First-trimester Uterine Artery Doppler Indices in the Prediction of Small-for-gestational Age Pregnancy and Intrauterine Growth Restriction in Low Risk Population

Mustafa Elsaid Hamed Abd ElAziz [1,*] MSc, Abd Alsattar Mohammed Ibrahim Farhan [1] MD,

Adel Aly Ahmed Elboghdady [1] MD

Corresponding Author:

Mustafa Elsaid Hamed Abd ElAziz

moustafaelsaid222@hotmail.com

[1]Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University Cairo, Egypt.

ABSTRACT

Background: Small-for-Gestational-Age (SGA) neonates have been connected with a higher risk of poor perinatal results, particularly when associated with placental insufficiency, which would be accountable for a large proportion of perinatal complications.

Aim of the work: To know the role of uterine artery Doppler indicators in the first trimester in the prediction of subsequent birth of small-for-gestational age (SGA) neonates or intrauterine growth restriction (IUGR).

Patients and methods: The think about included 1000 patients from the outpatient Gynecological Clinic, Al Hussein, Al Sayed Galal Clinics Al-Azhar College amid the period starting from August 2018 till August 2021. All patients were enduring low risk pregnancy.

Results: The first Doppler resistance index ranged (0.7-0.82) with a mean±SD (0.72±0.02), with end diastolic notch in 35% of the patients 11% right sided, 14% left sided and 10% bilateral. The first trimester Doppler showed 83.33% sensitivity to detect IUGR with specificity 96.81%. The second Doppler resistance index ranged (0.5-0.66) with a mean±SD (0.53±0.03), with end diastolic notch in 23% of the patients 7% right sided, 11% left sided and 5% bilateral. The second trimester Doppler showed 83.33% sensitivity to detect IUGR with specificity 92.55%.The fetal weight ranged (2000- 3800) gm with a mean±SD (3237.5±357.63) gm, with IUGR percentage 5%.

Conclusion: Uterine artery Doppler is a good predictive method for IUGR whether done in 1st or 2nd trimester.

Keywords: *Color Doppler uterine artery; IUGR; small for gestational age; fetal weight.*

INTRODUCTION

When a baby is in the uterus, its growth slows or stops. This is known as intrauterine growth restriction (IUGR). It's part of a larger group of fetuses known as SGA fetuses, which involves fetuses that haven't reached their full growth potential and those who are naturally small.[1]

Constitutionally small fetuses account for 50–70% of fetuses having birth weight under the 10th centile for GA. The probability of IUGR increases when the centile for defining SGA decreases. A fetus with growth restriction, on the other hand, might not be SGA.[2]

SGA fetuses are usually healthy, with just a modest rise in perinatal morbidity and death when compared to properly growing fetuses. On the other hand, IUGR is linked to an increased risk of perinatal death and morbidity as a result of the insufficiency of chronic uteroplacental.[3] Detecting IUGR-risk pregnancies is critical, as antenatal detection of decreased fetal development has been demonstrated to lower perinatal death and morbidity by 4-5 fold.[4]

Many investigations have found a link between uterine artery Doppler resistance indices (RI) in the second trimester and the development of IUGR later on. Nevertheless, research suggests that trophoblast invasiveness is greatest in the 1st trimester, when uterine artery flow of blood can also be evaluated with a Doppler.[5]

While some research has looked at the association between UtAD and IUGR in the first trimester, their relevance is restricted due to the usage of SGA as a surrogate for IUGR.[6]

SGA is defined as a birth weight under the 10th or 5th centile, which encompasses a wide range of birth weights, from naturally small, healthy newborns born at term to those with significant placental damage necessitating emergency preterm delivery.

In a randomly selected, low-risk pregnant population, there is a strong association between the least UtA PI value and birth weights. Since fetal growth is a complex process wherein placentation is only one of the components implicated, using a single metric like Doppler velocimetry distant from the delivery to anticipate birth weights in a low-risk group appears to be less beneficial than in a high-risk group.[7]

PATIENTS AND METHODS

A total of 1000 low risk pregnant women were included in this study after taking their consent for this clinical trial after full explanation of the trial during the period from 2018 to 2021.

Grouping:

The study incorporated 1000 patients from the outpatient Gynecological Clinic, Al Hussein, Al Sayed Galal Clinics Al-Azhar College in the midst of the period starting from October 2018 till May 2021. All women in this study attended twice before delivery, first time was in the 1st trimester at 10th to 12th week of pregnancy, and second time was in 2nd trimester at 22nd to 26th week of pregnancy. In the two times UtAD indices were recorded. The weight of the newborn at time of delivery was measured; the relation between results was evaluated.

Inclusion Criteria:

Women had regular menstrual cycles for 3-6 months. Pregnancy was not preceded by hormonal use or lactational amenorrhea. Women were sure of date of last menstrual period.

Exclusion Criteria:

Cases on medication (aspirin, heparin, antioxidants or steroids) or smoking, Concurrent maternal disease (eg. renal disease, connective tissue disease, malnutrition, cardiac disease, diabetes and hypertension, Twin pregnancies and Patients who had a previous pregnancy affected by pre-eclampsia, SGA or IUGR.

Procedure:

A detailed history was taken from all patients including taking including: age, parity, gravidity, previous abortions, still births, neonatal deaths, excluding any chronic medical disorder or any acute problems.

All patients were examined generally, abdominally & vaginally to verify selection criteria.

During first trimester visit, at 10th to 12th week of pregnancy Gestational age was determined from the menstrual history and confirmed by the measurement of fetal crown-rumple length at the first-trimester scan. First-trimester scan: was performed to evaluate the uterine artery PI. The signal was updated until at least three similar consecutive waveforms were acquired, a protodiastolic notch was detected, and the RI was calculated. In this research, the RI was chosen above the pulsatility index (PI).

Second Doppler was in 2nd trimester at 22nd to 26th week of pregnancy. In the two times uterine artery Doppler indicators were recorded.

The weight of the newborn at time of delivery was measured.

Statistical analysis:

The data is statistically portrayed as mean, range, ± standard deviation (± SD), median, frequency (number of instances) and rates when fitting. Chi square (χ^2) test was performed for comparing categorical information. The correct test was utilized instep when the predicted recurrence was < 5. Statistically significant p values were < 0.05. All statistical computations have been performed using the computer software SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows. ANOVA (analysis of variance): It evaluates the uniformity of a few bunch means, was utilized to test the difference about mean values of some parameters among multiple groups. Receiver operating characteristic (ROC curve): It is a graphic representation of sensitivity vs. 1-specificity, was utilized to demonstrate the symptomatic properties of a test on a numeral scale.

RESULTS

In our study, 1000 patients of low risk pregnancy were included with no subgroup division (Table 1).

		N	%
History of abortion	*No*	420	42%
	Yes	580	58%
	Mean ± SD	**Median (IQR)**	**Range**
Gravidity	3.2 ± 1.52	3 (2 - 4)	1 - 8
Parity	2.25 ± 1.06	2 (1 - 3)	0 - 5
Abortions	0.94 ± 1.01	1 (0 - 2)	0 - 5

Table 1: Gestational history of the study group

Gestational Age	Mean ± SD	Median (IQR)	Range
1st Doppler	**11.98 ± 0.78**	**12 (11 - 13)**	**11 - 13**
2nd Doppler	**23.67 ± 1.12**	**24 (23 - 25)**	**22 - 26**

Table 2: Timing of 1st&2nd Doppler

Resistance index	Mean ± SD	Median (IQR)	Range
1st Doppler	0.72 ± 0.02	0.72 (0.7 - 0.73)	0.7 - 0.82
2nd Doppler	0.53 ± 0.03	0.52 (0.51 - 0.54)	0.5 - 0.66

Table 3: Resistance index of 1st & 2nd Doppler

End Diastolic Notch		N	%
1st Doppler	No	650	65.0%
	Right	110	11.0%
	Left	140	14.0%
	Bilateral	100	10.0%
2nd Doppler	No	780	78.0%
	Right	70	7.0%
	Left	100	10.0%
	Bilateral	50	5.0%

Table 4: End diastolic notch in 1st & 2nd Doppler

	Mean ± SD	Median (IQR)	Range
Fetal weight In gm.	3237.5 ± 357.63	3250 (3050 - 3500)	2000 - 3800

Table 5: Fetal weight at birth

		N	%
IUGR	No	950	95%
	Yes	50	5%

Table 6: Incidence of IUGR

Area under curve	Standard Error	Cutoff point	Sensitivity	Specificity	+PV	-PV	p value	sig.	95% CI
0.856	0.144	>0.75	83.33	96.81	62.5	98.9	0.0131	S	0.772 - 0.919

Table 7: Sensitivity & Specificity Of 1st trimester Doppler In Iugr

Area under curve	Standard Error	Cutoff point	Sensitivity	Specificity	+PV	-PV	p value	sig.	95% CI
0.975	0.0254	>0.54	83.33	92.55	41.7	98.9	0.0001	S	0.922 to 0.996

Table 8: Sensitivity & specificity of 2nd trimester doppler in IUGR

DISCUSSION

Small-for-Gestational-Age (SGA) fetuses have been connected with a higher risk of poor perinatal results, particularly when associated with placental insufficiency, which would be accountable for a significant proportion of perinatal complications. Abnormal findings in the umbilical artery Doppler velocimetry, which identifies growth-restricted fetuses, indicates placental insufficiency. Doppler velocimetry is used to track the hemodynamic changes caused by hypoxia in such foetuses[8].

Reduced fetal growth has consequences that extend beyond the newborn stage. Evidence is mounting that the impacts of reduced fetal growth persist into adulthood and, more importantly, through morbidity and mortality[9].

Doppler ultrasound provides data on vascular resistance as well as the flow of blood indirectly. The systolic/diastolic ratio (S/D ratio), the Resistance Index (RI = systolic velocity - diastolic velocity/systolic velocity), and the pulsatility index (systolic velocity – diastolic velocity/mean velocity) are three indicators that are regarded to be connected to vascular resistance. The major uterine artery is the vessel that is most frequently examined. The S/D ratio, or RI values, drops dramatically with increasing gestational age until 24 to 26 weeks of normal gestation. In the absence of such physiologic decline, there was an increase in the occurrence of hypertension and/or IUGR[10].

Many investigations have also found a link between uterine artery Doppler resistance indices (RI) in the 2nd trimester and the future development of IUGR, as shown by Albaiges et al., 2003[11].

Nonetheless, there has been evidence that trophoblast invasiveness has been greatest during the 1st trimester; consequently, uterine artery blood flow can be assessed using Doppler, which agrees with Dugoff et al., 2005[6], who looked at the relationship between UtAD and IUGR during the 1st trimester.

The current research aimed to evaluate the link between 1st trimester uterine artery Doppler indicators and the subsequent birth of SGA neonate or intra uterine growth retardation.

This research included 1000 patients into one group. All women who attended Al-Azhar University hospitals for a routine first-trimester ultrasound with a singleton pregnancy have been offered the opportunity to take part in the research.

The waveforms of the uterine artery were obtained using pulsed-wave Doppler. The existence of a protodiastolic notch has been documented, and RI has been determined when three comparable consecutive waveforms have been acquired. In this research, the RI has been favored above the pulsatility index (PI).

All women in this study attended twice before delivery, first time was in the 1st trimester at 10th to 13th week of pregnancy, and second time was in 2nd trimester at 22nd to 26th week of pregnancy. In the two times uterine artery Doppler indices have been recorded.

The weight of the newborn at time of delivery was measured, the relation between results were evaluated.

In this study the patient age ranged 20 – 35 years with a mean±SD (27.1±3.6). As regard obstetric history 42% had a history of previous abortion. Parity ranged (0-5) with a mean±SD (2.25 ± 1.06), abortions ranged (0-5).

The gestational age at which first Doppler was done ranged (11-13) weeks with a mean±SD (11.98±0.78). The results showed that the first Doppler resistance index ranged (0.7-0.82) with a mean±SD (0.72±0.02), with end diastolic notch in 35% of the patients 11% right sided, 14% left sided and 10% bilateral. The first trimester Doppler showed 83.33% sensitivity to detect IUGR with specificity 96.81%.

These results agree with Melchiorre et al., in 2014 [12], which discovered a connection between uterine artery Doppler RI in the first trimester and the later SGA development. In the 1st trimester, SGA with pre-eclampsia has a higher uterine artery Doppler sensitivity than IUGR alone. 3010 singleton pregnant women were assessed for uterine artery Doppler at 11–14 weeks in a prospective study. RI and the occurrence of bilateral notching have been contrasted among ladies with normal pregnancy (n = 2445) and those who delivered: SGA neonates (n = 377); SGA neonates with pre-eclampsia (n = 27); IUGR neonates with delivery at 37 weeks (n = 62); and IUGR neonates needing preterm birth (birth < 37 weeks) (n = 36). Women carrying SGA neonates had significantly higher 1st trimester uterine artery mean RI and bilateral notching incidence than women carrying normal pregnancy (median uterine artery RI,

0.74 versus 0.70, P < 0.001; bilateral notching incidence, 56.0% versus 43%, P < 0.001). SGA without pre-eclampsia, IUGR, preterm IUGR, and SGA with pre-eclampsia all had areas under the ROC curves of 0.602, 0.687, 0.776 and 0.708, respectively. In an SGA pregnancy without pre-eclampsia, there was a statistically significant inverse connection between mean uterine artery RI and pregnancy age at birth (R = - 0.329, P = 0.01).

These results disagree with Hollis et al., 2001[13] who conducted a cross-sectional study of 265 successive pregnant women undergoing regular ultrasound examinations between 11 and 14 weeks of pregnancy. The RI and the Doppler ultrasonography of the uterine arteries have both been measured. An early diastolic notch's presence or absence has also been noticed. Birth weight has been reported as Z-scores based on pregnancy results received from the birth suite database. The uterine artery RI 5th, 50th, and 95th centiles were 0.53, 0.71, and 0.85, respectively, between 11 and 14 weeks of pregnancy. Birth-weight Z-scores had a strong negative connection with first-trimester uterine artery mean RI (r = - 0.219, P = 0.001). The birth weight difference between fetuses with and without bilateral diastolic notches has been likewise significant (P < 0.001). Multiple regression analysis revealed that uterine artery notching (standardized regression coefficient =- 0.17, P = 0.017) and mean RI (standardized regression coefficient = - 0.14, P = 0.039) both led independently to birth-weight Z-score prediction. According to the study, there has been a significant negative relationship between birth weight and uterine artery Doppler parameters in the first trimester. However the study also recommended in future studies to use the birth weight percentiles for more accurate data which was done in our study.

In our study the gestational age at which second Doppler was done ranged (22-26) weeks with a mean±SD (23.67±1.12). The results showed also that the second Doppler resistance index ranged (0.5-0.66) with a mean±SD (0.53±0.03), with end diastolic notch in 23% of the patients 7% right sided, 11% left sided and 5% bilateral. The second trimester Doppler showed 83.33% sensitivity to detect IUGR with specificity 92.55%.The fetal weight ranged (2000- 3800) gm with a mean±SD (3237.5±357.63) gm, with IUGR percentage 5%.

These results agree with Papageorghiou et al., in 2001[14] which stated that, in the general population, second trimester uterine Doppler has a high prognostic value for pre-eclampsia as well as IUGR. In his studies, prediction of pre-eclampsia by uterine artery Doppler was more sensitive than prediction of low birth weights. His study covered all women with singleton gestations at 19–22 weeks' gestation in a prospective multicenter trial. The study had a total of 6,586 women in it. For 6,035 of the women, complete outcome data has been collected (91.6%). PE appeared in 75 (1.2%) of the cases, while IUGR appeared in 69 (1.1%). The uterine Doppler mPI was 0.99, with the 90th centile being 1.40. The Uterine Doppler mPI detected 70.6% of pregnancies with early-onset PE and 73.3% of pregnancies with early-onset IUGR with a 10% false-positive rate. In late-

onset cases of the illness, the test's detection rate was low (30% for IUGR and 23.5% for PE). Our study performed the Doppler late in the 2nd trimester 22nd to 26th to improve the detection of IUGR which appears in our results.

These results also agree with Jeltsje and colleagues in 2008[15], who found that uterine artery Doppler ultrasound more accurately forecasts preeclampsia, a maternal consequence of placental diseases, than IUGR. In both low and high risk women, an elevated PI accompanied by notching in the 2nd trimester is the strongest indicator of preeclampsia. Severe preeclampsia was best predicted by an elevated PI or bilateral notching. In low-risk patients, an elevated PI alone or in conjunction with notching best predicted IUGR, but RI was the strongest indicator in high-risk patients. We chose the RI as the main parameter of IUGR detection based on these recommendations.

These results disagree with Goffinet et al., 2017[16], who stated that there is no basis for testing by uterine artery Doppler in a low-risk population. The utility of uterine artery Doppler screenings in predicting fetal weight has been questioned, resulting in significant controversy. In his study, the uterine artery Doppler was conducted on the Doppler group between 20–24 weeks. Women who had abnormal findings were given 100 mg of aspirin every day until their 35th week. The outcomes of intrauterine growth restriction were not significantly different between the two groups (RR = 1.22 [0.73 - 2.04] and 1.18 [0.93 - 1.51] respectively).

CONCLUSION

According to the current study results supported by the results of other studies, uterine artery Doppler is a good predictive method for IUGR whether done in 1st or 2nd trimester.

REFERENCES

1. Lees CC, Stampalija T, Baschat AA, da Silva Costa F, Ferrazzi E, Figueras F, Hecher K, Kingdom J, Poon LC, Salomon LJ, Unterscheider J. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol*. 2020; 56: 298–312.'

2. Small-for-Gestational-Age Fetus, Investigation and Management; Royal College of Obstetricians and Gynaecologists. Green top guideline (Mar 2013)

3. Breeze AC, Lees CC. Prediction and perinatal outcomes of fetal growth restriction. *Semin Fetal Neonatal Med*. 2007; 12: 383–397. Epub 2007 Aug 31..

4. Lindqvist PG, Molin J. Does antenatal identification of small for- gestational age fetuses significantly improve their outcome? *Ultrasound Obstet Gynecol* . 2005; 25: 258–64

5. Sharma D, Shastri S, Sharma P. Intrauterine Growth Restriction: Antenatal and Postnatal Aspects. *Clin Med Insights Pediatr*. 2016 Jul 14 10:67-83.

6. Dugoff L, Lunch AM, Cioffi-Ragan D, Hobbins JC, Schultz LK, Malone FD, D'Alton ME. for the FASTER Trial Research Consortium. Quad screen as a predictor of adverse pregnancy outcome. *Obstet Gynecol*. 2005 Aug;106(2):260-7.

7. Sarmiento A, Casasbuenas A, Rodriguez N, Angarita AM, Sarmiento P, Sepulveda W.(2013): First-trimester uterine artery Doppler velocimetry in the prediction of birth weight in a low-risk population. Jan;33(1):21-4. PMID: 23225135.

8. Martinelli S, Francisco RP, Bittar RE, Zugaib M. Hematological indices at birth in relation to arterial and venous Doppler in small-for-gestational-age fetuses. *Acta Obstet Gynecol Scand*. 2009;88(8):888-93.

9. Das UG and Sysyn GD. Abnormal fetal growth: intrauterine growth retardation, small for gestational age, large for gestational age. *Pediatr Clin North Am*. 2004 Jun;51(3):639-54, viii.

10. Suneet P. Chauhan, MD Eliza Berkley, MD Alfred Abuhamad, MD. Doppler assessment of the fetus with intrauterine growth restriction. *Am J Obstet Gynecol*. 2012 Apr;206(4):300-8.

11. Albaiges G, Missfelder-Lobos H, Parra M, Lees C, Cooper D, Nicolaides KH. Comparison of color Doppler uterine artery indices in a population at high risk for adverse outcome at 24 weeks' gestation. *Ultrasound Obstet Gynecol*. 2003; 21: 170–3. PMID: 12601841.

12. Melchiorre R. Sharma, and Thilaganathan B. "Cardiovascular implications in preeclampsia: an overview," *Circulation*, vol. 130, no. 8, pp. 703–14, 2014. PMID: 25135127.

13. Hollis B, Mavrides E, Campbell S, Tekay A, Thilaganathan B. Reproducibility and repeatability of transabdominal uterine artery Doppler velocimetry between 10 and 14 weeks of gestation. *Ultrasound Obstet Gynecol*. 2001 Dec;18(6):593-7. PMID: 11844196.

14. Papagerghiou AT, Yu CK, Bindra R, Pandis G, Nicolaides KH. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. *Ultrasound Obstet Gynecol*. 2001; 18: 441–9. PMID: 11844162.

15. Jeltsje S Cnossen, Rachel K Morris 1, Marloes Langejans, Stephen C Robson, Jos Kleijnen, Gerben Ter Riet, Ben W Mol, Joris A M van der Post, Khalid S Khan, Serum screening with Down's syndrome markers to predict pre-eclampsia and small for gestational age: systematic review and meta-analysis Rachel K Morris et al. *BMC Pregnancy Childbirth*. 2008 Aug 4;8:33. PMID: 18680570.

16. Goffinet F, Atallah A, Lecarpentier E, Doret-Dion M, Gaucherand P, Tsatsaris V. Aspirin for Prevention of Preeclampsia. *Drugs*. 2017 Nov;77(17):1819-1831.