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Aortic Isthmus Color Doppler Indices in intrauterine Growth-Restricted Fetuses (A case control study)

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ABSTRACT

Background and purpose: Intrauterine growth restriction (IUGR) refers to a condition in which the fetus is smaller than expected owing to either intrinsic or environmental causes. IUGR monitoring is of great significance for determining the best delivery time and preventing fetal complications. Changes in the nature of blood in the Aortic isthmus (AoI) results in the hemodynamic disorders; the accurate monitoring of its indices conducted by a Doppler is highly useful in the clinical management of IUGR. Thus, the present study was conducted to investigate the color ultrasound indices of AoI Doppler in IUGR. *Method:* In the present study, as many as 61 pregnant women were divided into two groups; IUGR group (mothers with fetuses weighing less than 10^{th} percentile for gestational age, n=30) and control group (mothers with fetuses weighing between 10^{th} percentile to 90^{th} percentile, n=31). After recording the demographic information and measuring the gestational age, the color Doppler of umbilical artery, middle cerebral artery, ductus venosus, and isthmus of aorta (including the investigation of criteria such as peak systolic (PSV), end-diastolic (EDV) and time averaged peak (TAPV) velocities, pulsatility index (PI), and resistance index (RI)), and the required comparison was conducted between the groups. *Results:* In IUGR fetuses, UA color Doppler was non-normal for 13 individuals (43.3%) and MCA color Doppler was non-normal for 8 cases (26.7%) (Two cases of them the DV Doppler was abnormal). There was no significant difference between the IUGR and control groups in terms of values of color Doppler indicators of isthmus of aorta. There was no significant difference between the IUGR and control groups in terms of comparing the color Doppler indicators of isthmus of aorta with the normal and abnormal umbilical artery Doppler. Moreover, no significant difference was observed between healthy fetuses and IUGR ones with normal and abnormal MCA Doppler. Conclusion: The results of the present study indicate that color Doppler sonography of AoI indices were not significantly different for IUGR fetuses and healthy ones. Thus, further studies are required for deciding on the usefulness of this too for the clinical monitoring and management of IUGR fetuses.

Keywords: color Doppler ultrasound, fetal aortic isthmus, intrauterine growth restriction (IUGR)

1. INTRODUCTION

Intrauterine growth restriction (IUGR)refers to the progressive conditions in which a fetus, given its race or gender, is smaller or less developed than normal or does not follow the natural pattern of fetal growth due to either intrinsic factors or environmental causes inside the uterus (Battaglia and Lubchenco, 1967).

The causes are associated with the mother (including malnutrition, high blood pressure, smoking, anemia, and diabetes), genetic diseases such as aneuploidy, and disorders relate to the placenta such as placental mosaicism and placental infarction (Fardiazar et al., 2013; Henrichs et al., 2016; Mureșan et al., 2016; Suhag and Berghella, 2013). Since there is no definitive treatment for IUGR, the accurate clinical monitoring and management is of high significance for determining the best delivery time and preventing the fetal complications such as neonatal mortality and perinatal morbidity (Cruz-Lemini et al., 2012). There are numerous methods for providing an accurate monitoring of the existing conditions. Since the abnormal velocity in the umbilical artery blood flow is significantly associated with IUGR, conducting the velocity measurement of the umbilical artery blood flow with Doppler (LARSEN et al., 1992) and pulsatility index (Kessous et al., 2014; Zelop et al., 2013) are the most efficient methods in IUGR monitoring. However, none of the aforementioned methods has been accepted as definitive treatments. Numerous studies are being developed for determining the new indices of cardiovascular Doppler that are likely to provide more useful clinical information (Sadro and Dighe, 2013; Unterscheider et al., 2013). In addition to the umbilical artery, there are some other arteries that of great significance. The accurate monitoring of their blood flow indices by the Doppler is greatly efficient and useful in the clinical management of IUGR. The fetal circulatory system includes two distinctive and key parts: A. brachiocephalic circulatory system that is established by the left ventricle and supplies the blood for the upper half of the fetal body; and B. subdiaphragmatic placental circulatory system that is established by the right ventricle and supplies the blood for the lower half of the fetal body (Acharya, 2009; Fouron, 2003; Mäkikallio, 2008). Apart of aorta that is located between the origin of the left subclavian artery and ductus arteriosus descending aorta constitutes the only real and physiological connection path between left and right ventricles; in other words, it is located between the two umbilical fetal circulatory system (brachiocephalic and subdiaphragmatic placental) (Mäkikallio et al., 2003). This key segment is called aortic isthmus (AoI) (Abdelrazzaq et al., 2013; Acharya, 2009). The blood flow indices existing in AoI indicate the output and resistance difference between two fetal circulatory systems (Acharya, 2009). These indices can be measured and monitored by Doppler ultrasound. Changes in the nature of AoI blood flow results in hemodynamic disorders in the entire cardiac system (Abdelrazzaq et al., 2013). Thus, it is likely that the AoI Doppler indices are associated with IUGR. Since few studies have been conducted in this regard in Iran, the present study aims at investigating the aortic isthmus color Doppler indices in intrauterine growth-restricted fetuses.

2. METHOD

Study design

The present study designed as a case-control study was conducted at the High-Risk Pregnancy Clinic of Tabriz Al-Zahra Hospital from September 23, 2018 to August 22, 2019. The protocol of conducting the study was confirmed by the Ethics Committee of Al-Zahra Hospital, Tabriz University of Medical Sciences (Approval code: No. 5-6-279357). The informed letters of consent were obtained from the participants. Moreover, the researchers observed the confidentiality principles based on the Declaration of Helsinki.

Participants

The inclusion criteria for entering the present study were as follows: singleton pregnant women diagnosed with IUGR (the fetal weight of less than 10th percentile for the gestational age based on ultrasound criteria and hadlock formula (Hadlock, 1990)), lacking underlying diseases or a history of midwifery complications in the recent pregnancy, the gestational age of 26-37 weeks. In case of observing fetal anomalies and chromosomal disorders, fetal infections, premature rupture of membranes, and multiple pregnancies, the participants were excluded from the study.

Moreover, the control group's participants included the mothers who referred to the midwifery clinic and didn't have the required risk factor for IUGR and whose fetal weight had been estimated to be between 10th-90th percentile (based on ultrasound criteria and hadlock formula).

Data collection

Demographic assessment

The participants' information including the mother's age, gestational age, parity, and gravity were collected by using the checklists. For all participants, ultrasound was conducted for determining the status of the placenta, fetus, and amniotic fluid index.

The gestational age was estimated based on the date of the last menstruation and its confirmation by the ultrasound of the first trimester. If the difference between the gestational ages measured based on the last menstruation and that of the ultrasound was more than 7 days, the crown-rump length assessment in ultrasound was considered as the criterion of the gestational age.

Color doppler sonography assessment

During without uterine contraction, without respiration, and without movement of fetuses, color doppler measurements of umbilical artery (UA), middle cerebral artery (MCA) and AoI were performed on the supine and left lateral tilt position. If the MCA doppler was abnormal, ductus venus (DV) doppler would be performed. Color doppler sonography was performed by ultrasound system (*Phillips, Affiniti 70,* USA).

The AoI doppler measurement was performed using the longitudinal aortic arch or three-vessel and trachea section with an insonation angle of <30° (Fig. 1). For each examination the following parameters were measured and compared to reference ranges (Del Rio et al., 2006). Measured parameters include peak systolic (PSV), end-diastolic (EDV) and time averaged peak (TAPV) velocities, pulsatility index (PI) and resistance index (RI). All color doppler sonography were performed by the blind observer for the study (Ferrazzi et al., 2002).

IUGR sub grouping

IUGR fetuses were assessed according to doppler assessment of UA, MCA and DV and the Sub grouped to UA, MCA and DV doppler normal and abnormal.

Abnormal UA indices were elevated pulsatility index (PI) orabsent or reversed end-diastolic flow. An MCA pulsatility index (PI) of <5th percentile for gestational age was considered as evidence of cerebral redistribution or 'brain sparing'. An absent or reverse "a wave" at the DV was accepted as abnormal DV blood flow.

Statistical analysis

Statistical analysis was conducted using SPSS statistical software version 22 (Chicago, IL, USA). Distribution of data related to normality was checked using Kolmogorov–Smirnov test. Comparison between groups was performed by an Independent T test and one-way ANOVA test for normal distribution or Mann-Whitney U and Kruskal–Wallis test for non-normal distribution. $P < 0.05$ was considered statistically significant.

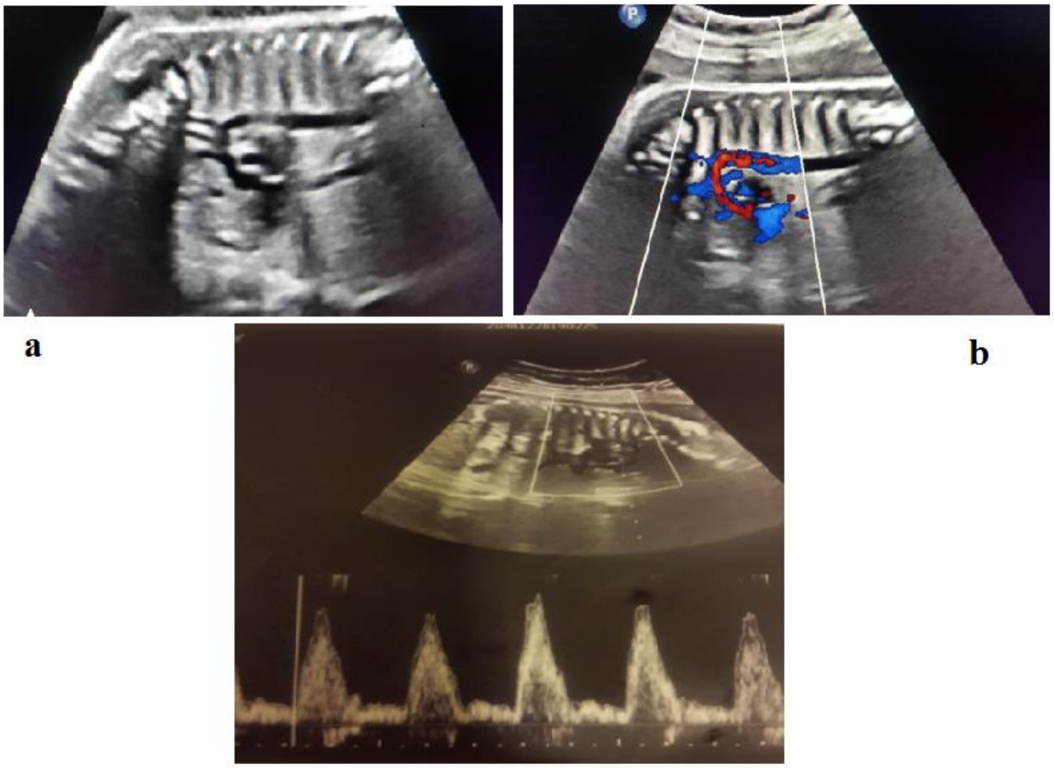

Figure 1 (a) longitudinal view of aortic arch (b) longitudinal view of aortic arch color Doppler (c) pulse-wave waveform of aortic arch

3. RESULTS

Demographic characteristics

In the present study, the case group includes 30 pregnant women referring to the high-risk pregnancy clinic with the diagnosis of IUGR fetus. Moreover, as many as 31 women having healthy fetuses (following the ultrasound examinations) were placed in the control group.

In the case group, the mean gestational age was 32.88 ± 3.16; the minimum was 26 weeks and the maximum was 37 weeks. As many as 10 participants (33.3%) were nulliparous, and the rest were multiparous. There was no significant difference between the case and control groups in terms of mothers' age, gestational age, and gravidity (table 1).

Table 1. Baseline characteristics of studied patients

	AGA N=31	IUGR N=30	P value
Maternal age, year, Mean±SD	(6.33) ±31.47	(5.17) ±31.14	0.83
Gestational age, Week, Mean±SD	(2.78) ±32.55	(3.16) ±32.88	0,65
Gravidity, Maedian (IQR)	2 (1-2)	2 (1-3)	0.71

†Mann-Whitney U test was used to analysis.
†† Independent T test was used to analysis.

Color Doppler ultrasound findings

According to the ultrasound findings in IUGR fetuses, the UA color Doppler was non-normal in 43.3% women, Moreover, the MCA color Doppler was non-normal in 8 cases (26.7%); for two cases of them, the DV color Doppler was reported to be abnormal. The increased values (higher than 95th percentile) of AoI-PI and AoI-RI were observed in 10.30 (33.3%) and 20/30 (66.7%) of IUGR fetuses. As for healthy fetuses, the aforementioned values were measured to be 10/31 (32.3%) and 15/31 (48.4%) respectively (figures 2 and 3). Furthermore, the decreased values (lower than 5th percentile) of EDV, PSV, and TAPV were respectively 1/30 (3.3%), 20/30 (66.7%), and 21/30 (70%) in IUGR fetuses. As for the healthy fetuses, the aforementioned values were respectively 0.31 (0%), 21/31 (67.7%), and 17/31 (54.8%) (Figures 4-6).

No significant difference was observed in comparing the aortic isthmus color Doppler indices between the healthy fetuses and IUGR fetuses with normal and non-normal umbilical Doppler (p>0.05) (table 3). Moreover, there was no significant difference between healthy fetuses and IUGR ones with normal and non-normal MCA Doppler (p>0.05) (table 4).

Table 2 indicates the AoI Doppler flow in IUGR and healthy fetuses. No significant difference was observed between the two groups in terms of aortic isthmus color Doppler indices (p>0.05).

Table 2 Comparison of AoI Doppler Flow Measurements in IUGR and AGA Fetuses

	AGA N=31	IUGR N=30	P value
AoI PI	3.24 (2.41 - 4.78)	3.03 (2.68 - 3.71)	0.81†
AoI RI	0.95 (0.88 - 1.00)	1.00 (0.92 - 1.00)	0.25†
AoI PSV	84.60 (70.40 - 98.70)	84.60 (56.70 - 99.20)	0.78†
AoI EDV	5.31 (0.00 - 11.50)	0.00 (0.00 - 6.95)	0.11†
AoI TAPV	28.34±(11.66)	28.23±(7.51)	0.96††

Continuous variables presented as Mean±(SD) for normally distributed variables or median (IQR) for data that are not normally distributed.
†Mann-Whitney U test was used to analysis.
†† Independent T test was used to analysis.

Table 3 AoI Doppler indices in AGA and IUGR Fetuses with normal and abnormal UA Doppler

AoI data	AGA N=31	IUGR with normal UA doppler N=17	IUGR with abnormal UA doppler N=13	P value
AoI PI	3.24 (2.41 - 4.78)	3.10 (2.73 - 3.80)	2.94 (2.53 - 3.75)	0.84†
AoI RI	0.95 (0.88 - 1.00)	0.99 (0.88 - 1.01)	1.00 (0.97 - 1.01)	0.05†
AoI PSV	84.60 (70.40 - 98.70)	83.60 (56.70 - 87.15)	85.60 (69.65 - 113.00)	0.74†
AoI EDV	5.31 (0.00 - 11.50)	0.66 (0.49 - 9.28)	0.66 (0.27 - 2.65)	0.84†
AoITAPV	28.38 ± (11.66)	26.73 ± (7.27)	30.08 ± (7.93)	0.65††

Continuous variables presented as Mean±(SD) for normally distributed variables or median (IQR) for data that are not normally distributed.
†Kruskal Wallis test was used to analysis.
††One Way ANOVA test was used to analysis.

Table 4 AoI Doppler indices in AGA and IUGR Fetuses with normal and abnormal MCA Doppler

AoI data	AGA N=31	IUGR with normal MCA doppler N=22	IUGR with abnormal MCA doppler N=8	P value
AoI PI	3.24 (2.41 - 4.78)	3.03 (2.68 - 3.71)	3.11 (2.64 - 3.83)	0.96†
AoI RI	0.95 (0.88 - 1.00)	0.99 (0.88 - 1.01)	0.99 (0.99 - 1.01)	0.09†
AoI PSV	84.60 (70.40 - 98.70)	83.80 (56.70 - 86.87)	106.10 (63.40 - 113.00)	0.20†
AoI EDV	5.31 (0.00 - 11.50)	0.71 (0.52 - 8.41)	0.44 (0.05 - 0.84)	0.23†

AoI TAPV	28.38 ± (11.66)	27.50 ± (6.66)	30.05 ± (10.08)	0.82††

Continuous variables presented as Mean±(SD) for normally distributed variables or median (IQR) for data that are not normally distributed.

†Kruskal Wallis test was used to analysis.

†† One Way ANOVA test was used to analysis.

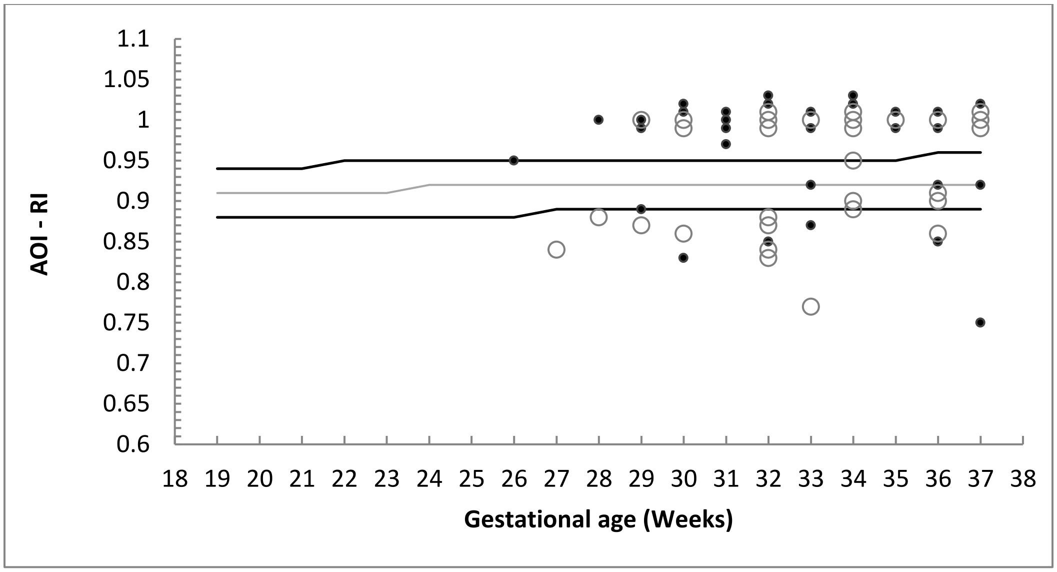

Figure 2 Resistance index in the aortic isthmus (AoI-RI) in IUGR (•) and AGA (◦) fetuses expressed as 5th, 50th and 95th centiles (-) according to gestation in appropriate for gestational age.

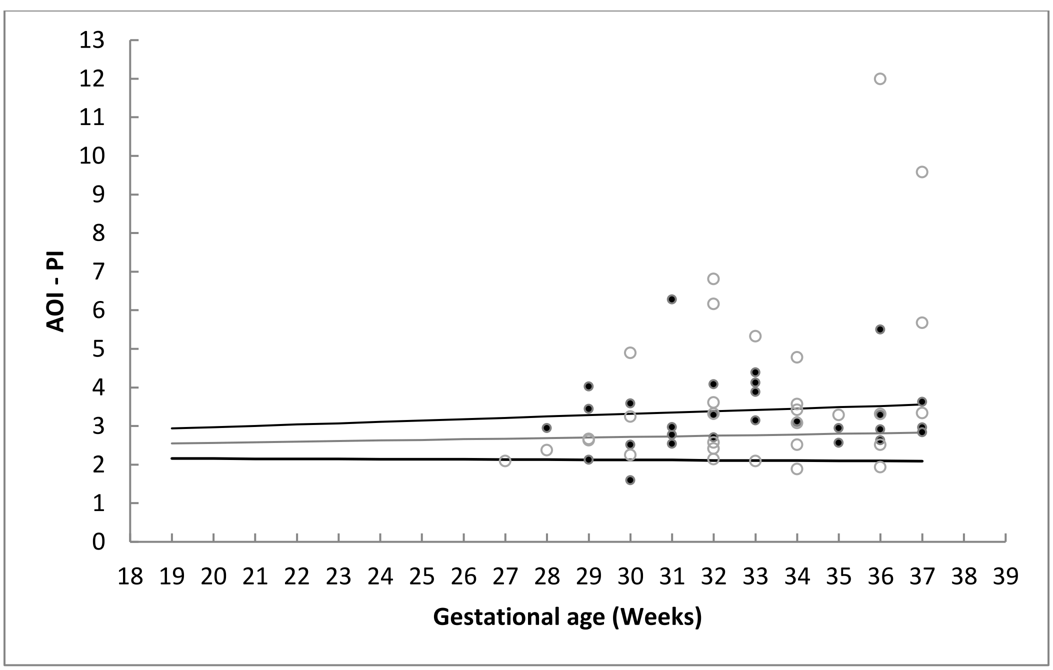

Figure 3 Pulsatility index in the aortic isthmus (AoI-PI) in IUGR(•) and AGA (◦) fetuses expressed as 5th, 50th and 95th centiles (-) according to gestation in appropriate for gestational age.

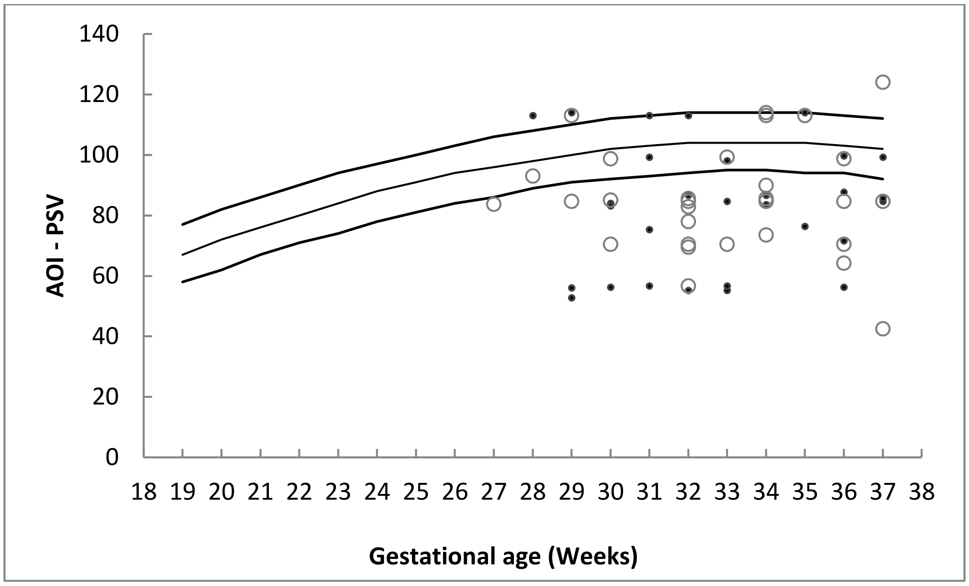

Figure 4 Peak systolic velocity in the aortic isthmus (AoI-PSV) in IUGR (•) and AGA (◦) fetuses expressed as 5th, 50th and 95th centiles (-) according to gestation in appropriate for gestational age.

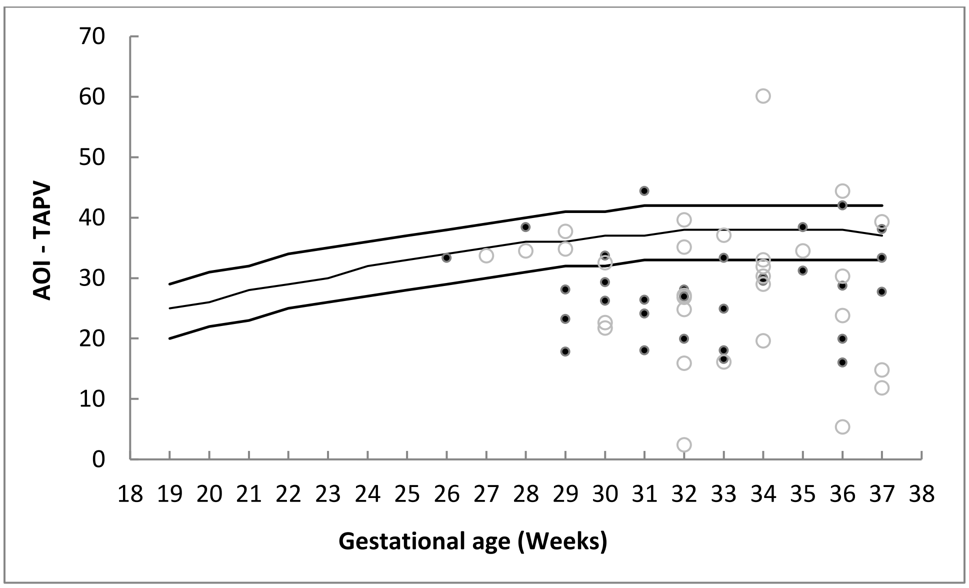

Figure 5 Time averaged peak velocity in the aortic isthmus (AoI-TAPV) in IUGR (•) and AGA (◦) fetuses expressed as 5th, 50th and 95th centiles (-) according to gestation in appropriate for gestational age.

4. DISCUSSION

In IUGR fetuses, there are some hemodynamic indices the changes of which have a precise pattern; these changes can be measured by applying Doppler sonography. This is the basis of using Doppler in IUGR clinical monitoring (Baschat et al., 2001; Del Rio et al., 2006; Ferrazzi et al., 2002; Hecher et al., 2001). The accurate monitoring of these indices in different arteries such as UA (Kessous et al., 2014), MCA (Baschat, 2004), and DV (Cruz-Martinez et al., 2011; Rizzo et al., 2008) provides significant clinical information that are highly useful and efficient in the clinical cares of IUGR fetuses.

Since AoI is the only arterial connection between left and right ventricles in the fetal circulatory system, its hemodynamic pattern indicates the balance between placental and cerebral blood perfusion (Mäkikallio et al., 2003; Mäkikallio et al., 2002). Thus, the present study aims at investigating the aortic isthmus color Doppler indices in IUGR fetuses.

The complications of IUGR on fetal circulatory system is the increased output of the left ventricle (Baschat, 2004). Therefore, the information obtained from investigating the Doppler indices of a part of aorta (such as AoI) as the main outflow tract of the left ventricle has more validity in comparison to other arteries such as UA, MCA, and DV that are the secondary aortic branches. Thus, choosing AoI for investigating the Doppler indices can be regarded as the main advantage and strong point of this study. The findings of the present study indicated that there is no significant difference between IUGR and healthy fetuses in terms of aortic isthmus color Doppler indices.

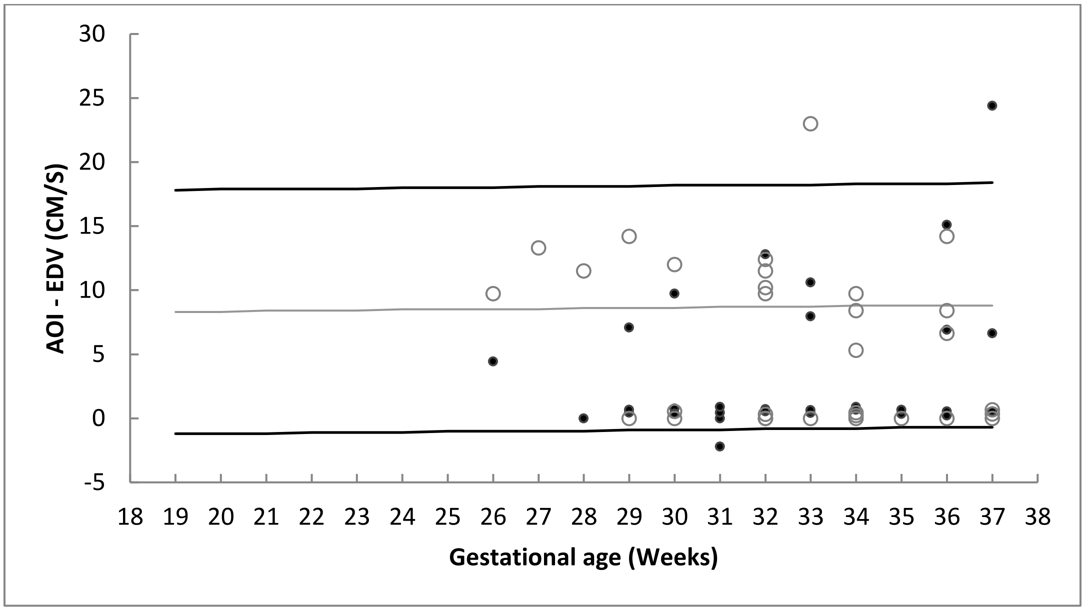

Figure 6 End-diastolic velocity in the aortic isthmus (AoI-EDV) in IUGR (•) and AGA (◦) fetuses expressed as 5th, 50th and 95th centiles (-) according to gestation in appropriate for gestational age.

IUGR is the outcome of disorder in placental blood supply to the fetus. The reaction provided by the fetal circulatory system to this disorder is a compensatory mechanism in favor of the left ventricle (increased left ventricular output), so that the blood supply to the lower half of the fetal body (lower than diaphragm) is limited and instead, the blood supply to the upper half of the body is increased so that an optimal oxygen supply is provided to the vital organs i.e. heart and brain; this reaction mechanism is conducted by AoI (Karakus et al., 2015). Thus, it is expected that in IUGR fetuses, the blood flow and Doppler indices of aorta (as the outflow tract of left ventricle) and consequently AoI as a part of aorta (Del Rio et al., 2006) undergo numerous changes. The findings of the study conducted by Karakus et al. confirm these changes. In a study conducted on 74 IUGR fetuses and 71 AGA fetuses with the gestational age of 26-40 weeks, Karakus et al. observed a significant change in EDV and TAPV indices in IUGR fetuses. Moreover, in their study, the amniotic fluid volume of IUGR fetuses was significantly less than that of the AGA fetuses (P<0.001) (Karakus et al., 2015).

In the study conducted by (Younesi et al., 2018), the RI index was compared in the aortic isthmus color Doppler of 30 IUGR and healthy fetuses; no significant difference was observed between them (P=0.08). This is in line with the findings of the present study. Moreover, in the study conducted by (Kennelly et al., 2012), no significant changes were observed between AGA, SGA, and IUGR fetuses in terms of PI and PSV indices. This is in line with the findings of the present study as well.

In the present study, the investigated IUGR fetuses were mainly in the phase of arterial disorder. It seems that AoI can be greatly useful as a differentiation criterion in the outcome of IUGR fetuses in advanced phases of reduced blood supply in which there are disorders in venous color Doppler.

5. CONCLUSION

According to the findings of the present study, investigating the AoI color Doppler indices as the predictor of hypoxia in IUGR fetuses cannot be a helpful index. This is possibly owing to fewer cases of IUGR fetuses with venous color Doppler disorder in comparison to IUGR fetuses with arterial color Doppler disorder. Thus, different results are likely to be obtained by conducting other studies with larger numbers of advanced-phase IUGR fetuses the venous color Doppler disorder of which is more definitive and confirmed.

Conflict of interest statement

Authors declare no conflicts of interest.

Financial resources

This study did not receive any financial support from any resources.

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