Correlation of serum markers and ultrasound markers in the prediction of threatened miscarriage outcome

Mohammed El-Husseny Radwan

Obstetrics & Gynecology Department, Faculty of Medicine, Zagazig University, Egypt
hussenyradwan@gmail.com

Abstract: Objective: The aim of the present investigation is to explore the linkage between sonographic findings, progesterone level and serum CA-125 in women presenting with symptoms of threatened pregnancy loss and first trimester pregnancy outcome. **Methods:** The study was conducted on 120 pregnant females through a prospective study. The data was obtained from pregnant females attending to antenatal obstetric outpatient clinic in Zagazig University Hospital through a designed questionnaire. **Results:** No significant difference was recorded between groups in maternal age, BMI, gestational age, residence and Parity. Actual miscarriage significantly high in threatened miscarriage group as it had a percent of 35% among cases and 15% among controls who all were presented with threatened abortion. Cases were significantly higher regard CA 125 with a level of 35.06 IU/ml (±19.76) among cases and 15.05IU/ml (±9.85) among controls and significantly lower regard progesterone level as it was 8.02ng/ml (±4.69) among cases and 14.91 ng/ml (±7.36) among controls. There was no significant difference among groups in CRL and GSD but YSD was significant higher among cases. CA 125 significantly higher in actual miscarriage with a level 47.9IU/ml (±31.52) between those who had actual miscarriage before 13 weeks and 17.4IU/ml (±10.67) between those who continued pregnancy after 13 weeks while progesterone showed level 11.1ng/ml (±10.38) between those who aborted before 13 weeks and a level of 11.6ng/ml (±6.19) between those who continued. GSD and YSD significantly higher in actual miscarriage as the mean was 51.4mm (±18.56) and 6.73mm (±0.6) respectively for those who aborted and 38.52mm and 6.11mm respectively for those who continued pregnancy. **Conclusion:** The use of the transvaginal sonography biomarkers (maternal serum CA-125 and progesterone level) in the first trimester of pregnancy is an early and rapid non-surgical method that can be considered as a good indicator of pregnancy outcomes in cases of threatened abortion.
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1. Introduction:

First-trimester bleeding has long been considered one of the most commonly encountered obstetric problems, as it affects about 25% of all pregnancies **(Cunningham et al., 2010).** Threatened miscarriage is clinically suspected if bleeding occurs during the first half of pregnancy but through a closed cervical os **(Johns et al., 2006)**. Missed abortion (MA) is a possible event in ≤15% of clinical pregnancies and characterized by delayed evacuation of conception products **(Le, 2008).** Age extremes (more commonly > 35 years), prolonged exposure to stress, prior miscarriage, abnormal uterine anatomy (presence of adhesions or tumors) and use of substances like cigarettes, alcohol, and certain drugs are well known risk factors **(Maconochie et al., 2007).** In natural conceptions the most reliable biochemical pregnancy outcome parameter is early pregnancy measured serum progesterone **(Elson et al., 2003).** When the relation between serum progesterone and susceptibility of the first trimester pregnancy loss is evaluated, excluding pregnancies with medical progesterone support is of paramount importance to avoid misleading results **(Vicdan et al., 2001).** Low body mass index, lower progesterone levels prior to miscarriage and obesity are known to be significant risk factors **(Arck et al., 2008).** Multiple biomarkers like serum cancer antigen 125 and progesteronne had been studied as tools to identify healthy gestations **(Rubio et al., 2003).** It is reported that low hCG concentrations in threatened miscarriage is a predictor of unfavorable outcome for the pregnancy. Also, first trimester lower progesterone concentration is also valuable in this context but its level exhibits narrow variation between normal and abnormal cases **(Melissa et al., 2015).** Transvaginal ultrasonography, is the most valuable tool used in early pregnancy evaluation. Direct visualization of the products of conception and the possibility of any remnants through their natural, medical or surgical evacuation **(Jeve et al., 2011).** Distortions in both shape and size of pregnancy sac and / or fetus had been evaluated by several authors **(Angiolucci et al., 2011)**. Despite the importance of yolk sac (YS), the first

ultrasonographically obvious structure within the gestational sac, has not been well studied intensity. The YS is charecterized as a circular structure, composed of an anechoic center, and surrounded by anechogenic, round, regular and well-defined verge. It is the initial origin of fetomaternal exchange prior the creation of placental circulation **(Jauniaux et al., 2005)**. Its functions include variable roles in early embryogenesis like hematopoietic, nutritional, metabolic, endocrine, and immunologicwhich are indispensable for healthy gestation **(Pereda et al., 2008)**. Abnormal early embryogenesis **is re**flected in YS morphology and size **(Kupesic et al, 2001)**. Reference measurements for the YS size, that reaches maximum at the tenth week, then decreases had been subject of research by **Bagratee et al. (2009)**. Evaluation of YS size had proven valuable either in prediction or even etiological diagnosis of presumed miscarriage **(Angiolucci et al., 2011)**. Of novel methods for effective screening is combining maternal history and measures of the uterine artery plasticity index (PI) at 12 weeks of pregnancy **(Nicolaides et al., 2011).**

2. Patient and Methods:

All participants were recruited from gynecological & obstetric department in Zagazig university hospital from May 2015 to April 2016. A written informed consent form was signed by each participant before participation with explanation of the strategy of research. Approval of the study design by Ethical Committee was obtained according to local regulations.

Type of study:

This is a case-control study included a total of 120 pregnant patients at 7 and 13 weeks of pregnancy that a singleton embryo with visible cardiac pulsation were included in the study half of them are control group with uneventful pregnancy without any problem and the other 60 patients having threatened abortion, 21 cases of the 60 cases ended by constituting threatened abortion "aborted" group (35%) and 39 cases (65%) continued constituting threatened abortions "continued" till 20 weeks of gestation. Exclusion criteria included cases suffering from medical disease such as diabetes, thyroid disease or antiphospholipid syndrome, presence of uterine malformations e.g. sepate uterus diagnosed by history of recurrent miscarriage, HSG or 3D ultrasound, existence of local (gynecological) disease as fibroid or adnexal masses excluded by normal semblance of both uterus and ovaries by ultrasound, intake of natural or synthetic progesterone, exposure to local trauma (abdominal or sexual), patients with other pathologies that increase in CA-125 level are excluded like endometriosis.

Statistical analysis:

Data aggregation from history, medical evaluation, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) **(Statistical Package for the Social Sciences)** software to be data analyzed.

3. Results:

Table (1): Patients' Characteristics; maternal age, gestational age, BMI, residence and parity ((n=120).

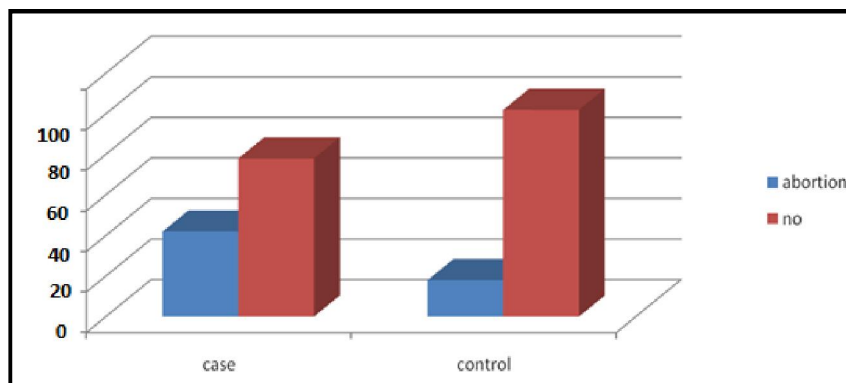|		Cases (n=60)	Control (n=60)	*P*-value
Maternal age (years) Mean (±SD)		27.05(±3.31)	26.5(±4.01)	0.414
BMI (Kg/m2) Mean (±SD)		26.5(±2.96)	26.3(±3.59)	0.555
Gestational age (weeks) at time of recruitment Mean (±SD)		9.2(±1.79)	9.00(±2.13)	0.58
Residence	Rural	48 (80%)	42 (70%)	0.21
	Urban	12 (20%)	18 (30%)	
Parity	nulliparous	15 (25.0%)	12 (20.0%)	0.85
	Para 1	18 (30%)	18 (30%)	
	Para 2	12 (20%)	12 (20%)	
	Para 3	12 (20%)	12 (20%)	
	Para 4	3 (5%)	8 (10%)	

Figure (1): Actual miscarriage significantly high in threatened miscarriage group as it had a percent of 35% vs. 15%

Table (2): Progesterone and CA 125 level among cases and control.

	Cases (n=60)	Control (n=60)	*P*-value
Progesterone level (ng/ml) Mean (±SD)	8.02(±4.69)	14.91(±7.36)	0.00**
CA 125 (IU/ml) Mean (±SD)	35.06(±19.76)	15.05(±9.85)	0.00**

** Highly significant.

Table (3): Difference in CRL, GSD and YSD between cases and control groups.

	Group	N	Mean	Std. Deviation	t/ Mann Whitney	*P*
CRL	**Cases**	60	23.81	11.2	-0.46	0.64
	Controls	51	24.84	12.22		
GSD	**Cases**	60	42.12	15.04	0.38	0.69
	Controls	54	40.96	16.91		
YSD	**Cases**	60	6.37	0.52	2.01	0.05*
	Controls	42	6.13	0.24		

* Significant difference.

Table (4): Progesterone and CA 125 level among actual miscarriage before 13 weeks and continued pregnancy after 13 weeks.

	Actual miscarriage before 13 weeks (n=30)	Continued Pregnancy after 13 weeks (n=90)	*P*
Progesterone level (ng/ml) Mean (±SD)	11.1 (±10.38)	11.6 (±6.19)	0.76
CA_125 (IU/ml) Mean (±SD)	47.9(±31.52)	17.4 (±10.67)	0.00**

Table (5): P value of CRL, GSD and YSD in actual miscarriage before 13 weeks and continued pregnancy after 13 weeks.

	Actual miscarriage before 13 weeks (n=30)	Continued pregnancy after 13 weeks (n=90)	P
CRL (mm) Mean (±SD)	27.46(±16.55)	23.26(±9.46)	0.10
GSD (mm) Mean (±SD)	51.40(±18.56)	38.52(±13.72)	0.00**
YSD (mm) Mean (±SD)	6.73(±0.6)	6.11(±0.23)	0.00**

4. Discussion:

In this study, the women of the two study groups did not show any statistically significant difference as regards patient characteristics (maternal age, BMI, gestational age, residence and parity) as shown in Table (1).

These findings running in agreement with prospective cohort Iranian study done to characterize the pregnancy outcome in pregnant women who present with symptoms of threatened with abortion. It was carried out on 1000 pregnant women, 500 of them had a classic history suggestive of threatened miscarriage through the first four months of pregnancy, while the women in control group are not having any of that history. The two groups of cases and control were observed strictly from 20 weeks of pregnancy until delivery. The examined patients of the two groups did not show any significant differences regarding to age and parity **Dadkhah et al. (2010)**.

Maged and AI Mostafa (2013) conducted a study comparing three groups two of them with threatened abortion one aborted the other continued and the third group with uneventful pregnancy. They showed no significant differences in the studied parameters (age, parity, BMI and gestational age) among the study groups.

Figure (1) shows that actual miscarriage was significantly higher in threatened miscarriage group as in cases it was 21/60 (35%) and in controls it was 9/60 (15 %) this is in accordance with **Falco et al. (1996)** that investigated the relationship between sonographic findings and the occurrence of abortion between two groups with threatened abortion one continued and the other aborted in both fetal cardiac activities was documented upon admission. The prevalence of abortion was 23/149 (15%).

Table (2) presented cases with significantly higher level regarding CA 125 and significantly lower level regarding progesterone.

As Serum CA-125 level was higher in threatened abortion group (mean values were 35.06(±19.76) IU/ml) in control group 15.05(±9.85) IU/ml). Highly significant difference was observed between each of the threatened abortion and control group as (p= 0.00) while progesterone levels showed lower values in threatened abortion group as mean values were 8.02(±4.69) IU/ml in control group 14.91(±7.36).

This is running in accordance with **Sweed et al. (2016)** who performed a study between 120 women with threatened abortion (cases) and 60 women with no past or present history of bleeding in current pregnancy (controls). CA125 level indicated a statistically significant difference among the study groups as mean was 25.45 versus. 35.1 IU/ml for controls versus cases respectively.

Hamed et al. (2016) conducted a prospective study between a group of 80 pregnant women with normal cycles before pregnancy 41 of them, were primigravida (controls) and 39 with previous history of abortion (cases). They reported that serum CA125 was higher in the threatened miscarriage group as (mean values were 23.26(±2.29) IU/ml) and (mean values were 19.21(±1.37) IU/ml) in the control group and for progesterone it showed lower levels in pregnant with previous abortion as mean values were (26.55(±1.36) IU/ml) and in primigravida group they were (32.46(±2.07) IU/ml).

Table (3) shows insignificant difference between groups regarding GSD 42.13(±15.04) for cases and 40.96(±16.92) for controls and CRL23.81 (±11.20) for cases and (24.85(±12.23) for controls but YSD 6.38 (±0.52) for cases and 6.13(±0.24) for controls shows difference as cases were significant higher.

The upper limit of normal yolk sac diameter in the early first trimester is approximately 4.5 mm when measured inner-inner **(Lindsay et al., 1992)**, and 6mm when measured outer-outer **(Cepni et al., 1997)**. A large yolk sac is an indicator of poor prognosis. Although the causal relationship between a large yolk sac and pregnancy prognosis is unclear, a number of studies have observed direct relationship between YS diameter especially >7mm and pregnancy failure **(Lindsay et al., 1992 and Stampone et al., 1996).**

A study conducted by **Oun et al. (2016)** compared between two groups with threatened abortion one continued and the other aborted. They reported that no significant difference among groups as regards gestational age by ultrasound and the crown rum length which agree with this study. In contrast to gestational sac diameter as there was statistically significant increase in who continued pregnancy to those who aborted (3.57±0.49 vs. 3.10±0.27 cm respectively)

Maged and AI Mostafa (2013) presented a study indicating lack of significant association between the studied groups as regards gestational or yolk sac diameters. The first group was presented by threatened abortion ended by abortion, second was presented by threatened abortion but continue pregnancy and the last one presented with normal pregnancy. **Oh et al. (2002)** prospectively evaluated GSD at early gestation in sixty seven patients specifically at 4th to 5th weeks dated from 1st day of LMP. Term gestation (n = 32) or involuntary abortion (n = 35) Are the two awaited outcomes. Comparing MSD in both groups data revealed lack of significant association between both groups (2.6 mm vs. 2.7 mm).

Reljic (2001) prospectively studied 310 cases, presenting with threatened termination prior 13 weeks of pregnancy among 310 cases. Significant positive

association was observed between deficit in the CRL for pregnancy and the extent of recurrent idiopathic pregnancy loss particularly in foetuses with CRL < 18mm.

Study found that of 50 patients suffering from first-trimester bleeding and a gestational sac ≤16 mm 32 (64%) underwent miscarriage. **Falco et al. (2003)** recorded a high level of statistical significance in size of gestational sac (p value 0.023).

Table (4) shows that Serum CA-125 levels were higher in threatened abortion aborted group (mean values were 47.9(±31.52) IU/ml) than continued group (mean value 17.4 (±10.67) IU/ml). On the other hand, a significant difference between each of the threatened abortion aborted and continued groups as (p 0.00) was observed.

These findings are running in accordance with most studies: **Ayaty et al. (2007)** compared levels of CA-125 in 50 healthy pregnant women (first group) and 50 threatened miscarriage women (second group) with special emphasis on final outcome of pregnancy. Mean CA-125 level in group 1 was noticed to be lower in comparison with group 2 26.2 ± 3.25 IU/ml vs. 37.44 ± 2.72 IU/ml respectively. Also higher mean CA-125 level in failed pregnancy patients compared with normal pregnant patients, 58.17±7.25 IU/ml Vs. 26.61±1.76 IU/ml. on the other hand, the CA-125 level in threatened miscarriage group that kept pregnancy 30.89 IU/ml.

A significant differences between mean serum CA-125 in the cases, that their pregnancy was aborted prior 20th week of pregnancy, (58.7 ± 7.25IU/ml) and in favourable pregnancy group (26.61 ± 1.76 IU/ml) (p= 0.000).

Also, significant differences were recorded between studied groups as regards the final mean serum CA-125 level in cases that was aborted (12 cases) was 58.17 ± 7.25 IU/ml and in those with favorable pregnancy after 20th weeks of gestation (38 cases), was 30.89 ± 2.93 IU/ml (p < 0.01).

Fiegler et al. (2003) reported that determination of CA-125 level is valuable in women with imminent termination accompanied with abdominal pain, vaginal bleeding or both.

Kamiński et al. (2002) reported that patients with threatening miscarriage showed higher values of serum CA 125 antigen more than patients in control group. The women that were characterized by highest values of the antigen later miscarried.

Sherif et al. (2000) evaluated 57 women who threatened to abort, but whose pregnancy continued 43 patients having the same history ending with pregnancy failure compared to 50 control patients and a highly significant raise in serum CA125 level in the first group in rapprochement with other two groups (P <0.001). A fairly sensitive and specified indicator of

pregnancy outcome in threatened miscarriage is CA-125.

Azougi et al. (1996) stated that cancer antigen-125 measurement in maternal serum serves as an accurate predictor of the eventual outcome in early pregnancies who are complicated by vaginal bleeding even with a proven fetal viability and a demonstrable fetal heart motion on ultrasonography. In their study, all pregnancies complicated with first trimesteric bleeding who had serum values of CA-125 above 125 IU/ml, with a mean value of 133±4.8 IU/ml ending with pregnancy failure, while the mean value for those who had a successful pregnancy outcome was only 36.9±20 IU/ml indicating significant difference.

It was reported that estimation of single serum of CA 125 in first trimester pregnant women is not valuable tool to distinguish idiopathic, missed, threatened abortion, ectopic or normal pregnancies but sequential measurements of maternal CA 125 was highly accurate prognostic predictor in cases with threatened miscarriage **Schmidt et al. (2001)**.

Ocer et al. (1992) studied 25 cases of threatened abortion and 25 control pregnancies to evaluate value of serum CA125 measurement and concluded that mean serial values of serum CA125 level in women with unfavourable pregnancy outcome was significantly higher than that of the patients with a favourable outcome. It is probable that direct relation between decidual destruction and CA125 measurement in threatened miscarriage which may be linked to pregnancy outcome.

The results of this study disagreed with **Mahdi (2010)** who found insignificant difference between two groups in spite of its higher level in aborted group. This may refer to the small number of the patients included in the study as only forty-two pregnant women were recruited in this study. The mean measurement of CA-125 indicated higher value for the group that ended the pregnancy with involuntary abortion (39.9 ± 15.4), in relation to the other group that continued pregnancy (20.03 ± 4.5).

Table (4) also shows the role of progesterone value in evaluating prognosis of first trimester pregnancy loss. Serum progesterone levels were nearly the same in threatened abortion, continued pregnancy after 13 weeks (mean values were 11.6 (±6.19) IU/ml) compared with (mean value 11.1 (±10.38) IU/ml) in the second group according to the statistical analysis, no significant difference between the two studied groups was observed (p=0.756).

Our results were on contrary with **Edwar et al. (2011)** who studied 78 pregnant women presented by vaginal bleeding 44 continued pregnancy and 34 ended with spontaneous abortion. Highly significant difference (p value<0.000) in serum progesterone level was observed 5.7+10.9 in continuing pregnancy

and 6.7+4.8 in involuntary abortion which contradict our results.

The study of biomarkers and ultrasongrahic predictors of outcome in involuntary threatened miscarriage presented by **Maged and AI Mostafa (2013)** observed a significant difference between the study groups as regards the level of progesterone with lower level in the first group. Mean values 20.4 (±6.78) IU/ml in aborted group and 39.6 (±10.86) in continuing pregnancy group.

Hamed et al. (2016) reported that progesterone was lower in aborted group 19.51 (±2.66) than in continuing pregnancy group 35.29 (±2.16), with P=0.004 which is highly significant.

This disagreement caused as in the present study progesterone was measured just one time at the time of recruitment while its regular measurement more than once shows its significance.

Our study showed that Abortion is associated with high parity and was not affected by either maternal age 28.40 (±3.38) for Actual miscarriage before 13 weeks group 26.23 (±3.62) for Continuing pregnancy after 13 weeks group, residence or BMI 28.68 (±2.48) for Actual miscarriage before 13 weeks group 25.95 (±3.56) for Continuing pregnancy after 13 weeks group.

This agrees with **Oun et al. (2016)** who reported that maternal age was 25.96 (±2.14) in those continued pregnancy and 26.75 (±2.98) in those who aborted but disagree regarding parity as their study showed no significance.

5. Conclusion & recommendations:

First trimester combination of ultrasound and maternal serum CA-125 in the represent non-invasive, early and fast methods that can be considered as a useful tool in predicton ofthe pregnancy outcome among threatened miscarriage patients.

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