# Prediction of pregnancy outcomes with combined ultrasound scanning of yolk sacs and serum CA 125 determinations in early threatened abortion

**Y.J. Xie, M. Chen, S.J. Chen**

*Department of Ultrasonography, the First Affiliated Hospital of Henan University of Science and Technology, Luoyang (China)*

**Summary**

*Objectives:* To assess the predictive value of the combination of ultrasound scanning, yolk sacs and CA125 levels for pregnancy outcomes in early threatened abortion. *Materials and Methods:* A total 196 pregnant women at less than 12 weeks gestation were enrolled. They were assigned into: (A) normal pregnancy (n = 61); (B) early threatened abortion but with favorable outcomes after active treatment (n = 56); (C) pregnancy with spontaneous miscarriage and threatened abortions (n = 79). The yolk sacs were examined and serum CA125 levels were measured. *Results:* The visualization rate in groups A and B were significantly higher than that in group C. For the mean yolk sac diameter, there was a statistically significant difference between groups A and C ($p < 0.05$), B and C ($p < 0.05$), but no statistically significant differences were observed between A and B ($p > 0.05$). The mean serum CA125 levels were significantly different ($p < 0.05$) among three groups. The sensitivity, specificity, and Youden Index for predicting adverse outcomes using irregular shape, abnormal size, or non-visualization of the yolk sac were 81.01%, 85.71%, and 0.67, respectively. *Conclusion:* The combination of ultrasound scanning of yolk sacs and measurement of serum CA125 levels is of great value for predicting pregnancy outcomes.

*Key words:* Ultrasound scanning; Yolk sacs; CA125.

## Introduction

Early threatened abortion is the most common complication in the first trimester of pregnancy; it presents as vaginal bleeding and/or cramping, which occurs in about a fifth of cases. About half of the women with early threatened abortion will be normal after positive clinical treatment, and the other half will have a miscarriage. Occasionally, bleeding may persist for weeks; thus, it becomes necessary to determine the possibility of continuing the pregnancy.

In the gestational sac, the earliest sonographic finding is the yolk sac, which can always be detected as a round anechoic area between the fifth and 12$^{th}$ week of pregnancy; rarely, it can be identified until the end of pregnancy.

The tumor marker CA 125, discovered using monoclonal antibodies against cells derived from the ovarian cancer cell line OVLA 433 [1], is present at high concentrations in human amniotic fluid throughout gestation [2]. Extracts of human decidua and chorion have been found to contain significant quantities of CA 125. In contrast, serum CA 125 levels are low in both maternal and fetal blood, and very little is found in the amnion and trophoblasts [3]. During the first trimester of pregnancy, serum CA 125 increases modestly, frequently reaching a peak value and then returning to its non-pregnancy range in late pregnancy.

The present study was performed to assess the value of the ultrasound scanning of yolk sacs and measuring CA125 levels, respectively, in predication of pregnancy outcomes of early threatened abortions. The authors then estimated the value of predicating pregnancy outcomes with the combination of the two indexes. The sensitivity and specificity were also calculated.

## Materials and Methods

The present study was conducted in the First Affiliated Hospital of Henan University of Science and Technology. A total of 196 women in their first trimester of pregnancy were referred to the study center between October 2008 and May 2009; women with multiple pregnancies, impregnated by artificial insemination, with abnormal uterine development, and those with a history of smoking, hypertension, and diabetes were excluded. The study was conducted in accordance with the Declaration of Helsinki and approval by the People's Hospital of the First Affiliated Hospital of Henan University of Science and Technology. Informed written consent was obtained from all subjects. All pregnancies were examined through ultrasonography using a Voluson 730 real-time scan system, with a carrier frequency of 5-10 MHz for the vaginal probe. Gestational age was determined by ultrasonographic measurements of gestational sac diameter and fetal crown-rump length. The yolk sac diameter (YSD) was determined by placing the calipers on the inner limits of the longer diameter. Meanwhile, venous blood samples were collected from all pregnancies, which were centrifuged at 3,000 rpm and stored at –20°C. The CA125 levels were measured using commercial ReadyPack kits.

All pregnancies were followed for survival until 28 weeks by either a subsequent ultrasound scan or a telephone interview. According to the pregnancy outcomes, the women were divided into three groups. The first (A) group included 61 women with normal pregnancy, whereas the second (B) group was composed of 56 women who experienced early threatened abortion but with fa-

Revised manuscript accepted for publication June 18, 2013

vorable outcomes after active treatment. Meanwhile, 79 women whose respective pregnancies resulted in spontaneous miscarriage with threatened abortion were assigned into the third (C) group.

Statistical analysis was performed using SPSS 11.5 software. For continuous variables, the comparisons among groups were evaluated using analysis of variance (ANOVA). Determination of the significance of the differences between proportions for the count data was through a $\chi^2$ test. *P*-values less than 0.05 were considered statistically significant.

## Results

The mean age (ranging from 20 to 44 years) and mean gestational age (ranging from five to 12 weeks) of the three groups were calculated and they are shown in Table 1. There were no significant differences among the three groups ($p > 0.05$).

The yolk sac visualization rate in the three groups is shown in Table 2. The yolk sac was visualized in 56/61 cases (91.8%) in group A and 48/56 (85.71%) in group B, which are in contrast to 26/79 (32.91%) in group C. Therefore, significant differences were observed between groups A and C ($p < 0.05$) and between groups B and C ($p < 0.05$). No significant difference ($p = 0.381 > 0.05$) was observed between groups A and B.

The YSDs of women in the three groups are shown in Table 3. The mean diameter, maximum diameter, and minimum diameter of group A were 4.02, 6.10, and 2.86 mm, respectively; for group B, they were 3.72, 5.8, and 2.24 mm, respectively; and for group C, 5.34, 10, and 1.8 mm, respectively. Accordingly, a significant difference was observed between groups A and C ($p < 0.05$) and between groups B and C ($p < 0.05$), but there was no significant difference between groups A and B ($p > 0.05$). The mean YSD in the three groups by week are illustrated in Figure 1.

The serum CA125 levels of women in the three groups were measured and they are depicted in Table 4. The mean level, maximum level, and minimum level in group A were 17.38, 23.12, and 11.68 U/ml, respectively; in group B, 25.73, 60.74, and 17.57 U/ml; and in group C, 57.63, 84.47, and 45.64 U/ml, respectively. There was a significant difference among the three groups, and the trend of the serum CA125 in the three groups by week is presented in Figure 2.

The sensitivity, specificity, and Youden Index of the ultrasound scanning of the yolk sacs and the serum CA125 levels, and the combination of the two are shown in Table 5.

Table 1. — *The basic information of women among three groups.*

| Group | N | Mean age (years) | Mean gestational age (weeks) |
|---|---|---|---|
| A | 61 | 27.58 ± 3.3 | 7.8 ± 1.25 |
| B | 56 | 28.13 ± 3.5 | 7.9 ± 1.32 |
| C | 79 | 27.51 ± 3.2 | 8.2 ± 1.42 |

Table 2. — *The visualized rate of women in the three groups (%).*

| Group | N | Visualized | Not visualized |
|---|---|---|---|
| A | 61 | 56 (91.80) | 5 (8.20) |
| B | 56 | 48 (85.71) | 8 (14.29) |
| C | 79 | 26 (32.92) | 53 (67.08) |
| Total | 196 | 130 (66.32) | 66 (33.68) |

Table 3. — *The yolk sac diameter of women in three groups.*

| Group | N | Mean diameter (mm) | Max diameter (mm) | Min diameter (mm) |
|---|---|---|---|---|
| A | 61 | 4.02 ± 1.12 | 6.10 | 2.86 |
| B | 56 | 3.72 ± 1.23 | 5.80 | 2.24 |
| C | 79 | 5.34 ± 1.46 | 10.00 | 1.80 |

Table 4. — *The serum CA125 levels of women in three groups (U/ml).*

| Group | N | Mean level (U/ml) | Max level (U/ml) | Min level (U/ml) |
|---|---|---|---|---|
| A | 61 | 17.38 ± 6.02 | 23.12 | 11.68 |
| B | 56 | 25.73 ± 7.34 | 60.74 | 17.57 |
| C | 79 | 57.63 ± 9.08 | 84.47 | 45.64 |

Table 5. — *The predictive rate of three indexes' comparison.*

| Item | Sensitivity (%) | Specificity (%) | Youden index |
|---|---|---|---|
| Yolk sac | 81.01 | 85.71 | 0.67 |
| CA125 | 91.14 | 83.93 | 0.75 |
| Yolk sac+ CA125 | 98.32 | 71.94 | 0.70 |

## Discussion

The present study is one of few to assess simultaneously the yolk sac through ultrasound scanning and the serum CA125 level during the first trimester of pregnancy.

Revolutionary technologic improvements and high-frequency transvaginal scanning have enabled the resolution of ultrasound imaging in the first trimester to increase, such that detailed early fetal development can now be well visualized [4]. Transabdominal ultrasound provides little information regarding the fetus before the eighth week of pregnancy. Transvaginal ultrasound can identify earlier the yolk sac, fetus, and embryonic cardiac activity, and can confirm intrauterine pregnancies at younger gestational ages [5]. In the present study, transvaginal ultrasound was performed in women at less than eight weeks gestation, and transabdominal or transvaginal ultrasound in women with more than eight weeks gestation in the trimester.

In a gestational sac, the earliest ultrasonographic finding is the yolk sac. A yolk sac with abnormal or irregular shape

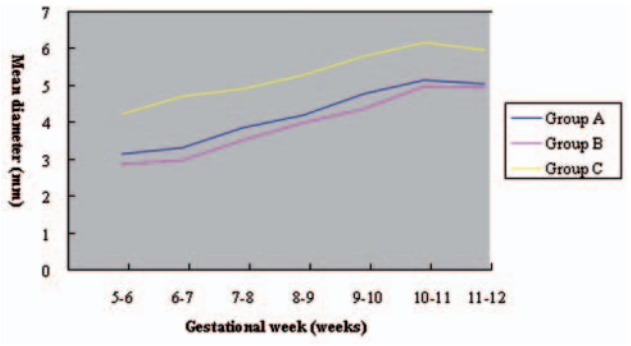


Figure 1. — The trend of the mean yolk sac diameter of women in three groups by week.

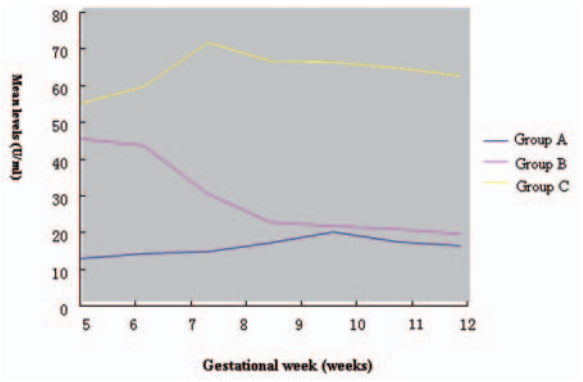


Figure 2. — The trend of mean serum CA125 levels of women in three groups by week.

that is not detected by transvaginal ultrasonography or is either too small or too large usually indicates adverse pregnancy outcomes.

The yolk sac is a round, sonolucent structure with a bright rim. However, transvaginal ultrasonography can be used to survey abnormally shaped yolk sacs, which generally results in poor outcomes [6]. In the present study, five women experienced adverse pregnancy outcomes because of abnormally shaped yolk sacs.

The yolk sac first appears during the fifth week of pregnancy. A yolk sac that is not visible under vaginal ultrasonography between five and ten complete weeks menstrual age is an indicator of a developmental disturbance during early pregnancy [7]. In the present study, the visualization rate in group A was 91.8% (in 56/61 cases), which is very close to the previous study, which indicates that with a reliable gestational age between five to ten weeks, the yolk sac is recognized in 158 of 172 normal pregnancies (91.9%) [7]. In group B, the yolk sac was visualized in 48/56 cases (85.71%). In contrast, the visualization rate was 32.92% (in 26/79 cases) in group C, which is in accordance with a previous study [7]. The five cases in group A and eight cases in group B wherein the yolk sacs were not visualized during ultrasound scanning resulted in favorable pregnancy outcomes based on the authors' follow up. However, all 53 women with non-visualized yolk sacs in group C ended in spontaneous abortion. Using statistical analysis, no significant difference was observed between groups A and B, but significant differences were observed between groups A and C ($p < 0.05$) and between groups B and C ($p < 0.05$).

Through ultrasound scanning, the YSD was determined by placing the calipers on the inner limits of the longer diameter. Normal-sized yolk sacs are usually indicative of favorable pregnancy outcomes, whereas abnormal-sized yolk sacs (too large or too small) are usually indicative of inevitable abortions. In the present study, in group A, the increase in YSD was found to be correlated with advancing gestational age, which is consistent with prior studies [8, 9]. Based on the results, 56 visualized yolk sacs had a mean diameter of 4.02 mm, which is in accordance with a previous finding that demonstrated that the mean YSD of normal pregnancy is within four to five mm [10]. Only one yolk sac with a diameter exceeding six mm was detected, which is quite close to the results of a study that stated that a yolk sac diameter exceeding six mm was observed in five of 253 normal pregnancies (2.0%) [7]. In group B, the mean diameter of 48 visible yolk sacs is 3.72 mm, which is slightly smaller than that in group A. However, statistical analysis revealed no significant difference between groups A and B ($p > 0.05$). In group C, among the 26 visualized cases, nine women who had YSDs exceeding six mm, which is in accordance with a previous statement, argued that YSDs above six mm can serve as an indicator of developmental disturbances in early pregnancy [7]. Up to 15 women with normal-sized yolk sacs and two women with small-sized yolk sacs had adverse pregnancy outcomes based on telephone follow up. The mean, maximum, and minimum diameters were 5.3, 10, and 1.8 mm, respectively. The mean diameter in group C was significantly larger than that in group A ($p < 0.05$).

Accordingly, the sensitivity, specificity, and Youden Index for predicting adverse outcomes using the ultrasound results of yolk sacs with irregular shapes, abnormal sizes, or non-visualized yolk sacs were 81.01%, 85.71%, and 0.67 respectively. The present results indicate that the early yolk sac measurement during gestation may be a useful marker for pregnancy outcomes [11].

In the present study, serum CA125 was also used to evaluate pregnancy outcomes. Serum CA 125 levels increase in early pregnancy and immediately after birth, thereby implicating the disintegration of the maternal decidua (i.e., blastocyst implantation and placental separation) as a possible source of the increase in tumor marker levels [12]. A significant increase in serum CA 125 levels was also reported in patients with vaginal bleeding and

impending spontaneous abortion [13, 14]. According to the present results, serum CA 125 levels remained low in group A, which slowly increased to a peak value and then dropped slowly to a certain low level. In group B, the serum CA125 levels were slightly higher from five to six gestational weeks, but decreased sharply from six to eight gestational weeks to levels during normal pregnancy. The values then declined slowly from eight to 11 gestational weeks to levels closer to normal pregnancy. In group C, the CA 125 levels slowly increase from five to seven gestational weeks. However, they increased sharply from seven to eight gestational weeks to a maximum value, and then decreased slowly to a rather higher level. The mean serum CA125 levels in the three groups were 17.38, 25.73, and 57.63 U/ml, respectively. There was a significant difference between groups A and C and between groups B and C. Therefore, the present findings coincide with those of a previous study, which demonstrates a highly significant increase in serum CA125 in women who aborted compared with those in the other two groups (the group with normal pregnancy outcomes and the group with women with threatened abortions but with continued pregnancies) [15].

The CA125 levels at 95% CI were calculated for group C, which has a lower limit of 55.57 U/ml. No woman was observed to have CA125 levels above 55.57 U/ml in group A. Meanwhile, nine women in group B with CA125 levels exceeding 55.57 U/ml resulted in favorable pregnancy outcomes after positive clinical treatment. When 55.57 U/ml was used as the cut-off value, the 72 women in group C with CA125 levels above the cut-off value and the nine women in group B had sensitivity, specificity, and Youden Index values of 91.14%, 83.93%, and 0.75, respectively. The present study shows that serum CA-125 measurement may be an inexpensive, easily available, sensitive, and specific predictor of outcome in threatened abortion, which results in loss [16].

In the present study, these two predictors combined together were also evaluated to have greatly improved sensitivity of up to 98.32%, specificity of 71.94%, and Youden Index of 0.70. The present findings are in line with a previous study [17].

In conclusion, the combination of ultrasound yolk sacs scanning and measurement of CA125 levels is of great value for predicting pregnancy outcomes, and may be an easy, cheap, and reliable way for predicting pregnancy outcomes for women with threatened abortion in the first trimester.

## References


[1] Bast R.C. Jr., Feeney M., Lazarus H., Nadler L.M., Colvin R.M., Knapp R.C.: "Reactivity of monoclonal antibody with human ovarian carcinoma". *J. Clin. Invest.*, 1981, *68*, 1331.

[2] O'Brien T.J., Hardin J.W., Bannon G.A., Norris J.S., Quirk J.G.: "CA-125 antigen in human amniotic fluid and fetal membranes". *Am. J. Obstet. Gynecol.*, 1986, *155*, 5.

[3] Quirk J.G., Brunson G.L., Long C.A., Bannon G.A., Sanders M.M., O'Brien T.J.: "CA-125 in tissues and amniotic fluid during pregnancy". *Am. J. Obstet. Gynecol.*, 1988, *159*, 644.

[4] Oztekin O.: "First trimester ultrasound: current approaches and practical pitfalls". *J. Med. Ultrasonics*, 2009, *36*, 161.

[5] Lazarus E.: "What's new in first trimester ultrasound". *Radiol. Clin. North Am.*, 2003, *41*, 663.

[6] Lindsay D.J., Lovett I.S., Lyons E.A., Levi C.S., Zheng X.H., Holt S.C., *et al.*: "Yolk sac diameter and shape at endovaginal US: predictors of pregnancy outcome in the first trimester". *Radiology*, 1992, *183*, 115.

[7] Rempen A.: "The embryonal yolk sac in disordered early pregnancy". *Geburtshilfe Frauenheilkd*, 1988, *48*, 804.

[8] Varelas F.K., Prapas N.M., Liang R.I., Prapas I.M., Makedos G.A.: "Yolk sac size and embryonic heart rate as prognostic factors of first trimester pregnancy outcome". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2008, *138*, 10.

[9] Cepni I., Bese T., Ocal P., Budak E., Idil M., Aksu M.F.: "Significance of yolk sac measurements with vaginal sonography in the first trimester in the prediction of pregnancy outcome". *Acta Obstet. Gynecol. Scand.*, 1997, *76*, 969.

[10] Kupesic S., Kurjak A.: "Volume and vascularity of the yolk sac assessed by three-dimensional and power Doppler ultrasound". *Early Pregnancy*, 2001, *5*, 40.

[11] Stampone C., Nicotra M., Muttinelli C., Cosmi E.V.: "Transvaginal sonography of the yolk sac in normal and abnormal pregnancy". *J. Reprod. Med.*, 1990, *35*, 499.

[12] Kobayashi F., Takashima E., Sagawa N., Mori T., Fujii S.: "Maternal serum CA 125 levels in early intrauterine and tubal pregnancies". *Arch. Gynecol. Obstet.*, 1993, *252*, 185.

[13] Schmidt T., Rein D.T., Foth D., Eibach H.W., Kurbacher C.M., Mallmann P., *et al.*: "Prognostic value of repeated serum CA125 measurements in first trimester pregnancy". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2001, *97*, 168.

[14] Predanic M.: "Differentiating tubal abortion from viable ectipic pregnancy with serum CA125 and beta-human chorionic gonadotropin determinations". *Fertil. Steril.*, 2000, *73*, 522.

[15] Sherif L.S., El-Metwaly A.G., Shalan H., Badawy A.M., Abu-Hashem E.: "Can a single serum CA125 assay predict the outcome of threatened abortion?" *J. Obstet. Gynaecol.*, 2000, *1*, 65.

[16] Fiegler P., Katz M., Kaminski K., Rudol G.: "Clinical value of a single serum CA-125 level in women with symptoms of imminent abortion during the first trimester of pregnancy". *J. Reprod. Med.*, 2003, *48*, 982.

[17] Lei K.R., Liang Q.F., Wang H.L.: "The value of ultrasonography and CA125 in predicting early abortion". *China Prac. Med.*, 2008, *3*, 25.



Address reprint requests to:
M. CHEN, M.D.
No. 24 JingHua road, Jian Xi zone,
Luoyang, Henan Province (China)
e-mail: meichencn@126.com