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Original Article

Yolk sac size & shape as predictors of first trimester pregnancy outcome: A prospective observational study

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ABSTRACT

Objective. – To determine the value of yolk sac size and shape for prediction of pregnancy outcome in the first trimester.
Material and methods. – 500 pregnant women between 6^{+0} and 9^{+6} weeks of gestation underwent transvaginal ultrasound and yolk sac diameter (YSD), gestational sac diameter (GSD) were measured, presence/absence of yolk sac (YS) and shape of the yolk sac were noted. Follow up ultrasound was done to confirm fetal well-being between 11^{+0} and 12^{+6} weeks and was the cutoff point of success of pregnancy.
Results. – Out of 500 cases, 8 were lost to follow up, YS was absent in 14, of which 8 were anembryonic pregnancies. Thus, 478 out of 492 followed up cases were analyzed for YS shape and size and association with the pregnancy outcome. In our study, abnormal yolk sac shape had a sensitivity and specificity (87.06% & 86.5% respectively, positive predictive value (PPV) of 58.2%, negative predictive value (NPV) of 96.8% in predicting a poor pregnancy outcome as compared to yolk sac diameter (sensitivity and specificity 62.3% & 64.1% respectively and PPV and NPV of 27.3% and 88.7% respectively). The degree of association for both the variables was significant to the level of $p < 0.000$.
Conclusion. – The presence or absence of yolk sac has a strong predictive value for poor pregnancy outcome. Yolk sac shape was a better predictor of poor pregnancy outcome in terms of higher specificity and negative predictive value as compared to yolk sac diameter.

Introduction

Accurate differentiation between normal pregnancy and pregnancy loss in early gestation remains a clinical challenge. It is estimated that approximately 30–40% of implanted pregnancies results in spontaneous abortion during first trimester [1–3].

The various modalities of predicting the pregnancy outcome in the first trimester include the imaging transvaginal ultrasound (TVS) and biochemical markers such as beta HCG (Beta Human Chorionic gonadotropin), PAPP-A (Pregnancy Associated Plasma Protein-A), unconjugated estriol, maternal serum alpha fetoprotein. However, these biochemical markers are used only in specific situations for screening of aneuploidy. TVS on the other hand is a routine baseline procedure done for all pregnancies and parameters like gestational sac diameter, yolk sac diameter, crown rump length, presence of decidual reaction and subchorionic hemorrhage have been used to predict the pregnancy outcome in the first trimester.

In the first trimester, yolk sac (YS) is the primary source of exchange between mother and fetus before placental circulation is established. It has hematopoietic, metabolic, secretory, excretory and immunogenic functions [3]. The primary yolk sac forms at approximately 24 days of gestational age (calculated from the first day of the last menstrual period). As the extra embryonic coelom forms, the primary yolk sac is pinched off and the secondary yolk sac (termed only as the yolk sac) is formed at 27–28 days of gestational age, which is the first embryonic structure visualized in gestational sac sonographically [3].

In normal pregnancies, yolk sac is identified when the mean gestational sac diameter (MGSD) is 5 mm at TVS. It should be clearly observed when the gestational sac measures more than 8 mm [3]. TVS can detect the yolk sac as early as the 5th week of pregnancy [4].

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Normally, yolk sac appears as a round structure with an anechoic center surrounded by a uniformly thick and well-defined echogenic wall [5]. Usually, the inner diameter of the yolk sac measures 3–5 mm. Its size increases progressively from the 5th gestational week to the end of the 10th gestational week; subsequently it decreases in size gradually [6].

Many studies on the prognostic significance of the Yolk sac for the pregnancy outcome have been performed with conventional sonography and more recently with TVS. The results are conflicting. The yolk sac size and shape have been suggested as sensitive predictors of pregnancy outcome. Thus, further studies on the measurement of yolk sac size, shape and its association with normal and abnormal pregnancy outcome, could help as an early predictor of pregnancy outcome [4–6].

Approximately, 40% of early pregnancies result in miscarriage. Abortions (spontaneous, threatened, complete, incomplete, inevitable and missed) can be due to unknown etiology, morphologic and chromosomal abnormalities, infection, anatomic defects, endocrine factors, immunologic factors and maternal systemic disease. The risk of miscarriage lessens as the gestation progresses.

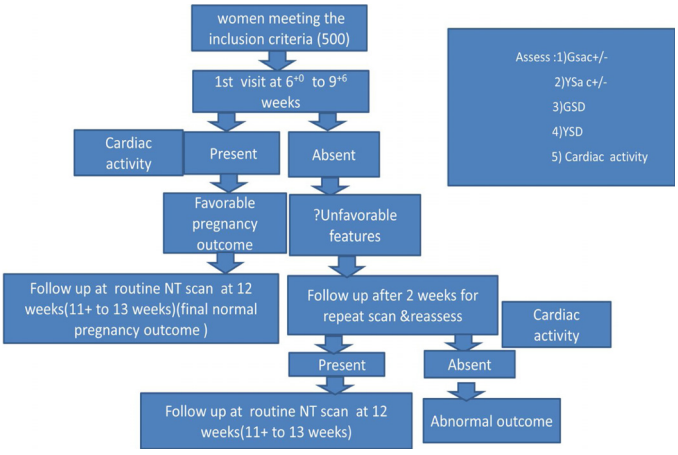
When the crown-rump length measures 4–10 mm, the fetal heart beat should be detectable. When the gestational sac diameter is more than 8 mm, yolk sac should be visible at about 5 weeks of gestation. If the gestational sac diameter is more than 20 mm, an embryo is usually visible. If not, the scan should be repeated one week later to confirm the problem. Absence of the yolk sac, too large (>6 mm), too small (<3 mm), irregular shape or having degenerative changes (calcifications or decreased translucency) (Fig. 1) are the various abnormal ultrasound appearances of YS [3,7–15,20]

Materials and methods

It was a prospective observational study conducted at the Obstetrics and Gynecology Department at Bangalore Baptist Hospital, a tertiary care centre, over a period of one year, from July 2015 to July 2016. After obtaining the ethical committee and institutional review board clearance, 500 antenatal women between the gestational age of 6^{+0}–9^{+6} weeks, were recruited following an informed written consent (along with the PNDT consent) from the patients, after ruling out cases with structural anomalies of uterus and cervix, hypothyroidism and overt diabetes mellitus and multiple gestations. Transvaginal ultrasound (TVS) on an empty bladder was done by the VOLUSON S6 pro sonographic equipment with 5–9 MHz multi frequency transvaginal transducer (GE Healthcare), with minimal intra observer and inter observer variation. The methodology followed is depicted in the flowchart below. A viable pregnancy at 12 weeks was taken as the endpoint and final normal pregnancy outcome in the study.

Gestational sac diameter (GSD) or Mean sac diameter (MSD) was the average of three perpendicular diameters (in orthogonal planes) measured from one inner edge to the other inner edge of the trophoblast. Yolk sac diameter (YSD) was the average of two perpendicular diameters with the calipers placed at the inner edge of the yolk sac.

Statistical software namely SPSS 16.0 was used for the analysis of the data and Microsoft excel was used to generate graphs, tables etc.



Flowchart of methodology of study. A viable pregnancy at 12 weeks was taken as the endpoint and final normal pregnancy outcome in the study.

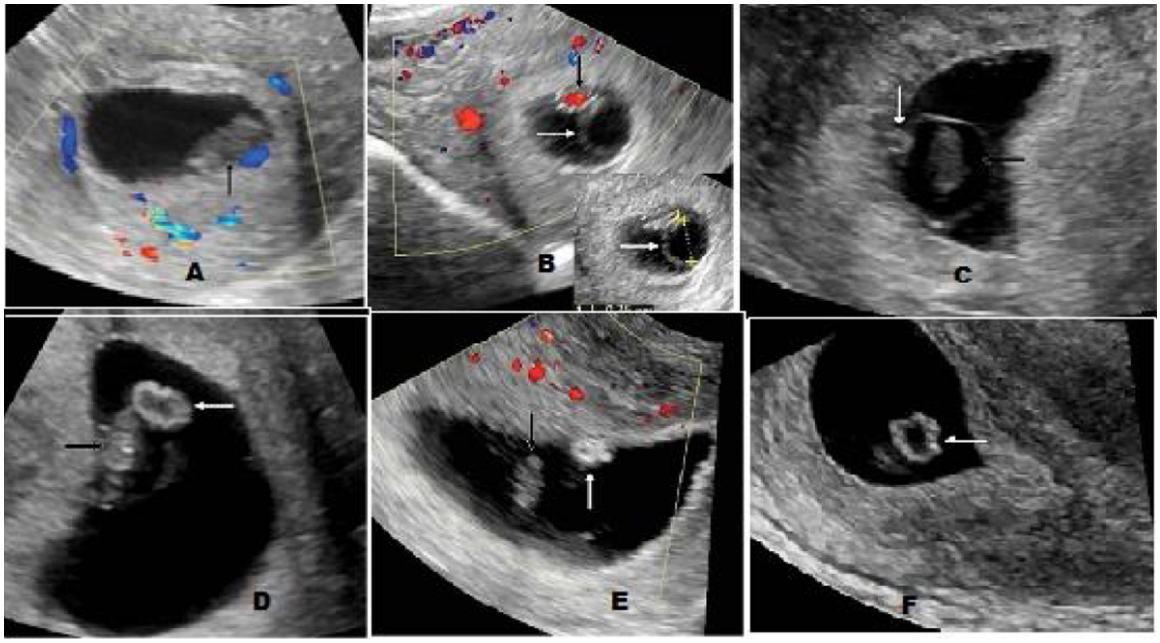


Fig. 1. TVS showing YS abnormalities (white arrow): (A) absent YS; (B) large YS; (C) small YS (D) echogenic YS; (E) calcified YS; (F) Irregular YS [15].

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Results

Out of 500 cases, three hundred and four were Primigravida and 31 cases (6.2%) out of 196 multigravida had a prior missed abortion. It was seen that out of 500 patients scanned at recruitment, yolk sac was present in 486 patients (97.8%) and absent in 14 patients (2.8%). Out of 486 cases that were analyzed for YS size and shape, 8 were lost to follow up. Thus, out of 478 cases that were analyzed for YS size and YS shape and related outcome, 351 (70.2%) and 127 (25.4%) had normal and abnormal shape respectively, 284 (56.8%) and 194 (38.8%) had normal and abnormal size respectively (Table 1).

Table 1 shows the observations on TVS at recruitment and at follow up in terms of various ultrasound parameters. 478 cases that were analyzed for YS size and YS shape and related outcome, 351 (70.2%) and 127 (25.4%) had normal and abnormal shape respectively. 284 (56.8%) and 194 (38.8%) had normal and abnormal size respectively.

Out of 500 cases scanned at first visit, four hundred and one (80.2%) were asked to come back for NT scan at 11–14 weeks while remaining ninety nine patients (19.8% were asked to follow up after 2 weeks for rescan before NT scan. During the follow up of the cases, eight of the four hundred and one who were asked to follow up for NT scan were lost to follow up (1.6%). In the remaining four hundred and ninety two patients, three hundred and ninety three patients (78.6%) (continued till 12 weeks which were considered as having normal outcome. Ninety nine patients had an unfavorable outcome which included ninety one (18.2%) missed abortions and eight (1.6%) blighted ovum (anembryonic pregnancies). Out of the 91 missed abortions, yolk sac was absent in six pregnancies. Thus 478 pregnancies were analyzed for yolk sac size and shape and their association with the outcome (Table 2).

Outcomes analyzed according to gestational age (GA) showed that, sixty eight (80%) missed abortions were in the beginning of pregnancy between 6 and 6^{+6} weeks. which decreased to one (1.2%) as the pregnancies approached to 9–9^{+6} weeks.

The comparison between prior pregnancy outcome and the outcome in the present pregnancy showed a significant association. Fourteen (16.4%) of eighty five missed abortions in our study had a previous missed abortion. It was seen that fourteen out of twenty nine (48.2%) women who had prior missed abortion, had a missed abortion in the present pregnancy as well ($p = <0.000$).

Table 2
Distribution of outcome according to gestational age.

GA (weeks)	Good outcome (%)	Missed abortion (%)	Total (%)
6^{+0}–6^{+6}	145 (36.9)	68 (80)	213 (44.5)
7^{+0}–7^{+6}	129 (32.8)	11 (12.9)	140 (29.3)
8^{+0}–8^{+6}	80 (20.4)	5 (5.9)	85 (17.8)
9^{+0}–9^{+6}	39 (9.9)	1 (1.2)	40 (8.4)
Total	393 (100)	85 (100)	478 (100)

Out of 500 women, eight were lost to follow up. Out of 99 missed abortions, YS was absent in 14 cases of which eight were blighted ovum. There was significant association between the presence of yolk sac and the pregnancy outcome. Presence of yolk sac had a Sensitivity of 100% in predicting the good outcome, while an absent yolk sac had sensitivity of 14.12% and specificity of 85.52% in predicting poor outcome (Table 3).

Presence of fetal pole at first scan had a significant association with the pregnancy outcome ($p = 0.000$). Three hundred and ninety one (99.5%) cases who had fetal pole at first scan had a good outcome. Sensitivity of the test was 99.5% while the specificity for absent fetal pole and missed abortion was only 20%. Of the 478 cases that were followed up for rescan, three hundred and ninety three (100%) cases had a viable pregnancy with fetal pole being present. On the other hand, missed abortion was seen in equal proportion in both groups. Forty four (51.7%) cases fetal pole present and forty one (48.2%) cases had absent fetal pole (Table 3).

Of the 478 cases that were analyzed, cardiac activity was seen at first scan in three hundred and ninety two (99.7%) cases with good outcome. whereas thirty two (37.6%) cases of missed abortion had absent cardiac activity at first visit ($p = 0.000$) (Table 3).

Seventy four out of eighty five (87.06%) missed abortions had irregular yolk sac. Results showed a sensitivity of 87.06%, specificity of 86.5%, a positive predictive value of 58.2% but a negative predictive value of 96.8%. Thus a significant association was seen in yolk sac shape predicting the pregnancy outcome ($p = 0.000$) (Table 3).

Yolk sac diameter (YSD) (Normal range was taken as 3–5 mm. YSD <3 mm & >5 mm was considered abnormal). There was a significant association between abnormal YSD and poor pregnancy

Table 1
Ultrasound (TVS) observations.

Feature	Finding	At recruitment (*n*)/500	Percentage	At follow up/12 weeks (n)	Percentage
Fetal pole	Present	470	94	439	87.8
	Absent	17	3.4	53	10.6
	Faint	13	2.6	8 (lost to f/u)	1.6
Cardiac activity	Present	437	87.4	392	78.4
	Absent	47	9.4	100	20
	Bradycardia	16	3.2	8 (lost to f/u)	1.6
YS	Present	486	97.80	478	95.6
	Absent	14	2.8	14	2.8
				8 (lost to f/u)	1.6
YS shape	Normal	358	71.6	351	70.2
	Abnormal	128	25.6	127	25.4
	Absent	14	2.8	14	2.8
				8 (lost to f/u)	1.6
YS size	Normal	290	58	284	56.8
	Abnormal	196	39.2	194	38.8
	Absent	14	2.8	14	2.8
				8 (lost to f/u)	1.6

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Table 3
Fetal biometry vs pregnancy outcome.

Feature	Finding	Good outcome ($n=393$)	Missed abortion ($n=85$)	Chi square	p value
Fetal pole (at first visit)	Present	391 (99.50)	68 (80.00)	70.605	0.000
	Absent	1 (0.25)	8 (9.41)		
	Faint	1 (0.25)	9 (10.59)		
Fetal pole (at F/U)	Present	393 (100)	44 (51.76)	2.007	0.000
	Absent	0 (0)	41 (48.24)		
Cardiac activity (at first visit)	Present	392 (99.74)	53 (62.35)	152	0.000
	Absent	1 (0.26)	32 (37.65)		
Cardiac activity (at F/U)	Present	393 (100)	0 (0)	4.64	0.000
	Absent	0 (0)	85 (100)		
Yolk sac	Present	393 (100)	85 (85.85)	48.1	0.000
	Absent	0 (0)	14 (14.2)		
Yolk sac shape	Regular	340 (86.51)	11 (12.94)	1.93	0.000
	Irregular	53 (13.49)	74 (87.06)		
Yolk sac diameter	Normal	252 (64.12)	32 (37.64)	20.31	0.000
	Abnormal	141 (35.88)	53 (62.36)		

outcome ($p < 0.000$). Fifty three out of eighty five (62.36%) had an abnormal YSD. YSD, as a predictor of abnormal outcome, had a sensitivity of 62.3% & specificity of 64.1%. The positive and negative predictive values were 27.3% and 88.7% respectively (Table 3).

Mean gestational sac diameter (MGSD) was 2.27 ± 0.75 in the pregnancies who had a good outcome while it was 1.62 ± 0.56 in the missed abortion group ($p = 0.000$). Of the 478 patients, fetal pole was absent in eight cases at first visit. Hence four hundred and seventy cases were statistically evaluated for CRL (at first visit) and their pregnancy outcome. There was a significant association between CRL and outcome ($p < 0.000$). With mean CRL of 1.2 ± 0.65 cm & 0.62 ± 0.40 cm in the viable pregnancies & missed abortion group respectively (Table 3).

There was a significant association between ratio of gestational sac diameter to yolk sac diameter (GSD/YSD ratio) and outcome ($p < 0.000$). The mean GSD/YSD ratio was 6.79 ± 2.58 in the good outcome group & $5.4\ 6 \pm 3.13$ in the missed abortion group respectively. There was a significant association between ratio of yolk sac diameter to gestational sac diameter (YSD/GSD ratio) and outcome ($p < 0.000$). The mean YSD/GSD ratio was 1.711 ± 0.712 in the good outcome group & 2.48 ± 0.12 in the missed abortion group respectively (Table 4).

MGSD was 2.27 ± 0.75 in the pregnancies who had a good outcome while it was 1.62 ± 0.56 in the missed abortion group. Mean CRL was 1.2 ± 0.65 cm & 0.62 ± 0.40 cm in the viable pregnancies & missed abortion group respectively. There was a significant association between GSD/YSD ratio and outcome ($p < 0.000$) with mean ratio of 6.79 ± 2.58 & $5.4\ 6 \pm 3.13$ in the viable pregnancies & missed abortion group. There was a significant association between YSD/GSD ratio and outcome ($p < 0.000$) with mean ratio of 1.711 ± 0.712 in the good outcome group & 2.48 ± 1.2 in the missed abortion group respectively.

Mean YSD increased from 3.27 at 6 weeks to 3.9 mm till 9^{+6} & then decreased after 10 weeks. The MYSD was on higher side as compared to the MYSD in the normal outcome group for the same GA with a large yolk sac at 9^{+6} weeks with YSD of 6.2 mm. It was seen the YSD in normal pregnancy outcome had a diameter ranging from 3 mm to 5 mm (increases from 5th week to 9th week and then decreases over the 10th week). The mean yolk sac diameter (MYSD) in both outcome groups was 0.36 cm. The MYSD was on

Table 4
Mean diameters vs outcome.

Outcome	Good outcome (393)			Missed abortion (85)			T value	p value
Parameter	Mean	SD	SE	Mean	SD	SE		
GSD (cm)	2.27	0.75	0.038	1.62	0.56	0.061	7.423	0.000
CRL (cm)	1.2936	.65775	.03318	.6258	.40856	.04656	8.58	0.000
GSD/YSD	6.79	2.58	0.13	5.46	3.13	0.34	4.1	0.000
YSD/GSD	1.711	0.711	0.00	2.48	1.2	0.13	7.15	0.000

Table 5
MYSD at particular gestational age (GA) vs. outcome.

	Good outcome			Missed abortion			Total
GA Weeks	No. (%)	MYSD (mm) ±2SD	Range (mm)	No. (%)	MYSD (mm) ±2SD	Range (mm)	
6^{+0}–6^{+6}	145 (36.3)	3.27 ± 0.85	1.3–6.7	68 (80%)	3.52 ± 1.89	1.2–10.7	213
7^{+0}–7^{+6}	129 (32.8)	3.48 ± 0.98	2.1–8.4	11 (12.9)	3.80 ± 2.05	1.9–8.8	140
8^{+0}–8^{+6}	80 (20.3)	3.84 ± 0.97	2.3–6.8	5 (5.8)	3.56 ± 2.80	1.5–8.5	85
9^{+0}–9^{+6}	39 (9.9)	3.87 ± 0.75	2.6–5.6	1 (1.3)	6.2	6.2–6.2	40
Total	393 (100)			85 (100)			478

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higher side in the missed abortion group as compared to the MYSD in the normal outcome group for the same GA with a large yolk sac at 9^{+6} weeks with YSD of 6.2 mm (Table 5).

Discussion

500 pregnant women attending the antenatal clinic were included in our study. Among these five hundred women, eight patients (who were asked to follow up for NT scan) were lost to follow up. Eight women had anembryonic pregnancies. Thus, 478 cases (393 with good outcome and 85 missed abortions) were analyzed for yolk sac biometry.

The presence or absence of yolk sac had a significant association with the pregnancy outcome. According to our study, an abnormal yolk sac shape had a higher sensitivity and specificity (87.06% & 86.5% respectively), a positive predictive value of 58.2% but a negative predictive value of 96.8%, in predicting a poor pregnancy outcome as compared to yolk sac diameter (sensitivity and specificity 62.3%& 64.1% respectively). The positive predictive value and negative predictive value for YSD were 27.3% and 88.7% respectively, though the degree of association for both the variables was significant to the level of $p < 0.000$. On analyzing the ratio of YSD/GSD in both the groups, there was a significant association with the ratio and pregnancy outcome. A ratio of YSD/GSD <0.2 is associated with a poor outcome.

According to Cepni et al. study, a steady increase occurs in YSD from 5 to 11 weeks of gestation in normal pregnancies with disappearance of yolk sac after 12 weeks [17].

Lindsay et al. reported that no pregnancy with normal outcome had a YSD of greater than 5.6 mm at less than 10 weeks of gestation. In 6 patients YSD was more than 5.6 mm & all 6 had abnormal outcome. Of the 7 patients with abnormal yolk sac shape at initial scan, 3 had abnormal yolk sac shape at follow up and all 3 had abnormal outcome [3].

Kucuk et al. found YSD out of 2 standard deviations of the mean for the gestational age allowed the prediction of an abnormal pregnancy outcome with a specificity of 97%, sensitivity of 65%, a positive predictive value of 71% and a negative predictive value of 95%. An abnormal yolk sac shape allowed prediction of poor outcome with a sensitivity of 29%, specificity of 95%a positive predictive value of 47% and a negative predictive value of 90.5%. They found a significant correlation between yolk sac and gestational age, YSD and CRL, and YSD and MGSD to the level of $p < 0.001$, $p < 0.0001$ and $p < 0.0001$ respectively [18].

A study conducted by Khaled et al. found that YSD <3.1 mm predicts abnormal outcome with a sensitivity of 75% and specificity of 63.5%. However, the YSD/GSD ratio <0.2 showed absolute sensitivity &specificity of 100% for prediction of abnormal outcome [19].

Below is the table comparing the various studies done before and our study. The results of our study are in sync with the prior studies the most of the studies evaluated yolk sac shape as a predictor and our study evaluated the role of YSD in addition. Studies with abnormal yolk sac shape and diameter as predictor of poor pregnancy outcome.

Conclusion

Yolk sac shape was a better predictor of poor pregnancy outcome in terms of higher specificity and NPV as compared to YSD. YSD/GSD ratio was also seen to have a strong association in prediction of the poor pregnancy outcome. Abnormalities of YS size or shape, early regression or absence can be used as poor predictor of first trimester pregnancy outcome, even before studying the fetal morphology.

This concept may also be explored to clinical practice in embryo reduction in the era of artificial reproductive techniques.

Recommendations

Yolk sac shape and size assessment gives a good overview of pregnancy outcome in first trimester. Hence, it is advised that yolk sac biometry be done routinely in first trimester.

Ethics

As the study is observational, no interventions were done and none of the women were denied the prescribed care. The first trimester scan is a part of standard care and routine assessment of all antenatal women visiting our hospital and they did not bear any additional charges.

Conflict of interest

All authors declare that they have no conflicts of interest.

Ethical standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki declaration of 1975 as revised in 2008.

Informed consent

Written informed consent was obtained from all patients for being included in the study.

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Parameter	Yolk sac shape				Yolk sac diameter			
Study	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
Kucuk et al. [18]	65	97	71	95	29	95	47	90.5
Chama et al. [2]	91.4	66	88.8	–	66	91.4	95.6	–
Lindsay et al. [3]	26.9	92.7	51.1	–				
C. Stampone et al. [16]	68.7	99	91.6	95.2				
Our study	62.3	64.1	27.3	88.7	87.06	86.5	58.2	96.8

(All values in %).

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