Original Paper

Can Ultrasound Analysis of the Yolk Sac be a Predictor of Pregnancy Outcome?

MIHAELA MARIN[1], CIPRIAN LAURENȚIU PĂTRU[2], MARIA MAGDALENA MANOLEA[2], LILIANA NOVAC[2], ANDA LORENA DIJMĂRESCU[2], MIHAI VIRGIL BOLDEANU[3], MIRCEA-SEBASTIAN ȘERBĂNESCU[4], LIDIA BOLDEANU[5], DOMINIC GABRIEL ILIESCU[2]

[1]*Ph.D. Student, University of Medicine and Pharmacy of Craiova, Romania*

[2]*Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, Romania*

[3]*Department of Immunology, University of Medicine and Pharmacy of Craiova, Romania*

[4]*Department of Medical Informatics and Biostatistics, University of Medicine and Pharmacy of Craiova, Romania*

[5]*Department of Microbiology, University of Medicine and Pharmacy of Craiova, Romania*

ABSTRACT: The Yolk sac is the first source of transfer between the mother and the embryo, with a nutritional and gas exchange function, vital for the development of the embryo, to which we can add primitive hematopoiesis, the production of stem cells and germ cells. Although normal-term pregnancies with abnormal aspects of the yolk sac have been described, the smaller or larger size of the yolk sac is associated with pregnancy loss. Our study aimed to determine whether the yolk sac size change, determined by measuring diameter (2D ultrasonography) or volume (3D ultrasonography), is independently associated with adverse pregnancy outcomes. The results of the study did not show a statistical significance between 2D and 3D measurements with adverse pregnancy outcomes, noting only an abrupt increase in the diameter and volume of the yolk sac preceding pregnancy loss. However, the evaluation of the yolk sac remains an important element in the ultrasound evaluation of pregnancy in the first trimester

KEYWORDS: *Yolk sac, ultrasonography, pregnancy outcome.*

Introduction

Inside the gestational sac, in the first trimester, when the placental circulation is not yet established, a round structure with hypoechoic characteristics and an echogenic contour is visualized. This is the yolk sac and represents the first source of transfer between the mother and the embryo, with a nutritional and gas exchange function, vital for the development of the embryo, to which are added primitive hematopoiesis, the production of stem cells and germ cells.

The yolk sac can be seen on ultrasound for about 5 weeks, sometimes before the embryo is viewed, with a size of 5 to 6mm. A size greater than 6mm may be associated with miscarriage or fetal abnormalities, even if normal pregnancies have been described in these considerations [1,2]. In normal pregnancies, the yolk sac increases in size to about 11 weeks of gestation, after which it disappears to 12 weeks of gestation. Changes in the size and shape of the yolk sac may be representative of a poor prognosis of pregnancy, especially with miscarriages in the first trimester [3]. Most studies refer to the short-term prognosis, the first trimester when it refers to the outcome of pregnancy. And indeed, both the shape and size of the yolk sac are involved in the production of miscarriage. Some studies have confirmed these claims [1,4], while other studies do not agree with this [5]. Odland Karlsen's study showed that the yolk sac is involved in regulating embryonic growth, even having a compensatory capacity, to ensure normal embryonic growth [6]. This was demonstrated by estimating fetal weight (EFW) and the birth weight of the newborn [7]. Visualization of the yolk sac may be of increased quality by transvaginal use of 3D ultrasound in the first trimester [8]. But even in this situation, some authors have not confirmed clinical benefits in terms of prediction of miscarriage [9], while others show that 3D ultrasonography can be used as a predictor for miscarriage [10].

This study aimed was to determine whether yolk sac size, measured transvaginally in the first trimester, by 2D and 3D ultrasound, can predict adverse pregnancy outcomes, related to miscarriage in the first trimester and subsequent complications, premature birth, and birth of small for gestational age (SGA) children.

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Material and Method

The study was performed in the Antenatal Diagnostic Unit of Obstetrics and Gynecology Department of the Emergency County Hospital from Craiova during 2016-2019. We included 82 patients diagnosed with intrauterine singleton pregnancy by transvaginal ultrasound starting from 5 weeks of gestation. The data were collected using a General Electric Voluson ultrasound machine using 2D and 3D ultrasonography. We used the VOCAL "manual mode" technique for the PV calculation-after a degree rotation in plane A (axial).

Patients were followed until delivery, the weight and evolution of newborns being monitored. The inclusion criteria were singleton pregnancy, pregnant women with gestational age between 5.5-11.6 weeks of gestation. The exclusion criteria were pregnant women with first-trimester pregnancy pathology, including subchorionic hemorrhage, ectopic pregnancy, imminent abortion, hydatiform mole. All patients were counseled, informed, and signed written informed consent.

We defined as normal, the yolk sac according to the dimensions established at each gestational age, according to the nomograms, with a diameter between 3-5mm, round shape with an echogenic contour. We defined it as abnormal, the yolk sac smaller or larger than the dimensions established at each gestational age, according to the nomograms, with an irregular shape, and an echogenic yolk sac.

The study was approved by the Ethics Committee of the University of Medicine and Pharmacy from Craiova.

The statistical assessment was carried out in Excel (Microsoft, USA). Since all available data was categorical for statistical significance we used the Chi-square test. A p-value less than 0.05 was considered statistically significant for all tests performed.

Results

The clinical characteristics of the investigated cases are presented in Table 1.

The mean age of the investigated cases was 30 years±3.84 SD (range: 23-41 years); the mean BMI was 25.17kg/m2±3.96 SD (range: 19.56-35.16); gestational age at birth was 37.4 weeks±2.08 SD (range: 29.4-39.2); birth weight (percentiles) was 20±29.90 SD (range: 4-98); Apgar score at 1 min was 7±2.80 SD (range: 6-10); Apgar score at 5 min was 8±3.07 SD (range: 7-10).

Table 1. Clinical characteristics of the cases.

Parameter	Mean	StDev	Minimum	Maximum
Age (years)	**30.65**	**3.84**	**23**	**41**
BMI (kg/m2)	**26.33**	**3.96**	**19.52**	**35.16**
Gestational age at birth (weeks)	**37.09**	**2.08**	**29.4**	**39.2**
Birth Weight (percentiles)	**30.16**	**29.33**	**4**	**98**
Apgar score 1 min	**7.02**	**3.18**	**6**	**10**
Apgar score 5 min	**8.03**	**3.44**	**7**	**10**
Miscarriage first trimester (weeks)	**10.02**	**0.67**	**8.5**	**10.6**
Premature birth (weeks)	**35.23**	**2.33**	**29.4**	**36.5**
SGA (percentiles)	**7.69**	**1.84**	**4**	**9**

Up to 10.6 weeks of pregnancy miscarriage occurred in 8 cases, in the last week between 11 and 11.6 weeks of pregnancy no abortion occurred. The mean gestational age at which abortions occurred was 10.02 weeks±0.67 SD (range: 8.5 weeks-10.6 weeks). They gave birth prematurely to 25 pregnant women with a gestational age of 35.23 weeks±2.33 SD (range: 29.4 weeks-36.5 weeks). Pregnancies were completed with 13 newborns SGA with mean percentiles 7.69±1.84 SD (range: 4-9 percentiles).

Analysis of the mean diameter and volume of the yolk sac showed us that in the case of miscarriage of the first trimester of pregnancy, they were similar in the first weeks of pregnancy, then, in pregnancies where pregnancy loss occurred, mean diameter and volume, presented an abrupt rise (Figure 1).

Until 11 weeks of pregnancy, however, there was no numerical significance between values (Table 2).

The mean volume yolk sac showed an increase, similar to mean yolk sac diameter, in cases that ended with miscarriage, but without a statistical significance of the values.

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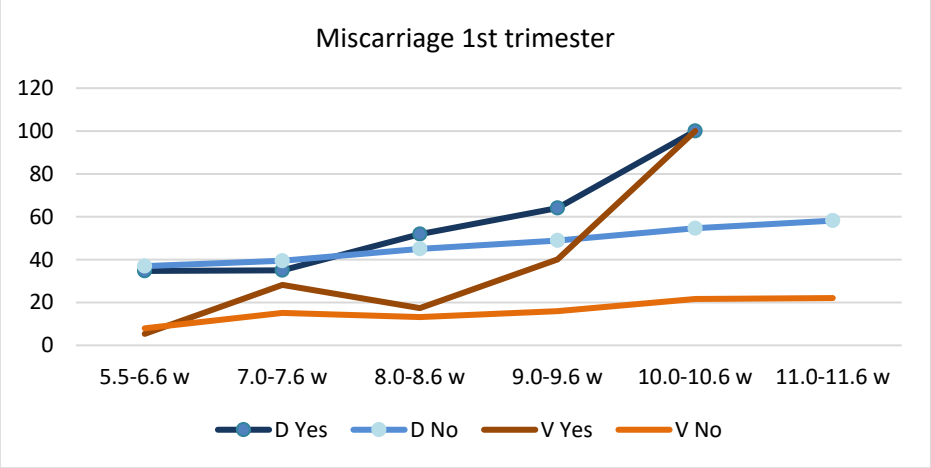

Figure 1. Distribution of miscarriage according to yolk sac diameter and volume.

Table 2. Correlation of mean yolk sac diameter with miscarriage.

	5.5-6.6 w	7.0-7.6 w	8.0-8.6 w	9.0-9.6 w	10.0-10.6 w	11.0-11.6 w
Yes	3.0	3.0	4.4	5.5	8.5	
No	3.2	3.4	3.8	4.2	4.7	5.0
Miscarriage			1	2	5	8
P value	0.65	0.23	0.27	0.23	0.22	N/A

Table 3. Correlation of mean yolk sac volume with miscarriage.

	5.5-6.6 w	7.0-7.6 w	8.0-8.6 w	9.0-9.6 w	10.0-10.6 w	11.0-11.6 w
Yes	0.04	0.19	0.11	0.26	0.66	
No	0.05	0.10	0.09	0.11	0.14	0.15
Miscarriage			1	2	5	8
P value	0.06	0.47	0.14	0.08	0.19	N/A

We wanted to see if the aspect and size of the yolk sac influence the outcome of ongoing pregnancies after the first trimester, with 25 premature births and 13 cases with newborn SGA.

In cases of premature birth, mean yolk sac diameter showed values within normal limits, but lower than in cases with normal evolution, having a statistical significance only at the end of the first trimester of pregnancy. (Table 4, Figure 2).

Mean yolk sac volume had no statistically significant values for preterm birth, only a p-value at the limit at 9 weeks of gestation (Table 5, Figure 2).

Table 4. Correlation of mean yolk sac diameter with premature birth.

	5.5-6.6 w	7.0-7.6 w	8.0-8.6 w	9.0-9.6 w	10.0-10.6 w	11.0-11.6 w
Yes	3.3	3.4	3.7	4.1	4.7	4.5
No	3.1	3.3	4.0	4.4	4.9	5.2
P=	0.32	0.67	0.26	0.17	0.42	0.02

Table 5. Correlation of mean yolk sac volume with premature birth.

	5.5-6.6 w	7.0-7.6 w	8.0-8.6 w	9.0-9.6 w	10.0-10.6 w	11.0-11.6 w
Yes	0.1	0.2	0.1	0.1	0.1	0.1
No	0.0	0.1	0.1	0.1	0.2	0.2
P value	0.49	0.15	0.79	0.049	0.10	0.12

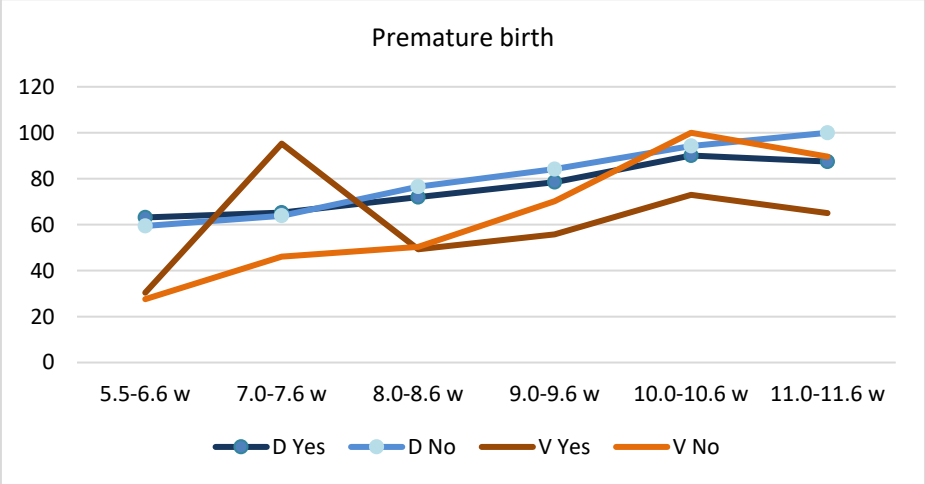

Figure 2. Distribution of premature birth according to yolk sac diameter and volume.

In cases with newborn SGA, mean yolk sac diameter also showed values in the normal range, but to the lower limit. We found no statistical significance until around the age of 6 weeks of pregnancy, but this cannot be used as a predictive element (Table 6, Figure 3).

Regarding mean yolk sac volume, we did not find a statistical significance of the measured values, but there is approximately the same course of value curves in both newborn SGA and those with birth weight percentages over 10, but with lower values in those with SGA (Table 7, Figure 3).

Table 6. Correlation of mean yolk sac diameter with SGA.

	5.6-6.6 w	7.0-7.6 w	8.0-8.6 w	9.0-9.6 w	10.0-10.6 w	11.0-11.6 w
Yes	3.6	3.5	4.2	4.2	4.7	4.9
No	3.1	3.3	3.8	4.3	4.8	5.0
P=	0.01	0.27	0.22	0.90	0.54	0.72

Table 7. Correlation of mean yolk sac volume with SGA.

	5.5-6.6 w	7.0-7.6 w	8.0-8.6 w	9.0-9.6 w	10.0-10.6 w	11.0-11.6 w
Yes	0.1	0.1	0.1	0.1	0.1	0.1
No	0.0	0.1	0.1	0.1	0.2	0.2
P value	0.49	0.56	0.40	0.35	0.32	0.13

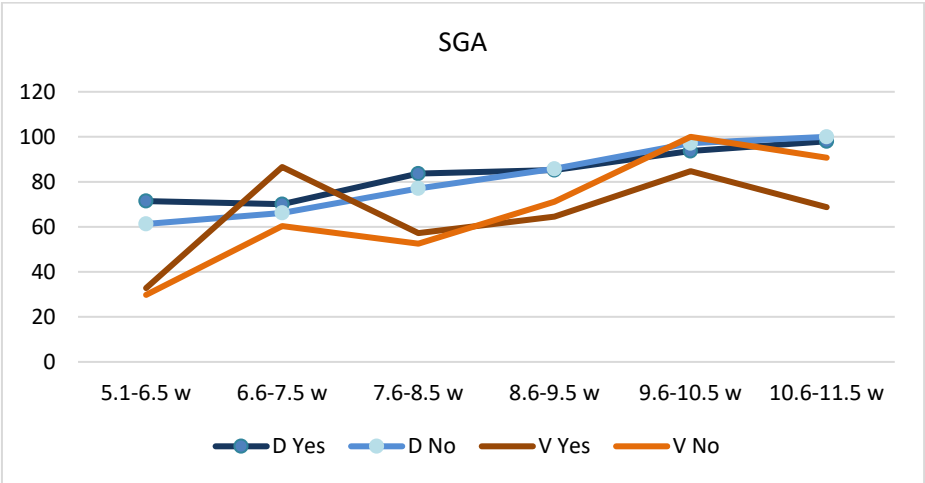

Figure 3. Distribution of SGA according to yolk sac diameter and volume.

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Discussions

The yolk sac is the first structure that can be seen sonographically at the level of the gestational sac when its mean diameter is 5-6mm, but the monitoring of the yolk sac must be started when the diameter of the gestational sac is over 8mm [11].

During early gestation, the yolk sac performs some vital functions for the development of the embryo, which includes the first stage of exchanges between mother and embryo, nutrition, and gas exchange, to which is added primitive hematopoiesis and germ cell production. Its development progresses from 5 weeks of gestation until the end of the 10th week of gestation, after which it disappears towards the end of the first trimester and is no longer visualized sonographically at approximately 14 weeks of gestation [12].

The yolk sac has been studied and has been established as a marker of miscarriage. A larger or smaller size was associated with pregnancy loss [1,13,14].

But keep in mind that an abnormal appearance of the yolk sac does not necessarily mean pregnancy loss, as normal pregnancies with an enlarged yolk sac have also been encountered. In this situation, the abnormal morphological appearance and dimensions over 9mm of the yolk sac may show a fetal growth disorder [6,15].

In our study, according to other studies [1,5,12,17], we found that an abrupt increase in the diameter of the yolk sac can precede a miscarriage. But because we had no significant statistical significance, it shows that in our study mean yolk sac diameter and miscarriage were not correlated, probably due to the small number of cases with changes in the yolk sac and the random and consecutive choice of cases, this being a limitation of our study. Also, due to the partial genetic investigation of the cases, along with the others previously exposed, we can say that this study represents only a descriptive model and cannot be considered as a validation study.

But not all authors have found a concordance between the mean diameter and the mean volume increase of a yolk sac with pregnancy loss. Both Küçük and Cho showed that in the presence of fetal heartbeats, the abnormal appearance and small yolk sac are much more involved and specific for miscarriage than the large yolk sac [4,18].

Given the studies performed by 3D ultrasonography, which report that 3D measurements of the volume of intrauterine structures correlate with conventional 2D measurements, and given the increased relevance of 3D ultrasound especially in the first trimester of pregnancy [19], we also measured the volume of the yolk sac. But unlike these studies, the values we measured did not correlate with miscarriage in the first trimester and pregnancy outcome.

It has been shown that 3D ultrasound may be more accurate than 2D ultrasound in estimating first trimester measurements [20].

It seems that 3D measurement of volumes in the first trimester offers advantages through a more accurate visualization of the yolk sac [21], but Kamel et al. in a recent study, measuring various parameters, including yolk sac volume, in the first trimester, they showed that yolk sac volume as an individual predictor has a low specificity and sensitivity, as well as a negative and positive predictive value around 60%, without statistical significance. But the combination of several parameters seems to improve the prediction rate [23].

According to our study, it seems that the 3D ultrasonographic evaluation did not show us that the use of this ultrasonographic method would be superior in accuracy to the 2D investigation of the yolk sac. Moreover, Figueras et al. could not establish that yolk sac volume could be an independent predictor of miscarriage [9].

Contrary to these results, we consider that the evaluation of the yolk sac, 2D but also 3D, especially the follow-up in dynamics, should be part of the ultrasound examination in the first trimester, to select a pregnancy at risk, because not only the size of the yolk sac can give reports about the evolution of the pregnancy but also its appearance and shape, many pregnancies with changes in shape and echogenicity, having a normal evolution [23].

Conclusions

The evaluation of the yolk sac is crucial to identify pregnant women at high risk of pregnancy loss and to have lesser complications related to the evolution of pregnancy after the first trimester.

It is correct that the prediction of the evolution of the pregnancy should be made only after the analysis of several ultrasound parameters of the first trimester, which can be combined by 2D or 3D ultrasonography.

Conflict of interests

None to declare.

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Corresponding Author: Lidia Boldeanu, Department of Microbiology, University of Medicine and Pharmacy of Craiova, Romania, e-mail: lidia.boldeanu@umfcv.ro