12983.52 ± 3742.94		32390.80 ± 15350.59		Mann-Whitney 7.31	<0.001**
CA 125 (U/ml)	52.61 ± 9.76		25.82 ± 7.28		Mann-Whitney 7.09	<0.001**
Threatened abortion Yes	13	61.9	35	28.0	$\chi 2$	0.002*

No	8	38.1	90	72.0	9.37	
History of abortion					Fisher's exact	
Yes	18	85.7	105	84.0	0.04	1.0
No	3	14.3	20	16.0		

BMI =Body mass index; CA-125 =Cancer antigen 125; β HCG= Beta Human Chorionic Gonadotropin

Table 3: Comparison between results of the studied outcome regarding general and obstetric characteristics.

Variable	AUC	Cutoff point	Sensitivity %	Specificity %	Accuracy %	PPV %	NPV %
Yolk sac size	0.81	≥ 0.42	67	82	70.6	39	94
β HCG	0.93	≤ 20830	90.5	80	81.5	43	98
CA 125	0.98	≥ 33.25	95	87	88	55.5	99

Table 4: Validity of yolk sac size, B HCG and CA 125 regarding the outcome of pregnancy.

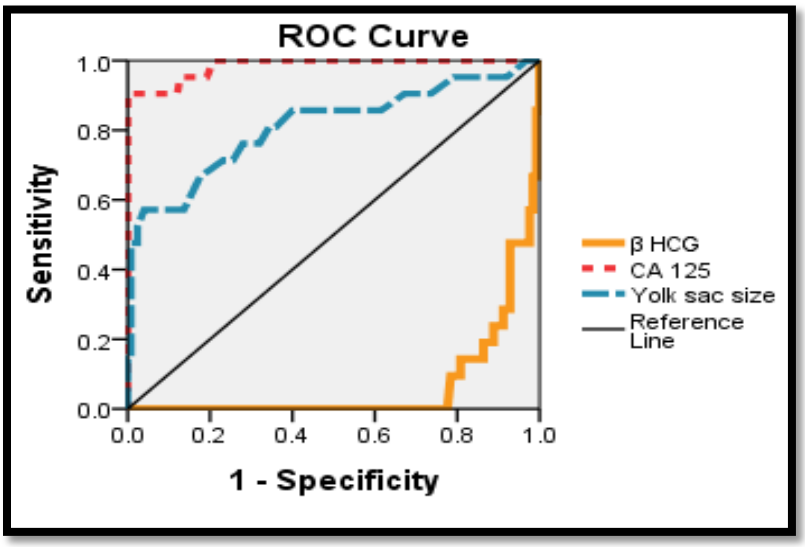

Figure 2: Roc curve for validity of yolk sac size, B HCG and CA 125 regarding the outcome of pregnancy.

4. Discussion

The clinical diagnosis of threatened miscarriage is presumed when any bloody vaginal discharge or bleeding appears during the first half of pregnancy; approximately half of women will abort [8]. In this study, yolk sac size, CA-125 and β-HCG were good predictors of pregnancy loss (spontaneous miscarriage). Yolk sac larger than five mm is a good indication that the probability of abortion will be significantly high [9-12]. A previous study on 305 pregnant women between the 6th to 9th weeks of gestation has revealed that an enlarged yolk sac visualized before the 7th week of gestation is strongly associated with a significantly increased risk for spontaneous miscarriage [10]. Revankar et al. [13] also stated that maternal serum CA-125 measurements appear to be a highly sensitive

laboratory marker in patients with viable pregnancy with first trimester threatened miscarriage. The sensitivity, specificity, positive predictive value and negative predictive value of serum CA-125 with a cutoff 60 IU/ml in predicting miscarriage was 43.5%, 100%, 100%, and 67.5% respectively. Also, Maged et al. [14] support our study, they stated that the CA-125 and HCG were significant predictors of miscarriage in their study which done on 250 pregnant women. The sensitivity, specificity, positive predictive value and negative predictive value of serum CA-125 at the level of 80 IU/ml was 80.2%, 78.3%, 69.6% and 82.4% respectively. The sensitivity, specificity, positive predictive value and negative predictive value of serum HCG at the level of 19887 mIU/ml was 66.6%, 81.1%, 75.6% and 89.9% respectively.

More recent studies confirmed that serum β- HCG is a good predictor of miscarriage [15-17]. On the other hand, many other studies disagree with using yolk sac size [18-20] or laboratory markers either CA-125 [21] or β- HCG to be valuable for predicting pregnancy outcome in first trimester threatened miscarriage. These differences may be attributed to different patient populations, different clinical scenarios as well as different ultrasonic and laboratory testing techniques. The large cohort included and uniform protocol of follow up, constitutes the main strength of the current study. Inability to include a control group was unintended limitation of this study secondary to costly laboratory tests. Future research should explore the cost-effectiveness of combined testing for prediction of pregnancy outcome in patients with first trimester threatened miscarriage in a multicentre design.

5. Conclusions

Yolk sac size and maternal serum CA-125 and β-HCG are good predictors of pregnancy outcome in first trimester threatened miscarriage.

Conflict of interest

None declared.

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