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

Esraa Magdy Fahmy Mohamed¹, Hala Elsayed Mowafy², Hend Salah Abdou², Basem Mohamed Hamed²

¹Obstetrics and Gynecology Department, Al-Ahrar teaching Hospital, Egypt

²Obstetrics & Gynecology Department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author: Esraa Magdy Fahmy Mohamed**

Email: esraa.magdy.fahmy@gmail.com, **Mobile:** 01114004845

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Abstract:

First trimester is crucial, since 80% of pregnancy losses occur spontaneously during this period.

Contributing factors are diverse, so there is difficulty in reliably predicting the outcome of pregnancy. There is a need for accurate method to assess the early pregnancies that allows early indication of unwanted outcomes. This can guide a tailored and pre-emptive management strategy, and aids in a much needed psychologic preparation of the expecting mother. Numerous ultrasound signs have been proposed as predictive of poor pregnancy outcome, including an excessively large, excessively small, or irregular gestational sac, a large or irregular yolk sac, weak decidual reaction and a slow embryonic heart rate. Yolk sac plays a pivotal role in exchange of essential substrates between mother and embryo before the placental circulation establishes. It reaches the highest level of functional activity during the fourth to seventh week and undergoes degeneration after the twelfth week. With transabdominal sonography (TAS), the yolk sac is mostly evident by seven weeks of gestational age, when its diameter reaches a mean of 20 mm. TAS is the routine practice at our set up, whereas transvaginal sonography (TVS) is preferred when difficulty in visualization and assessment of early pregnancies.

Keywords: Yolk Sac, First Trimester, Pregnancy Outcome.

Introduction:

It is evident from the formation and function of yolk sac that any deviation in these complicated processes could disturb the development of embryo. It plays an important role in the nutritive, metabolic and hematopoietic processes of the first trimester. Any abnormality in the shape, size, structure or circulation of the yolk sac indicates a major abnormality in development. **(1)**

Large yolk sac >5mm, Small yolk sac <3mm, Irregular shape, wrinkled margins, indented walls, collapsed walls, thick echogenic walls, doubled (appearance of 2 or more YS) or containing echogenic spots or bands, Calcified yolk sac due to longstanding embryonic demise, Floating yolk sac, Non-visualization is always abnormal, Thin yolk sac has a predictive value of 53.8% for an abnormal outcome, Thick yolk sac has a predictive value of 93.3% for an abnormal outcome. **(2)**

Large yolk sac

A **large yolk sac** is one measuring >5-6 mm in pregnancies between a gestational age of 5-10 weeks. Another study had shown that a yolk sac diameter of >5 mm can be associated with an increased risk of spontaneous miscarriage although few other authors have mentioned the existence of a very large yolk sac (e.g. around 8 mm) in a normal live pregnancy. Abnormally large yolk sac may indicate a poor obstetric outcome and close follow-up with sonography is often recommended for these pregnancies. In the surviving embryos the probabilities for chromosomal aberrations increase. **(3).**



Figure 1. abnormal large yolk sac **(3)**



Figure 2: Yolk sac of 9 mm. This is very sensitive marker for abortion. (1)

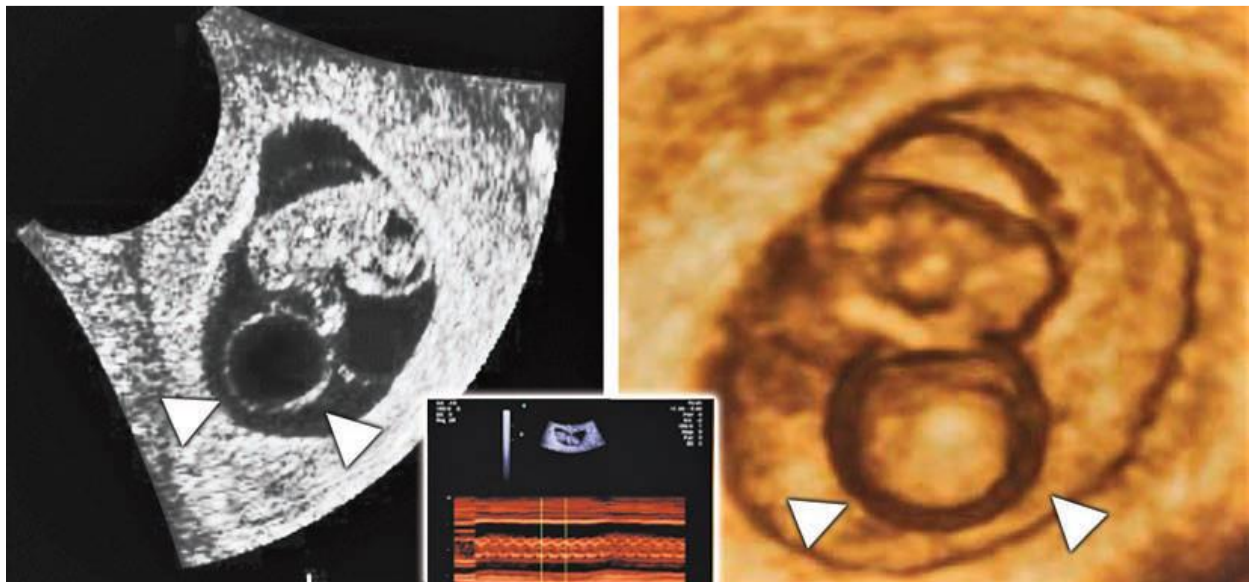


Figure 3: Huge yolk sac. Left: 2D image with normal appearance of early embryo and large yolk sac (arrowheads). Middle: Regular heartbeat of 174 beats per minute. Right: 3D image of fetus and yolk sac (arrowheads). 8 weeks and 3 days of menstrual age. Fetal demise was confirmed on the next day. Villous chromosome was 48, XY, +15,+ 21, double trisomy .(1)

Irregular yolk sac

An **irregular yolk sac** or an **abnormally shaped yolk sac** is an imaging feature that can be observed in early pregnancy scanning. It may be seen in up to 17% of early pregnancy scans. In contrast to an irregular gestational sac, the observation of an irregular yolk sac is not thought to

correlate with pregnancy failure with low sensitivity but high specificity. It should not be considered alone for the diagnosis of failed early pregnancy and follow-up ultrasonography at 7-14 days to assess the pregnancy for viability is indicated. (4).

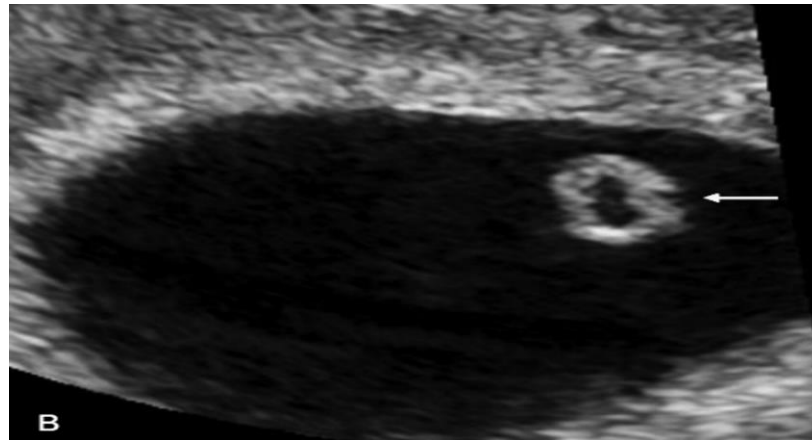
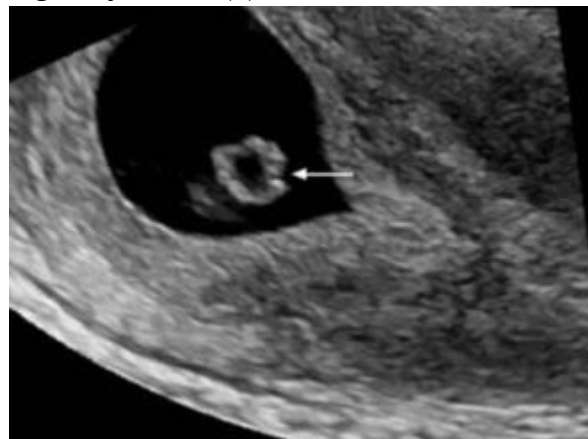


Figure 4. irregular yolk sac (4).



(B)



(A)

Figure (5): (A) Transvaginal sonography of a live embryo at 6 weeks 6 days shows a yolk sac with an irregular shape (arrow). (B) Irregular yolk sac. Transvaginal sonography at 7 weeks 1 day shows a live embryo (black arrow) and an irregular yolk sac (white arrow). The vitelline duct (arrow head) is also shown. (5)

Small yolk sac

Small yolk sac (more than two standard deviations below the mean yolk sac diameter for gestational age) can also predict poor pregnancy outcome. **Green and Hobbins (6)** reported a similar outcome with diameter less than 2 mm. **Küçük and coworkers (7)** found that the yolk sac diameter out of two standard deviations of the mean for gestational age allowed prediction of an abnormal pregnancy outcome with sensitivity of 65%, a specificity of 97%, a positive predictive value of 71% and a negative predictive value of 95%. (1)

The yolk sac size begins to decrease during the late weeks of the first trimester. This process is why gestational age should be taken into account when the size of the yolk sac is assessed. Some suggest that it may be prudent to perform serial sonographic examinations within a short period whenever a smaller than expected yolk sac is seen. It should not be considered alone for the diagnosis of failed early pregnancy and follow-up ultrasonography at 7-14 days to assess the pregnancy for viability is generally appropriate **(8)**.

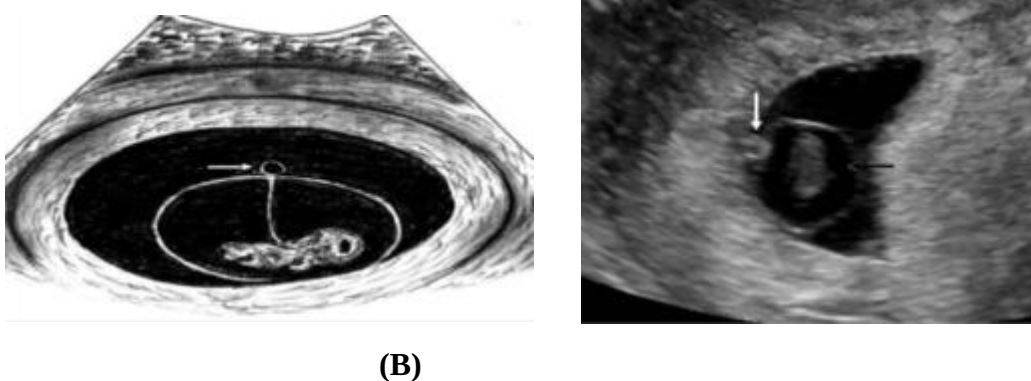


Figure (6): Small yolk sac. **A**, Diagram shows a small yolk sac (arrow) within the gestational sac. **B**, Transvaginal sonography at 7 weeks shows embryonic death (black arrow) and a small yolk sac (white arrow) with mean diameter of 1.9 mm. **(9)**.

Calcified yolk sac

A **calcified yolk sac** has been described as a sign of intrauterine demise. The cause of yolk sac calcification in failed pregnancies is uncertain but is likely related to dystrophic calcification **(10)**.

By ultrasound abnormal increased echogenicity of the yolk sac with posterior acoustic shadowing and possibly comet tail artefact. It is indeterminate yolk sac abnormality that should not be considered alone for the diagnosis of failed early pregnancy and follow-up ultrasonography at 7-14 days to assess the pregnancy for viability is indicated **(10)**.



Figure 7 . Calcified yolk sac with an embryonic demise after 2 weeks. (10)

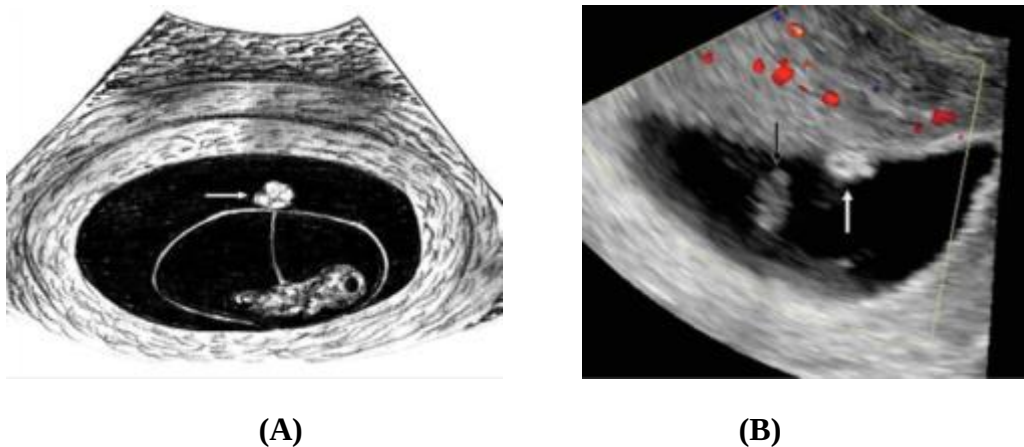


Figure (8): Calcified yolk sac. **A**, Diagram shows a calcified yolk sac (arrow) within the gestational sac. **B**, Transvaginal sonography at 6 weeks 5 days shows embryonic death (black arrow) and a calcified yolk sac (white arrow). (9)

Echogenic yolk sac

An **echogenic yolk sac** is an indeterminate finding in first-trimester fetal ultrasound. It differs from a calcified yolk sac, in that the contents of the yolk sac are echogenic, not just the rim. One study has suggested that this finding is associated with fetal demise, but other reports in the literature suggest that there may be no association. (11). Presence of hyperechogenic yolk sac is highly associated with chromosomal aneuploidy between 9th and 11th gestational weeks.(1) It should not be considered alone for the diagnosis of failed early pregnancy and follow-up ultrasonography at 7-14 days to assess the pregnancy for viability is generally appropriate(11).



Figure9. Echogenic yolk sac (11).

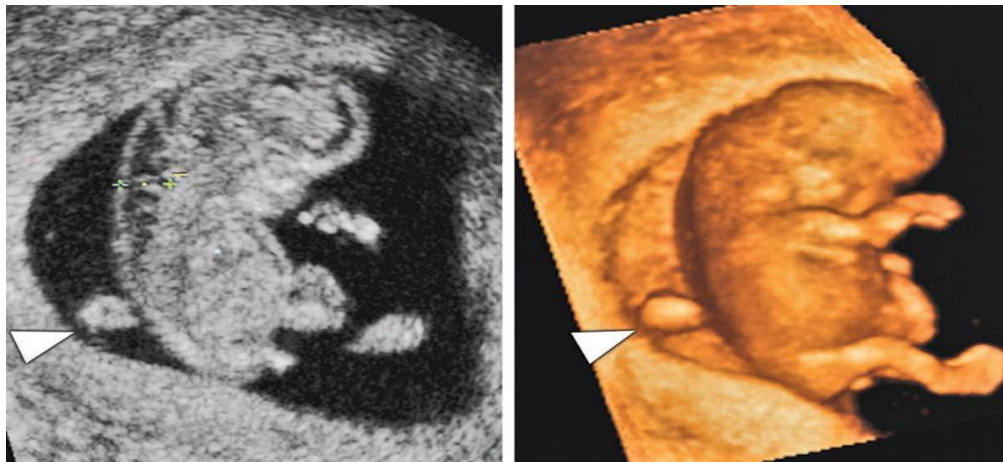


Figure 10: Hyperechoic yolk sac. Left: 2D image. Right: 3D image. 11 weeks and 3 days of gestation. Referral due to nuchal translucency. Normal heartbeat was seen. Amniocentesis resulted in trisomy 18 (1)

Absent yolk sac

The absence of yolk sac is the first sonographic indicator of an early maldevelopment. It is very important ultrasound finding of a blighted ovum (anembryonic pregnancy). In this case, we should distinguish between intrauterine and ectopic pregnancy (1). Absence of the yolk sac in the presence of an embryo on a transvaginal ultrasound is considered abnormal, and in general is associated with subsequent embryonic death (12).

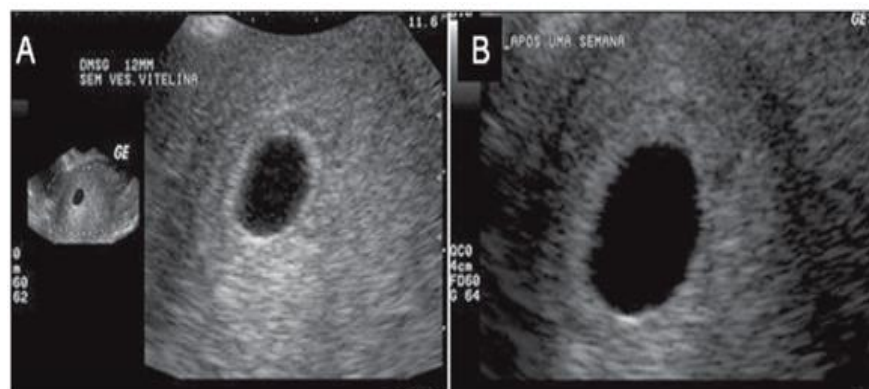


Figure11. Absent yolk sac (12)

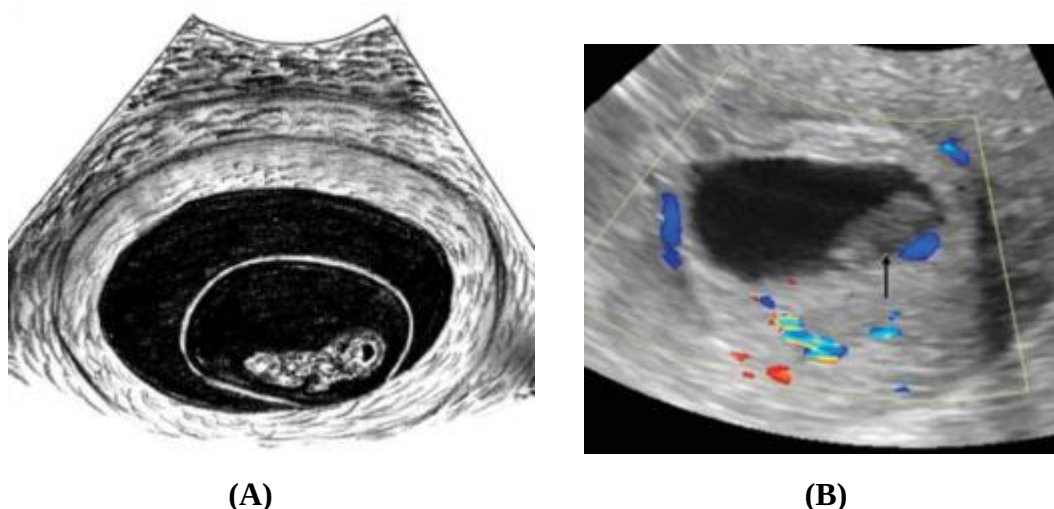


Figure (12): Absence of a yolk sac. **A**, Diagram shows absence of a yolk sac within the gestational sac. **B**, Transvaginal sonography at 6 weeks 6 days shows embryonic death (arrow) with absence of a yolk sac in the extraembryonic area. **(5)**

Persistent Yolk Sac:

When the 10th or 11th week of gestation is completed, the yolk sac begins to shrink rapidly and eventually disappears. **(13)**

The yolk sac sometimes can persist between the amnion and the chorion even after twelve weeks of gestation. The persistent yolk sac usually is found close to the site where the umbilical cord enters the placenta. The importance of a persistent yolk sac is not proved clinically. **(9)**

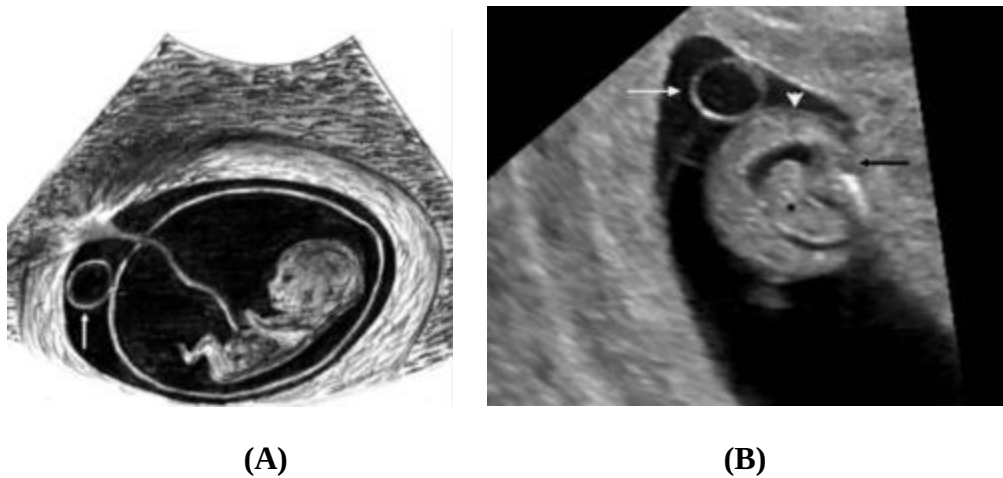


Figure (13): Persistent yolk sac. A, Diagram shows a persistent yolk sac (arrow) within the gestational sac. B, Transvaginal sonography at 12 weeks 3 days shows a live fetus with a persistent yolk sac (white arrow). The fetal head (black arrow), choroid plexus (star), and amniotic membrane (arrowhead) are indicated. (5)

Abnormal yolk sac circulation

Kurjak and co-workers (14) demonstrated the characteristics of yolk sac circulation. They found a noncontinuous low velocity waveform with absent diastolic flow. They also detected three different types of abnormal circulation signals in patients with missed abortions: irregular blood flow, permanent diastolic flow, and venous blood flow.

Mäkikallio and coworkers (15) examined the Doppler parameters of uterine, spiral, intraplacental, chorionic, umbilical and yolk sac hemodynamics in early pregnancies. They found that in patient, who later had preeclampsia at week 8, the maternal intraplacental resistance index (RI) was higher. A week later, the yolk sac RI and umbilical artery mean velocity were lower. In late first trimester, increased velocities and RI were observed in chorionic arteries. No difference in uterine, spiral artery hemodynamics and in umbilical artery PI was observed. (1)

Table 1: Normal and abnormal yolk sac characteristics . (1)

	Normal findings	Abnormal findings
Characteristics	Echogenic rim, hypoechoic center	Hyperechoic
Shape	Round	Distorted
Size	3–4 mm in the 5th week 5–6 mm in the 10th week	Less than 2 mm or more than 6 mm

Doppler	Noncontinuous, absence of diastolic flow	Irregular blood flow, permanent diastolic flow, venous blood flow
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Yolk Sac Diameter as a Prognostic Factor for First Trimester Pregnancy Outcome

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. TVS can detect the yolk sac as early as the 5th week of pregnancy (16).

Normally, yolk sac appears as a round structure with an anechoic center surrounded by a uniformly thick and well-defined echogenic wall. 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 (17).

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 (18).

Absence of the yolk sac, too large (>6 mm), too small (<3 mm), irregular shape or having degenerative changes (calcifications or decreased translucency) are the various abnormal ultrasound appearances of YS (19).

The presence or absence of yolk sac had a significant association with the pregnancy outcome. According to (20) 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 groups, there was a significant association with the ratio and pregnancy outcome.

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 (21).

Kucuk et al. (22) 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 (22).

A study conducted by **Mousa et al. (23)** 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 (23).

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 (24).

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