



ORIGINAL ARTICLE

Evaluation of Yolk Sac Diameter as a Prognostic Factor for First Trimester Pregnancy Outcome

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Submit date: 21-11-2025

Revise date: 15-01-2025

Accept date: 25-01-2025

Abstract

Background: Incidence of miscarriage in the first trimester is 80% of all pregnancy losses, this high incidence demands further inquiry to predict early pregnancy outcomes. Thus, using transvaginal sonography, the yolk sac diameter will be assessed as a predictor of the outcome of the first trimester of pregnancy. Therefore, our goal was to assess the reliability of measuring the yolk sac diameter as a predictor of pregnancy outcome in the first trimester.

Methods: This Prospective cohort study was conducted at tertiary care hospital at the ultrasound and fetal medicine unit of the Obstetrics and Gynecology department at Zagazig University Hospitals and Al-Ahrar Teaching Hospital on total 80 patients who presented in their first trimester between 5 to 11 weeks of gestation for antenatal care.

Results: There was a highly significant difference between normal and abnormal yolk sacs regarding 1st-trimester outcome. 54 out of 58 cases with normal yolk sacs had a normal outcome and only 4 had abnormal outcomes. While out of 22 cases with abnormal yolk sacs, 4 women had normal outcomes and 18 abnormal outcomes.

Conclusion: An important, practical, and non-invasive technique for the examination, diagnosis, and follow-up of pregnant women in their early pregnancy is the first trimester ultrasound measurement of the yolk sac diameter, which is taken between weeks 5 and 11. This is helpful when advising expectant mothers about the possibility of an aberrant outcome and the necessity of follow-up ultrasounds.

Keywords: Yolk Sac Diameter; First Trimester Pregnancy; Outcome.

INTRODUCTION

Since 80% of pregnancies end spontaneously during the first trimester, this time frame is crucial [1]. Ultrasound not only correctly diagnoses most pregnant women in the first trimester, but it also helps distinguish between viable and continuing pregnancies as well as between normal and abnormal pregnancies [2]. Due to the

increased frequency of transvaginal probes and their higher picture resolution, which creates new opportunities for studying early pregnancy, transvaginal sonography is frequently employed in the first trimester [3].

Using ultrasonography, The first anatomical structure discovered within the gestational sac is the yolk sac. The anechoic center is

surrounded by an echogenic, round, regular, and distinct rim, which is typically recognized as a circular shape [4]. The yolk sac performs hematological, immunologic, and other functions throughout organogenesis in embryonic life. metabolic, endocrine, and nutritional functions. It reaches its maximum degree of functional activity between weeks four and seven of embryonic development [5].

Transvaginal ultrasonography can readily identify the yolk sac when the average gestational sac diameter is between 5 and 6 mm; nevertheless, whenever the gestational sac diameter exceeds 8 mm, it should be assessed [3]. The yolk sac's inner diameter typically ranges from 3 to 5 mm [6], and during the first trimester, its volume rises steadily until 10 weeks of pregnancy, plateaus until 11 weeks, and then declines and vanishes by 12 weeks [7].

Numerous studies have examined the yolk sac's dimensions, composition, and role [8]. Miscarriages were more common in pregnancies where the yolk sac diameter was more than 5 mm. 3.8% of pregnancies with irregular yolk sacs and 37.5% of pregnancies with larger yolk sacs experienced pregnancy loss [9].

The likelihood of difficulties decreases as a pregnancy with a healthy yolk sac advances during the first trimester. With a typical yolk sac, the sensitivity to predict a normal pregnancy outcome is as high as 94.2% [10].

METHODS

This prospective cohort study was conducted at the ultrasound and fetal medicine unit of the Obstetrics and Gynecology department at Zagazig University Hospitals and Al-Ahrar Teaching Hospital in the period between June 2021 and September 2023.

The institutional review board at Zagazig University gave its approval for this work (IRB # 6921-17-5-2021). An informed

verbal and written consent was obtained from every subject.

Inclusion criteria:

any Pregnant women in the antenatal care unit who are between 5 and 11 weeks along in their first trimester, as measured from the first day of their most recent menstrual cycle with One sac for gestation and BMI below 35

Exclusion criteria:

Any women with uterine congenital defects; molar pregnancy; ectopic pregnancy, those with established medical conditions that can lead to suboptimal pregnancy outcomes, such as hypothyroidism, diabetes mellitus, or chronic hypertension also, those with Multiple gestations, Recurrent fetal loss ,Severe vaginal bleeding, BMI more than 35 and women who declined follow-up or transvaginal sonography.

All patients were classified according to yolk sac diameter and shape into 2 groups:

- **Group A:** normal yolk sac shape (round, anechoic center, surrounded by an echogenic, round, regular, and well-defined rim) and normal yolk sac diameter (3-5 mm) [4].

- **Group B:** echogenic yolk sac, aberrant yolk sac diameter of more over 5 mm or less than 3 mm, or abnormal irregular shape (oval, with wrinkled edges or indented walls) [4].

A thorough history was taken, a general and local examination was performed, and laboratory tests were performed on each patient. Thyroid stimulating hormone, HbA1C, HBsAg, HCV antibodies, random blood sugar, urine analysis, ABO and Rh groups, and total blood counts were among these assays.

Transvaginal Ultrasound:

All patients had transvaginal ultrasonography. They were evaluated using a 7.5 MHz vaginal probe at the ultrasound and fetal medicine unit in the department of

Obstetrics and Gynecology at Zagazig University Hospitals and a 2D ultrasound machine Mindray DC 70 with X-Insight at Al Ahrar Hospital:

- After emptying her bladder, the patient was either positioned in a supine posture with a cushion supporting her buttocks or in a dorsal lithotomy position.
- A cover sheet was used for privacy.
- Before beginning the examination, make sure the transvaginal transducer was clean, attached to the device, and turned on.
- A single-use condom (or latex glove) was placed over the transducer tip, and gel was applied to the exterior of the condom, being careful not to leave air bubbles underneath the cover.
- To lessen patient discomfort, the transducer was placed into the vaginal canal gently and at an inferior angle to the rectum.
- We confirmed the fetus's viability and calculated the exact gestational age. By placing the calipers at the inner margin, we were able to measure the inner yolk sac diameter. Abnormal yolk sac diameters were classified as being larger than 5 mm and smaller than 3 mm, whereas normal yolk sac diameters were described as being between 3 and 5 mm [11].

A subsequent ultrasound scan was performed on the patients in both groups up to 12 weeks of gestation. If the pregnancy continued past 12 weeks, the results were considered normal; if the patients experienced a spontaneous abortion, missed abortion, threatened abortion, incomplete abortion, or complete abortion before or at 12 weeks of gestation, the results were considered abnormal.

Statistical Analysis

SPSS (Statistical Package for Social Sciences) version 28.0.1.1 was used to analyze the data, and the receiver operating characteristic (ROC) curve, chi-square test, and independent t-test were employed.

RESULTS:

There was no significant correlation between pregnancy outcome and age groups ($p=.067$), BMI ($p=.122$), number of gravidity ($p=.092$), number of parity ($P=.143$), or the number of previous abortions ($p=.080$) (Table 1).

The aberrant outcome group (6.88 ± 2.11 mm) had a bigger yolk sac diameter than the normal outcome group in the seventh to ninth week of pregnancy, which was a significant difference between the groups under study (4.63 ± 0.35 mm) ($p=.020$), while there was no significant difference between them in the 5th to 7th and in the 9th to 11th week of gestation ($p=.890$) and ($p=.235$) respectively (Table 2).

A highly significant difference was found between normal and abnormal yolk sacs regarding 1st-trimester outcome ($P<.001$). 54 out of 58 cases with normal yolk sacs had a normal outcome and only 4 had abnormal outcomes. While out of 22 cases with abnormal yolk sacs, 4 women had normal outcomes and 18 abnormal outcomes (Table 3).

A significant difference was observed in the pregnancy outcome of the studied groups regarding the normality of the yolk sac ($p<.001$). All cases with absent or small yolk sacs had abnormal pregnancy outcomes. 12 out of 16 cases with large yolk sacs also had abnormal pregnancy outcomes. Meanwhile, only 4 out of 58 cases with normal yolk sacs had abnormal outcomes (Table 4).

FHR was present in (92%) and absent cardiac pulsation was (7.5%), and the mean of FHR was (140.51 ± 24.79 b/m) (Table 5). There was statistically significant difference between 1st trimester pregnancy outcome and FHR (Table 6).

The yolk sac diameter ROC curve revealed that the area under the curve (AUC) was 0.727 with $P =.002$. With a cut-off of 4.95 mm, the test's accuracy was 82.49%, its

sensitivity was 72.73%, its specificity was 86.21%, its positive predictive value (PPV) was 66.67%, its negative predictive value (NPV) was 89.29%, its positive likelihood

ratio (+LR) was 5.27, and its negative likelihood ratio (-LR) was 0.32 (Table 7) (Figure 1).

Table 1: Correlation between demographic data and 1st-trimester pregnancy outcome:

		continued beyond 12 weeks. (n=58)		aborted (n=22)		p
		n	%	n	%	
age group (years)	20-29	30	51.7	8	36.4	.067 (ns)
	30-39	26	44.8	10	45.4	
	≥40	2	3.5	4	18.2	
bmi group (kg/m ²)	20-25	6	10.3	2	9.1	.122 (ns)
	25-30	24	41.4	4	18.2	
	30-35	28	48.3	16	72.7	
gravidity	pg	10	17.2	0	0	.092 (ns)
	g2	12	20.7	4	18.2	
	g≥3	36	62.1	18	81.8	
parity	p0	12	20.7	0	0	.143 (ns)
	p1	16	27.6	8	36.4	
	p2	16	27.6	8	36.4	
	p≥3	14	24.1	6	27.2	
previous abortions	0	42	72.4	14	63.6	.080 (ns)
	1	14	24.1	4	18.2	
	≥2	2	3.5	4	18.2	

The Chi-square test was used to analyze the difference between the two groups. P <0.05 was defined as statistically significant NS: not significant.

Table 2:Yolk sac diameter in different gestational ages and its effect on pregnancy outcome:

	5 th -7 th week N=34	7 th - 9 th week N=34	9 th -11 th week N=10
Continued beyond 12 weeks (N=58)	3.82±0.53	4.63±0.35	5.00±0.42
Aborted (N=22)	3.92±2.27	6.88±2.11	5.40±0.00
Student t-test	.890 (NS)	0.020 (S)	0.235 (NS)

Student t-test was used to analyze the difference between the two groups. P <0.05 was defined as statistically significant. (S): significant. (NS): not significant.

Table 3: 1st-trimester pregnancy outcome in normal and abnormal yolk sacs

		Normal Yolk sac (Group A) N=58	Abnormal Yolk sac (Group B) N=22	P
Continued beyond 12 weeks (N=58)	N	54	4	<.001 (HS)
	%	93.1%	6.9%	
Aborted (N=22)	N	4	18	
	%	18.2%	81.8%	
Total		58	4	

The chi-square test was used to analyze the difference between the two groups. P <0.05 was defined as statistically significant. HS: highly significant.

Table 4: 1st-trimester pregnancy outcome in normal and different forms of abnormal yolk sacs:

		Normal (3-5mm) N=58	Small (<3mm) N=4	Large (>5mm) N=16	Absent N=2	P
Continued beyond 12 weeks (N=58)	N	54	0	4	0	<.001 (HS)
	%	93.1%	0	25%	0	
Aborted (N=22)	N	4	4	12	2	
	%	6.9%	100%	75%	100%	
Total		58	4	16	2	

The chi-square test was used to analyze the difference between the two groups. P <0.05 was defined as statistically significant. HS: highly significant.

Table 5: Distribution of the studied groups regarding FHR.

		No.	%
FHR (b/m)	FHR	74	92.5%
	Absent cardiac pulsation	6	7.5%
	Mean ± SD	140.51± 24.79	

Table 6: Relation between 1st trimester pregnancy outcome and FHR (b/m).

		1st trimester pregnancy outcome		t. test	P. value
		Normal pregnancy outcome	Abnormal pregnancy outcome		
FHR (b/m)	Mean ± SD	141.60± 23.58	137.11± 28.72	.667	.040

Table 7: Performance of yolk sac diameter in predicting pregnancy outcome among the studied women:

Cut-off (mm)	AUC	Sensitivity %	Specificity %	PPV %	NPV %	+LR	-LR	Accuracy %	P*
4.95	.727	72.73	86.21	66.67	89.29	5.27	0.32	82.49	.002

AUC; area under the curve, PPV: positive predictive value, NPV: negative predictive value, +LR: positive likelihood ratio, -LR: negative likelihood ratio. *P<0.05 is significant.

DISCUSSION

It is still clinically difficult to distinguish between normal pregnancy and pregnancy loss in the early stages of gestation. About 30 to 40 percent of implanted pregnancies are thought to end in spontaneous abortion in the first trimester [12].

Numerous methods, such as transvaginal ultrasound (TVS) and biochemical markers like maternal serum alpha fetoprotein, PAPP-A (pregnancy associated plasma protein-A), unconjugated estriol, and beta HCG (beta human chorionic gonadotropin), can be used to predict the outcome of a pregnancy in the first trimester. However, the application of these biochemical markers for aneuploidy screening is limited to certain circumstances. Contrarily, TVS is a standard baseline test performed for all pregnancies, and in the first trimester, measures such as subchorionic hemorrhage, Crown rump length, yolk sac diameter, gestational sac diameter, and the existence of decidual response have all been used to predict pregnancy outcomes [13].

Prior to the establishment of placental circulation, During the first trimester of pregnancy, the fetus and mother communicate primarily through the yolk sac (YS). It has immunogenic, secretory, excretory, metabolic, and hematopoietic properties. About 24 days of gestational age, measured from the beginning day of the last menstrual cycle, is when the major yolk sac forms [13].

Although transvaginal sonography shows the secondary yolk sac (SYS), the first extraembryonic component detectable in the

chorionic cavity can be seen from week five to week twelve of pregnancy and is detectable in normal pregnancies, the primary yolk sac is invisible on ultrasound [14].

Assessing the association of first trimester pregnancy outcome using measures of the yolk sac was emphasized as a primary area of interest because spontaneous abortions or early pregnancy failure constitute significant controversy [15].

To determine whether measuring yolk sac diameter is a reliable indicator of pregnancy outcome in the first trimester, this study was carried out.

Because 32 patients failed to show up for the follow-up, 80 individuals were included in the study after 112 participants had their eligibility evaluated.

The data of 80 patients who sought antenatal care during their first trimester, between weeks 5 and 11, served as the basis for the analysis.

Age, BMI, and other factors did not significantly affect the first trimester pregnancy outcomes, gravidity, parity, and history of prior abortions among the 58 women who continued their pregnancy with normal first-trimester outcomes, compared to 22 women who had abnormal first-trimester pregnancy outcomes, 16 women who had incomplete abortions, and 6 women who missed abortions, according to the current study (p values = 0.067, 0.122, 0.092, 0.143, 0.080).

Several research have examined the size and structure of the yolk sac as indicators of the fate of a first-trimester pregnancy; some of

these studies concur with our findings, while others do not.

Sakr et al. [12] evaluated the yolk sac (diameter and shape) and embryonic heart rate as predictive indicators of first trimester pregnancy outcome in a prospective cross-sectional study involving 200 pregnant women in the first trimester. The study found that between weeks 6 and 12, 16 out of 200 instances (8%) of fetal loss occurred.

Ghali et al. [14] carried out a prospective cohort study with 72 pregnant women in the first trimester to ascertain the function of ultrasonography assessment of the yolk sac's width and form during this time. According to the study, fetal loss happened in 9 out of 72 instances (12.5%) between weeks 6 and 11 of pregnancy, and the result of the pregnancy did not significantly correlate with the mother's age.

Abd Ellatif et al. [16] To determine the relationship between early pregnancy loss and the ultrasound characteristics measured in the first trimester, such as the size and form of the yolk sac, the gestational sac, and the embryonic heart rate, a prospective study including 100 pregnant women in the first trimester was done. According to the findings, fetal losses were found in 9% of cases.

Abo elwan H et al. [17] reported that 52 pregnant women in the first trimester from 6 weeks to 12 weeks gestation participated in a prospective cohort research that assessed yolk sac size and embryonic heart rate as predictors of first trimester pregnancy outcome. Their study found that there was a significant difference in the embryonic heart rate (EHR) between the groups that experienced miscarriage (bradycardia) and those that continued their pregnancies, with 11 out of 52 cases experiencing fetal loss, 10 cases having abnormal yolk sacs, and only one out of 42 cases having normal yolk sacs.

Suguna et al., [13] In order to determine the importance of yolk sac size and shape for

predicting pregnancy outcome in the first trimester, 492 pregnant women between 6+0 and 9+6 weeks of gestation took part in a prospective study. 393 patients (78.6%) were still receiving treatment after 12 weeks, which was seen as a typical result. Ninety-nine people experienced adverse outcomes, including eight (1.6%) blighted ovums (anembryonic pregnancies) and nineteen (18.2%) missed abortions.

As regards Yolk sac diameter, According to the study's findings, there was no discernible difference between the groups throughout the fifth to seventh and ninth to eleventh weeks of pregnancy ($p=.890$ and $p=.235$, respectively). but there was a significant difference between the groups in the 7th to 9th week of gestation, with the abnormal outcome group (6.88 ± 2.11 mm) being larger than the normal outcome group (4.63 ± 0.35 mm) ($p=.020$).

According to the results of our investigation, there was a highly significant difference in the first-trimester outcome between normal and aberrant yolk sacs ($P<0.001$). Only four of the 58 cases with normal yolk sacs had abnormal results; the other 54 cases had normal results. Four women had normal results and eighteen had bad outcomes out of 22 cases with abnormal yolk sacs.

Regarding the FHR, the results of our study showed that it was present in 92.5% of cases and absent in 7.5% of cases. The mean FHR was 140.51 ± 24.79 b/m, and there was a statistically significant difference between the FHR and the first trimester pregnancy outcome (p value = 0.040).

Therefore, ROC curve analysis showed that the area under the curve (AUC) was 0.727 with $P = .002$ when using yolk sac diameter to predict pregnancy outcome. 66.67% positive predictive value (PPV), 89.29% negative predictive value (NPV), 5.27 positive likelihood ratio (+LR), 0.32 negative likelihood ratio, 82.49% accuracy, 72.73% sensitivity, and 86.21% specificity

(-LR) were the test results, with a 4.95 mm cut-off.

In line with our findings, Sakr et al. [12] reported that the yolk sac diameter of the fetal loss group increased significantly at 6 weeks compared to the ongoing pregnancy ($P < 0.05$), but not at 12 weeks ($P > 0.05$). The threshold values for the yolk sac diameter at 6 and 9 weeks in order to forecast the pregnancy's prognosis. After six weeks, the accuracy was 61%, the specificity was 60%, and the sensitivity was 75%. At 9 weeks, the sensitivity was 62%, the specificity was 54%, the accuracy was 55%, and the threshold value was 5.

These results are consistent with those of Sheikh and Anjana [3], who found that the sensitivity of yolk sac diameter was higher for the 8–8+6 week group and the 10–10+6 week group, at 66.67%. The 7-week-seven-day group's sensitivity and PPV were subpar. The 9 weeks–9 weeks 6 days group has a high specificity of 95.08%. The 8 weeks–8 weeks 6 days group had the highest sensitivity, YSD is a more effective method for forecasting pregnancy outcome in this particular gestational age group, as evidenced by its specificity, PPV, and NPV of any gestational age group.

Aseri, [15] demonstrated a substantial correlation between the result and the size of the yolk sac of the first trimester of pregnancy and ranged from 2.5 to 7.0 with a mean of 4.892 mm.

Suguna et al., [13] revealed that the yolk sac diameter (YSD) ranged between 3 and 5 mm. A negative pregnancy outcome was significantly correlated with abnormal YSD ($p < 0.000$). with YSD < 3 mm and > 5 mm being considered abnormal. The YSD was abnormal in 62.36% of patients. YSD demonstrated a 62.3% sensitivity and a 64.1% specificity as a predictor of aberrant outcomes. 27.3% and 88.7%, respectively, were the positive and negative predictive values.

Abo elwan et al., [17] found that age, parity, and BMI did not differ statistically among the studied groups. It was discovered that four cases of enlarged YS, three cases of small YS, two cases of irregular YS, and one case of absent YS had abnormal pregnancy outcomes, while only one case with normal YSD did. With a total accuracy of 98.1%, YSD predicted miscarriages with 97.6% sensitivity and 100% specificity.

Between the fourth and fifth weeks of pregnancy, before the fetal pole and embryonic heart show, transvaginal ultrasound can detect the appearance of the yolk sac, a sign of a successfully expanding gestational sac [18].

The GS and YS diameters were good predictors of fetal loss ($p < 0.05$), which is consistent with our findings. Abd Ellatif et al. [16] discovered that at 6, 9, and 12 weeks, the fetal loss group's gestational sac diameter dramatically shrank, and an enlarged yolk sac suggested abnormal embryonic development and a high risk of miscarriage.

This is in line with Prashant et al.'s findings [18], which showed that the developing embryo feeds on the yolk sac before the placenta is completely developed. The yolk sac meets the metabolic, endocrine, immunologic, and hemopoietic needs of the embryo in its early stages of development and reaches its peak level of functional activity between weeks four and seven of pregnancy.

Furthermore, Figueras et al. [19] discovered that a substantial incidence of retrochorial bleeding and subsequent pregnancy loss was linked to a yolk sac volume outside the 5th to 95th percentile; in our investigation, abortion took place in 14 cases (63.63%) compared to 26 cases (26%), suggesting that a healthy yolk sac is critical to the embryo's survival. Our research also confirms the findings of that study.

In contrast to our results, **Ghali et al., [14]** showed that the normal and abnormal yolk sac diameter and shape in the cases under study did not significantly differ from the pregnancy outcome. Burton and Jauniaux also reported an anomalous finding with normal YS size and shape. [20].

The size and shape of the yolk sac alone may be linked to early pregnancy loss and is a poor indicator of the outcome of the pregnancy after 20 weeks [14].

These results confirm that YSD that is outside of the normal range will ultimately have a positive consequence. Rather than being the main reason for pregnancy loss, changes in YS morphology could be an indication of aberrant embryonic development or death. Another hypothesis is that the placenta, which is an essential source of blood supply for the embryo, replaces the yolk sac may be compromised between weeks 8 and 10 of pregnancy due to the simultaneous rise in placental blood flow from the umbilical cord and the loss of arterial signals in the circulation of the yolk sac. This can be considered a contributing factor to miscarriages [14].

The strength points of this study:

The prospective trial design and the fact that no patients were lost to follow-up during the study are its strong qualities. Making the diagnosis as soon as possible is a good way to prevent vaginal bleeding from happening at an inconvenient time or location and to reduce the parent's time of worry and uncertainty. To prevent inter-observer differences, the same investigator conducted all sonographic examinations.

The limitations of the study:

First, it is important to note the study's shortcomings, which include a smaller sample size than in prior research and the lack of a multicentric study, which poses a serious danger of publication bias. Second, the CRL and gestational sac width were not assessed as indicators of early pregnancy

loss. This research was conducted at a single facility.

Conclusions:

The first trimester ultrasound measurement of the yolk sac diameter, which is performed between weeks 5 and 11, is a crucial, useful, and non-invasive method for the assessment, diagnosis, and monitoring of expectant mothers in their early stages of pregnancy. This is helpful when advising expectant mothers about the possibility of an aberrant outcome and the necessity of follow-up ultrasounds.

Conflict of interest statement: The authors declared that there were NO conflicts of Interest.

Disclosure: The authors have no financial interest to declare in relation to the content of this article.

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SUPPLEMENTARY

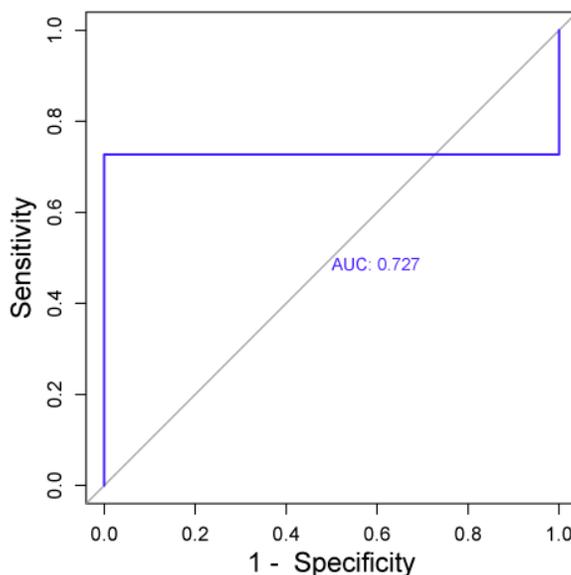


Figure (1): ROC curve of yolk sac diameter in predicting pregnancy outcome.



Figure (2): Normal yolk sac diameter 3.4mm, GS 2.56 cm, CRL 0.81 cm corresponding to 6 wks & 6 days gestation



Figure (3): Normal yolk sac diameter 4.0mm, CRL 1.71 cm, corresponding to 8 wks & 1day GA, FHR 180 b/m.



21.

Figure (4): Normal Yolk sac 4.4 mm, CRL 2.15 corresponding to 8wks & 5days GA, FHR 158 b/m.

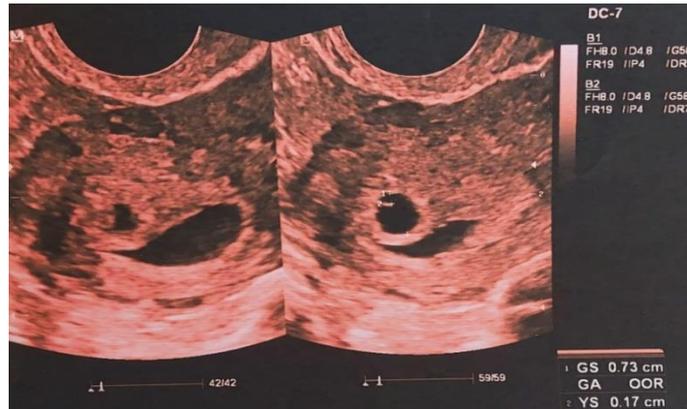


Figure (5): Small yolk sac diameter 1.7mm, GS 0.73 cm, with 6 weeks amenorrhea.

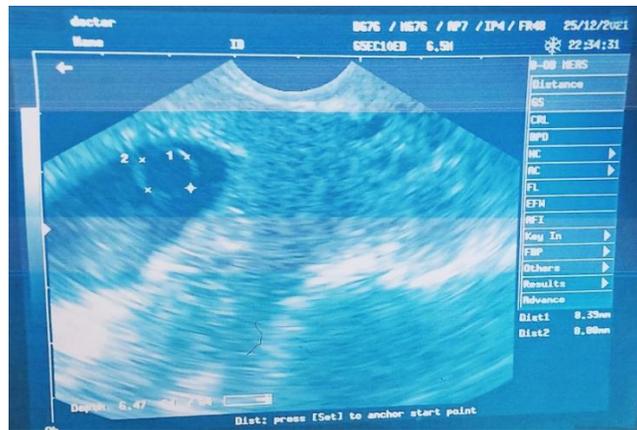


Figure (6): Large yolk sac diameter 8.3mm, GS corresponding to 8 weeks GA, fetal pole with no cardiac pulsation.





Figure (8) : Large Yolk sac 5.4 mm, CRL 2.67 cm, corresponding to 9 weeks &3days, FHR 192 b/m.

Citation

Mohamed, E., Mohamed Mowafy, H., Abdou, H., Hamed, B. Evaluation of Yolk Sac Diameter as a Prognostic Factor for First Trimester Pregnancy Outcome. Zagazig University Medical Journal, 2025; (1286-1298): -. doi: 10.21608/zumj.2025.352506.3791