

Original Article

Alterations in time intervals of ductus venous in growth-restricted fetuses

Obstetrics

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ABSTRACT

Background: Small-for-gestational-age (SGA) is a term used to describe an infant whose birth weight is below the 10th centile for the appropriate gestational age.

Objective: To screen the time intervals of ductus venosus waveforms in growth-restricted fetuses to predict fetal hypoxia, placental insufficiency and adverse outcome at delivery time to improve the perinatal outcome.

Methodology: This case control study involved fifty individuals with singleton pregnancies at 28-32 weeks' gestational age complicated by intrauterine growth retardation (IUGR), contrasted with a control group of 50 age-matched women, performed at Al-Zahraa Hospital, Al-Azhar University, over one year from January 2021 to December 2021.

Results: The mean systolic velocity (SDV) interval in IUGR group and control group was 275.27 ± 26.69 and 271.13 ± 31.17 respectively. The mean diastolic ductus venosus (DDV) interval was 221.87 ± 25.00 in IUGR group and 135.26 ± 40.65 in control group. DDV interval showed a statistically significant increase in IUGR group contrasted with the control group. DDV interval can significantly determine IUGR at a cutoff 197.85 and AUC was 0.975 with high sensitivity, high specificity, positive predictive value (PPV) and negative predictive value (NPV) were 94%, 100%, 100% and 94.3% consequently ($p < 0.001$). Meanwhile, SDV interval can insignificantly determine IUGR at cutoff 245.98 and AUC was 0.544 with sensitivity, specificity, PPV & NPV was 84%, 32%, 55% & 66.7% consequently ($p > 0.05$).

Conclusion: The study suggested that the screening of ductus venosus waveforms in growth-restricted fetuses can predict fetal hypoxia, placental insufficiency, and adverse outcomes, potentially improving perinatal outcomes.

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Keywords: SGA; small-for-gestational-age, ductus venous; fetuses, IUGR.

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INTRODUCTION

The term Small-for-gestational-age (SGA) refers to an infant that is born with a birth weight that is on the lower end of the 10th centile [1]. The population-based centiles are usually utilized to describe SGA birth. But babies identified using centiles specific to maternal characteristics (as maternal height, parity, weight, in addition to ethnic group), gestational age at delivery, and infant sex are more likely to be at a higher risk of death and morbidity than babies identified using population centiles. [2].

Abdominal circumference (AC) or estimated fetal weight (EFW) readings below the third percentile indicate severe SGA, and readings below the tenth percentile indicate mild SGA [3]. Fetal growth restriction (FGR) is not equivalent to SGA. A subset of

growth-restricted fetuses and babies are classified as SGA, while 50-70% of SGA fetuses are constitutionally small, exhibiting fetal growth that aligns with maternal size as well as the race [4].

An essential part of fetal circulation, the Ductus Venosus (DV) carries oxygenated blood from the umbilical veins to the heart. When it comes to fetal monitoring, the Doppler flow velocity waveform (FVW) has been widely used [5]. The objective of this study was to screen time intervals of DV waveforms in growth-restricted fetuses to predict fetal hypoxia, placental insufficiency and adverse outcome at delivery time to improve the perinatal outcome.

PATIENTS AND METHODS

This case-control study was performed on 50 individuals with singleton pregnancies 28-32 weeks' gestational age complicated by intrauterine growth retardation (IUGR) compared to a control group of 50 women normalized for age, at El-Galaa Teaching Hospital, in a one-year period from January 2021 to December 2021.

Inclusion criteria: pregnant females aged between 18-43 years, singleton pregnancies without any major congenital anomalies and gestational age between 28-32 weeks.

Exclusion criteria: cases with major fetal anomalies, bloody or meconium-stained amniotic fluid and pre-

existing vaginal bleeding, multiple pregnancy, chromosomal abnormalities.

Methods

Abdominal ultrasound, general examination, and complete history-taking were applied to all patients. The Voluson 730 ultrasound scanner (GE Healthcare Austria GmbH, Seoul, South Korea) is equipped with a three to five MHz convex array sector transducer. The abdominal ultrasound protocol involved placing a 3.0 MHz probe to the patient's right side, angled inferiorly to visualize the bladder, and tilted upward to reveal the cervix and uterine fundus. After a transverse scan, the probe was rotated clockwise to provide a longitudinal view, revealing the bladder anteriorly and inferiorly.



Figure (1): US image of ductus venosus

A. Axial/oblique plane, B. parasagittal plane of the fetal abdomen in color Doppler, showing the umbilical vein (UV) and the ductus venosus (DV). Note the narrow size of the DV in A and B, and the presence of aliasing on color Doppler, an important feature that helps in its recognition. In B, the parasagittal plane shows the DV in longitudinal view and is preferred in early gestation. C. An image of Ductus Venosus flow at 12 weeks' gestation. There is reversed flow in the "A" wave increasing the risk for aneuploidy (S: ventricular systole D: ventricular diastole)

Examination technique

In order to collect a good sample, the fetus should be still living as possible. Color flow mapping is then utilized to visualize the umbilical vein, DV, and fetal heart utilizing a right ventral mid-sagittal view of the fetal trunk. For a Doppler sample as small as 0.5-1 mm, the optimal angle of the probe is such that it passes through the fetal abdomen in a mid-sagittal or

transverse oblique plane; this produces a picture that is sufficiently enlarged to fill the entire screen. To provide a clear evaluation of the A wave, the insonation angle should be 30° or smaller, the sweep speed should be 2-3 cm/s, and the wall filter should be set low enough to avoid obstructing the waveforms (figures 1 and 2).

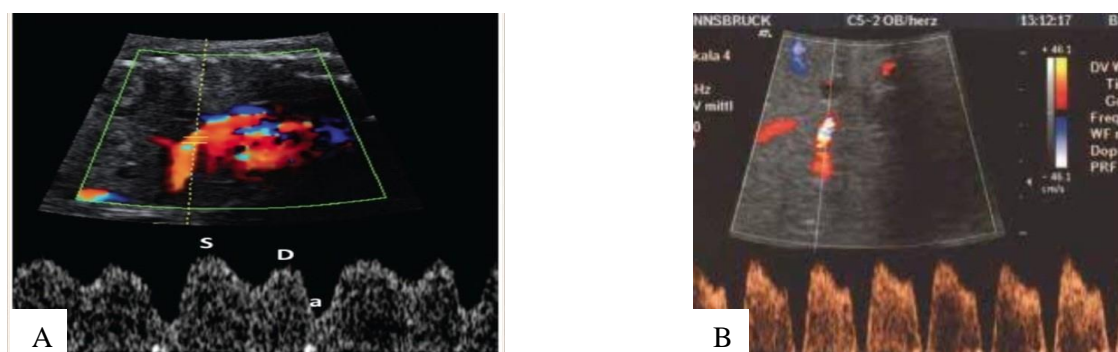


Figure (2): Doppler US of ductus venosus

A. Normal color Doppler of ductus venosus (S: ventricular systole D: ventricular diastole). B. Color Doppler US image of ductus venosus showing reverse flow in late diastole suggestive fetal compromise

Statistical analysis

Statistical Package for Social Science (SPSS) version 20.0 from IBM was utilized for data analysis (IBM Corporation, 2017). Percentages and numbers were utilized to qualitative data. A Shapiro-Wilk test was

carried out in order to guarantee that the distribution was normal. Mean \pm standard deviation (SD), median and interquartile range (IQR), as well as range (minimum and maximum) were used to describe the quantitative data. We used a 5% level of significance to

evaluate the results. Mann Whitney test, a Spearman/Pearson correlation analysis, a Chi-square test, a student t-test, Mann Whitney U test, and the receiver operating (ROC) curve were performed. For all used tests a p-value of < 0.05 is considered significant.

RESULTS

Table (1) the mean maternal age was 31.06 ± 4.15 years in IUGR group and 26.96 ± 4.41 years in control group. The mean parity was 2.12 ± 0.94 in IUGR group and 1.84 ± 1.02 in control group. The mean number of abortion was 0.86 ± 0.64 in IUGR group and 0.82 ± 0.75 in control group. In addition, the mean gestational age in IUGR and control groups was 34.62 ± 1.24 weeks and 37.18 ± 1.40 weeks respectively. Maternal age was significantly higher in IUGR group compared to control group ($p < 0.001$) while gestational age was significantly lower in IUGR group compared to control group ($p < 0.001$). No statistically significant difference was observed between the two groups regarding parity and abortion ($p > 0.05$). The IUGR group had significantly older mothers and older gestational ages in comparison to the control group. Neither group differed significantly from the other with respect to abortion or parity ($p > 0.05$). In IUGR group, 8% of women gave history of having SGA infants, 4% of them had LGA infants, 12% had preterm babies, and 8% of them reported preeclampsia. While in control group, 8% of women had SGA infants, none of them had LGA infants, 4% had preterm babies, and 8% of

them reported preeclampsia. None of women in both groups reported IUFD. without significant differences ($p > 0.05$).

Table (2) showed that the median (IQR) of systolic ductus venosus (SDV) in IUGR group and control group was 278.85 (256.58 - 296.87) and 275.74 (240.65 - 295.21) respectively. The median (IQR) of DDV was 222.5 (212.0 - 240.0) in IUGR group and 129.4 (101.6 - 174.0) in control group. In addition, the median (IQR) of Doppler perfusion index (DPI) was 0.86 (0.76 - 0.94) in IUGR group and 0.56 (0.47 - 0.62) in control group. DDV and DPI showed statistically significant increase in IUGR group in contrast to control group. While no significant distinction was observed among the two groups concerning SDV ($p > 0.05$).

Table (3) showed that the Median (IQR) of APGAR score in IUGR group and control group was 6.0 (5.0-7.0) and 8.0 (8.0- 8.0) respectively. The Mean \pm SD of birth weight was 1891.09 ± 280.2 gm in IUGR group and 2798.69 ± 262.1 gm in control group. More than half infants (58%) in IUGR group needed NICU admission while 10% infants in control group needed NICU admission. APGAR score and birth weight showed significant decrease in compared to control group. Also, IUGR group had significantly higher rate of NICU admission in contrast to control group.

Table (1): Comparison between the studied groups regarding the demographic data

Item		IUGR group n=50	Control group n=50	Stat. test	p-value
Age (years)	Mean \pm SD	31.06 \pm 4.15	26.96 \pm 4.41	t= 4.510	<0.001
	Range	25.0-41.0	18-40		
Gestational age (weeks)	Mean \pm SD	34.62 \pm 1.24	37.18 \pm 1.40	t= 7.247	<0.001
	Range	32-37	34-40		
Parity	Mean \pm SD	2.12 \pm 0.94	1.84 \pm 1.02	t = 1.193	0.233
	Range	0.0-2.0	0.0-3.0		
Abortion	Mean \pm SD	0.86 \pm 0.64	1.84 \pm 1.02	t = 0.492	0.622
	Range	0.0-4.0	0.0-4.0		
Obstetric history:					
IUFD	no. (%)	0 (0.0%)	0 (0.0%)	-	-
SGA	no. (%)	4(8.0%)	4 (8.0%)	FE ² = 0.0	1.00
LGA	no. (%)	2 (4.0%)	0 (0.0%)	FE = 2.041	0.495
Preterm	no. (%)	6 (12.0%)	2 (4.0%)	FE= 8.174	0.269
Preeclampsia	no. (%)	4 (8.0%)	4 (8.0%)	FE = 0.0	1.00

IUGR: Intrauterine growth retardation, t: Unpaired t test, FE: Fischer exact test, IUFD: Intrauterine fetal demise, SGA: Small for gestational age, LGA: Large for gestational age, *: Significant p-value (< 0.05).

Table (4) illustrates that the DPI was negative correlated with APGAR score ($r = -0.468$, $p = 0.001$), birth weight ($r = -0.515$, $p < 0.001$) and gestational age at delivery ($r = -0.442$, $p = 0.001$). Meanwhile, it was positive correlated with abortion ($r = 0.378$, $p = 0.007$), DDV ($r = 0.426$, $p = 0.002$), NICU admission ($r = 0.480$, $p < 0.001$).

Table (5) and figure (3) demonstrate that by using ROC-curve, the DDV can significantly determine IUGR at cutoff 197.85 and AUC was 0.975 with high sensitivity, high specificity, PPV and NPV was 94%, 100%, 100% and 94.3% respectively ($p < 0.001$). Meanwhile, SDV can insignificantly determine IUGR at cutoff 245.98 and AUC was 0.544 with sensitivity,

specificity, PPV and NPV was 84%, 32%, 55% and 66.7% respectively ($p>0.05$). DPI can significantly determine IUGR at cutoff 0.68 and AUC was 0.981 with high sensitivity, high specificity, PPV and NPV was 90%, 98%, 97.8% and 90.7% respectively ($p<0.001$). Moreover, DRI can significantly determine IUGR at cutoff 0.33 and AUC was 0.890 with high

sensitivity, high specificity, PPV and NPV was 72%, 98%, 97.3% and 77.8% respectively ($p<0.001$). A wave velocity can significantly determine IUGR at cutoff 28 and AUC was 0.868 with high sensitivity, high specificity, PPV and NPV was 86%, 92%, 91.5% and 86.8% respectively ($p<0.001$).

Table (2): Comparison between the studied groups regarding ductus venosus flow velocity waveforms

Ductus venosus flow velocity waveforms		IUGR group n=50	Control group n=50	Stat. test	p-value
SDV	Median (IQR)	278.85 (256.58 - 296.87)	275.74 (240.65 - 295.21)	U = 0.765	0.444
DDV	Median (IQR)	222.5 (212.0 - 240.0)	129.4 (101.6 - 174.0)	U = 8.190	<0.001*
DPI	Median (IQR)	0.86 (0.76 - 0.94)	0.56 (0.47 - 0.62)	U = 8.301	<0.001*

IQR: Interquartile range, IUGR: Intrauterine growth retardation, SDV: Systolic ductus venosus, DDV: Diastolic ductus venosus, DPI: Doppler perfusion index, U: Mann-Whitney U test, *: Significant p-value (<0.05).

Table (3): Comparison between the studied groups regarding fetal outcome

Fetal outcome		IUGR group n=50	Control group n=50	Stat. test	p-value
APGAR score	Median (IQR)	6.0 (5.0- 7.0)	8.0 (8.0- 8.0)	U = 6.525	<0.001*
BW (gm)	Mean± SD	1891.09 ±280.2	2798.69± 262.1	t = 16.73	<0.001*
NICU admission	no. (%)	29 (58.0%)	5 (10.0%)	X ² = 25.67	<0.001*

IQR: Interquartile range, APGAR: Appearance, pulse, grimace, activity and respiration, BW: Birth weight, NICU: Neonatal intensive care unit, U: Mann-Whitney U test t: independent t test, X²: Chi-Square test, *: Significant p-value (<0.05).

Table (4): Correlation between DPI with different parameters in IUGR group

Item	DPI	
	r	p- value
Age	-0.103	0.475
Parity	-0.038	0.794
Abortion	0.378	0.007*
SBP	-0.050	0.733
DBP	0.140	0.331
NICU admission	0.480	<0.001*
APGAR	-0.468	0.001*
BW	-0.515	<0.001*
GA at delivery	-0.442	0.001*
SDV	0.031	0.831
DDV	0.426	0.002*

DPI: Doppler perfusion index, SBP: systolic blood pressure, DBP: diastolic blood pressure, NICU: Neonatal intensive care unit, APGAR: Appearance, pulse, grimace, activity and respiration, BW: Birth weight, GA: gestational age, SDV: Systolic ductus venosus, DDV: Diastolic ductus venosus, r: Spearman correlation coefficients, *: Significant p-value (<0.05).

Table (5): Area under the curves, optimal cut-off points, and validity of time intervals of ductus venosus in diagnosis of IUGR

Parameter	Cutoff value	AUC	Sensitivity	Specificity	PPV	NPV	p-value
DDV interval	197.85	0.975	94%	100%	100%	94.3%	<0.001*
SDV interval	245.98	0.544	84%	32%	55%	66.7%	0.448
DPI	0.68	0.981	90%	98%	97.8%	90.7%	<0.001*
DRI	0.33	0.890	72%	98%	97.3%	77.8%	<0.001*
A wave velocity	28	0.868	86%	92%	91.5%	86.8%	<0.001*

SDV: Systolic ductus venosus, DDV: Diastolic ductus venosus, DPI: Doppler perfusion index, DRI: Diastolic Reversal Index, PPV: Positive predictive value, NPV: Negative predictive value, AUC: area under curve, *: Significant p-value (<0.05).

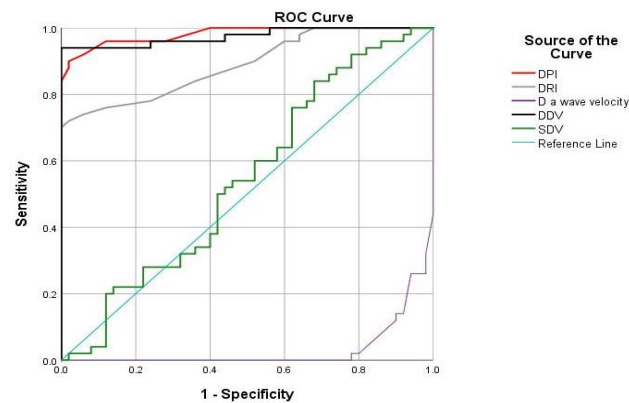


Figure (3): ROC curve of DDV, SDV, DPI, DRI, D A wave velocity in diagnosis of IUGR

DISCUSSION

The DV is a crucial part of the fetal circulatory system because it redirects oxygen-rich blood from the umbilical veins to the heart. One of the most used tools for monitoring the fetus is the Doppler FVW. It is believed that the maturity of diastolic ventricular function is reflected in the physiological reduction in DV-FVW pulsatility with advancing gestational age [6].

Our studies showed that the distribution of pregnant women who participated in the present study according to age was as follows: the mean age was 29.23 ± 5.05 years, varied from 18 years to 43 years. The majority of women (67%) aged 20 to 30 years. Regarding parity; seven (7%) women were nullipara, 22% of them were para 1, 43% were para 2 and 28% were Para 3 or more with a mean of 1.98 ± 0.69 . 53% of women had a history of abortion for once while 14% had a history of 2 abortions with a mean of 0.84 ± 0.69 .

Our studies showed that the age of the patients in the IUGR group was greater (31.20 ± 4.43 years old) than in the normal group (27.26 ± 4.89 years old), and this variation was shown to be statistically significant. In contrast, there was no significant disparity regarding parity and history of abortions. Our results were in agreement with Kiserud [7] who found that the average DV shunting in the sixty-four growth-restricted neonates was 39 percent, while it was 25 percent in the reference group (overall $P < 0.0001$).

Our study found that the IUGR group, in comparison to the control group, had a significantly higher DDV interval. The SDV interval was not significantly distinct among the two groups ($p > 0.05$). The results of our investigation were consistent with those of Wada et al. [8], who also discovered that the IUGR group exhibited a statistically significant increase in DDV interval. The results showed that in fetuses with IUGR, STV and SMV were significantly reduced ($p = 0.014$ and $p < 0.001$, correspondingly), whereas DTV and DMV were significantly increased ($p = 0.008$ and $p = 0.002$, correspondingly).

Both groups were evaluated for neonatal outcome in our study. The IUGR group had a lower GA at termination (34.72 ± 1.42 weeks) contrasted with the

normal group (35.68 ± 1.43 weeks). The IUGR group demonstrated a significantly lower APGAR score and birth weight in contrast to the control group. Furthermore, The IUGR group had a significantly greater rate of admission to the neonatal intensive care unit (NICU) in contrast to the control group. This research is in accordance with Peters et al. [9], who additionally revealed that there was a variance of about 2 kg in mean birth weights among IUGR and non-IUGR pregnancies (1229 ± 580 versus 3408 ± 558 g, accordingly; $p < .001$). We also discovered a significant disparity in birth weight among pregnancies involving intrauterine growth restriction (IUGR and those that did not. In agreement with the results of Kalanithi et al. [10], we observed that neonates delivered from IUGR pregnancies exhibited a heightened probability of obtaining Apgar scores below Five at both one and five minutes of life (17.2 percent in contrast to 2.0%; $P < .001$; as well as 4.7 percent contrasted with 0.5%; $P = .04$), as well as an increased risk of NICU admission (95.4% versus 14.2%; $p < .001$). Our findings corroborated those of Malhotra et al. [11], who also discovered a statistically significant distinction among the two groups in terms of newborn intensive care unit stay (0.0001) and birth weight ($p = 0.0001$). Higher rates of morbidity, including hyperbilirubinemia, intraventricular hemorrhage (IVH), and hemorrhage, were observed in the IUGR group. Braga et al. [12] also discovered that in comparison to the normal DV flow pattern group, the group with pathological blood velocity had a significantly lower birth weight (675 g/SD 179 g vs. 730 g/SD 190 g), and gestational age was also found to have a significant effect ($p < 0.0001$).

A negative correlation of 0.601 ($p < 0.001$), 0.808 ($p < 0.001$), and 0.724 ($p < 0.001$) was found among DDV interval and APGAR score, newborn weight, and gestational age at delivery, respectively, in our research. Our study showed that the DDV interval can significantly determine IUGR at cutoff 197.85 and AUC was 0.975 with high sensitivity, high specificity, PPV and NPV was 94%, 100%, 100% and 94.3% respectively ($p < 0.001$). Meanwhile, SDV interval can insignificantly determine IUGR at cutoff 245.98 and AUC was 0.544 with sensitivity, specificity, PPV and

NPV was 84%, 32%, 55% and 66.7% respectively ($p>0.05$).

CONCLUSION

Screening time intervals of DV waveforms in growth-restricted fetuses has shown a promising potential in predicting fetal hypoxia, placental insufficiency and adverse outcomes at delivery time which might help improve the perinatal outcome. This study may introduce a novel clinically significant measure for monitoring fetal circulation in instances of IUGR. DDV time-interval has been proven to be predictor of fetal out come in cases of IUGR. The standard parameters of the time intervals of the systolic and diastolic sections of the DV in growth-restricted fetuses can be better determined with a study that includes a larger number of patients and controls. This will help predict fetal hypoxia, placental insufficiency and adverse outcome at delivery time to improve the perinatal outcome.

Conflicts of Interest: The authors declare no conflicts of interest regarding the publication of this paper.

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الملخص العربي

التغيرات في الفواصل الزمنية للقناة الوريدية في الأجنة المقيدة النمو

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ملخص البحث:

الخلفية: الأجنة صغيرة العمر الجنيني بالنسبة لعمر الحمل هو المصطلح المستخدم لوصف الرضيع الذي يكون وزنه عند الولادة أقل من النسبة المئوية العاشرة لعمر الحمل المناسب.

الهدف: فحص الفواصل الزمنية لموجات القناة الوريدية في الأجنة محدودة النمو للتنبؤ بنقص الأكسجين لدى الجنين وقصور المشيمة والنتائج السلبية في وقت الولادة لتحسين النتائج حول الولادة.

الطرق: أجريت دراسة مراقبة الحالة على خمسين فردًا يعانون من حالات حمل مفردة في عمر حملي يتراوح بين 28 و32 أسبوعًا ومعقدة بسبب تأخر النمو داخل الرحم، مقارنةً بمجموعة تحكم مكونة من 50 امرأة متطابقة في العمر، أجريت في مستشفى الزهراء، جامعة الأزهر على مدار عام واحد من يناير 2021 إلى ديسمبر 2021.

النتائج: كان متوسط الفاصل الزمني للقناة الوريدية الانقباضية في مجموعة تقييد النمو داخل الرحم والمجموعة الضابطة 275.27 ± 26.69 و 271.13 ± 31.17 على التوالي. وكان متوسط الفاصل الزمني للقناة الوريدية الانبساطية 221.87 ± 25.00 في مجموعة تقييد النمو داخل الرحم و 135.26 ± 40.65 في المجموعة الضابطة. وأظهر الفاصل الزمني للقناة الوريدية الانبساطية زيادة ذات دلالة إحصائية في مجموعة تقييد النمو داخل الرحم مقارنة بالمجموعة الضابطة. يمكن أن تحدد فترة القناة الوريدية الانبساطية بشكل كبير تقييد النمو داخل الرحم عند نقطة القطع 197.85 وكانت المساحة تحت المنحنى 0.975 بحساسية عالية وخصوصية عالية وكانت القيمة التنبؤية الإيجابية والقيمة التنبؤية السلبية 94% و 100% و 100% و 94.3% على التوالي. وفي الوقت نفسه، يمكن أن تحدد فترة القناة الوريدية الانقباضية تقييد النمو داخل الرحم بشكل غير مهم عند نقطة القطع 245.98 وكانت المساحة تحت المنحنى 0.544 بحساسية وخصوصية وقيمة تنبؤية إيجابية وقيمة تنبؤية سلبية 84% و 32% و 55% و 66.7% على التوالي.

الاستنتاجات: أشارت الدراسة إلى أن فحص أشكال موجات القناة الوريدية في الأجنة محدودة النمو يمكن أن يتنبأ بنقص الأكسجين لدى الجنين، وقصور المشيمة، والنتائج السلبية، مما قد يؤدي إلى تحسين النتائج حول الولادة.

الكلمات المفتاحية: الأجنة صغيرة العمر الجنيني بالنسبة لعمر الحمل، القناة الوريدية، الأجنة، تأخر النمو داخل الرحم، تقييد نمو الأجنة.

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