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ORIGINAL ARTICLE

Retrograde Flow in the Aortic Isthmus: Trigger to Deliver Growth Restricted Fetuses Between 30 and 34 Weeks of Gestation?

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Abstract

Objective To evaluate the association of aortic isthmus (AoI) circulation assessed by doppler imaging in growth restricted fetuses with perinatal outcome.

Design Prospective longitudinal observational study.

Setting Tertiary referral center.

Population Fetal growth restriction (FGR) (n = 38) between 24 and 36 weeks' gestation.

Methods Doppler examination of the aortic isthmus, umbilical artery (UA), middle cerebral artery, and ductus venosus (DV) was performed. The relationship between perinatal outcomes and antegrade (n = 25) and retrograde flow (n = 13) in the AoI and other Doppler parameters was analysed.

Results Retrograde AoI group had higher rates of adverse perinatal outcome (92.3% vs. 72%) with 63.1% sensitivity and 87.5% specificity. Overall perinatal mortality (intrauterine death and neonatal death) was higher in the retrograde group (23%). No perinatal mortality was seen in the antegrade AoI group. Cases with absent end diastolic flow (AEDF) or reverse end diastolic flow (REDF) in the UA and retrograde flow in the AoI and normal DV flow had 40% prenatal mortality as 25% in those with abnormal DV Doppler.

Conclusion Retrograde blood flow in the AoI is associated with adverse perinatal outcome, particularly intrauterine fetal demise, neonatal death, Respiratory Distress Syndrome (RDS) and increased duration of Neonatal Intensive Care Unit (NICU) stay. Even if DV flow is normal, adverse outcome might be suspected in fetuses with AEDF/REDF in the UA and retrograde flow in the AoI. Consequently, retrograde flow in the AoI might be considered as an additional trigger for delivering FGR fetuses at 30–34 weeks with AREDF in the UA. Larger longitudinal studies are, however, required to vaidate this.

Keywords Fetal growth restriction, FGR, IUGR · Doppler ultrasound · Fetal aortic isthmus · Aortic isthmus · Perinatal outcome

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Introduction

Fetal growth restriction (FGR) due to placental insufficiency is predominantly a vascular disorder. It is associated with adverse short term and long term outcomes [1–3] Fetal well being tests and indices can be broadly classified as chronic and acute. Chronic indices (abnormal doppler flow in the UA or middle cerebral artery (MCA) become

progressively abnormal due to increasing hypoxemia or hypoxia while acute indices (reverse flow in the DV) represent severe fetal hypoxia and metabolic acidosis and usually precede fetal death in few days. Doppler examination of the UA and the MCA are good predictors of adverse perinatal outcome. However, because the risks of iatrogenic prematurity are very high before 32 weeks of gestation, additional doppler parameters are needed to assess fetal compromise. Venous Doppler patterns together with gestational age (GA) at delivery have been advocated as the best predictors of adverse perinatal outcome in FGR fetuses [4]. These are, however, late changes and represent the failed fetal defense mechanism against hypoxia [5]. There may be a gap of a few days or a few weeks between early and late signs. New parameters are needed to document the progression of fetal deterioration in more precise way. This will help to identify those fetuses whose defense mechanism against severe hypoxia and acidemia are about to fail but have not yet failed.

Aortic isthmus (AoI) blood flow patterns reflect the balance between both ventricular outputs and the existence of differences in the impedance in either vascular system [6]. Its role as a short term marker of adverse perinatal outcome [7] and a long-term predictor of neurodevelopmental outcome [8, 9] have been proposed. Abnormal AoI impedance indices occur prior to cardiac decompensation [10]. Retrograde flow in the aortic isthmus occurs commonly after the abnormal flow in the umbilical artery and before abnormal ductus venosus flow. The aim of this study was to evaluate the association between AoI doppler changes and adverse perinatal outcome in FGR fetuses and to find out whether retrograde flow in the aortic isthmus can be used as an additional trigger to deliver growth restricted fetuses between 30 and 34 weeks of gestation where there is a dilemma between continuing surveillance versus delivering prematurely due to lack of availability of clear indicators.

Material and Methods

This prospective longitudinal observational study was conducted from January 2018 to February 2019 in a tertiary referral fetal–maternal medicine centre. This was a pilot study. All pregnant women between 24-36 weeks of getstation visiting the out patient department with ultrasonography indicating FGR fetus by the Delphi consensus definition [11] and fulfilling inclusion criteria were included in the study. 45 cases were included in the study. Analysis was done only for 38 cases because 2 cases were lost to follow up and 5 cases got delivered at other hospitals. In the latter group aortic isthmus doppler analysis at least 48–72 h prior to delivery was not available. Written informed consent was obtained. This study was approved by the Institutional Ethics Committee of Edappal Hospitals Pvt. Ltd. Estimated fetal weight (EFW) percentile was calculated by using Hadlock growth charts. The inclusion criteria were: women willing to take part in the study, singleton pregnancy, GA confirmed by ultrasound in the first trimester, absence of structural malformations and chromosomal abnormality, women with ultrasound findings satisfying the definition criteria of FGR and a last Doppler examination performed within 48 h before delivery.

Ultrasound Examination

All studies were performed using a Doppler equipment GE Voluson E8 or E6 (General Electric Healthcare, Europe) ultrasound machine using a transabdominal transducer. Doppler studies of the Umbilical artery (UA), Middle cerebral artery (MCA), Ductus venosus (DV) and aortic isthmus (AoI) were perfomred during minimal fetal activity and the absence of fetal breathing movement, at an insonation angles $< 30°$. The PI was recorded for the UA, MCA and DV. Parameters were plotted against established centiles for gestation using Barcelona fetal medicine reference charts.

UA with PI $>$ 95th centile for gestational age (GA) or with AREDF, MCA-PI $<$ 5th centile or a Cerebroplacental ratio (CPR) $<$ 5th percentile for GA was considered as abnormal. DV PI $>$ 95th percentile for GA or with absent or reversal of 'a' wave was considered as abnormal.

Aortic Isthmus Doppler Velocimetry

AoI Doppler was assessed in the cross-sectional 3VT view during fetal quiescence with the angle of insonation close to 0° and no more than 30°. The AoI waveform was assessed as presence of diastolic flow or absent or reversed diastolic flow (Fig. 1a, b). In cases of some reversal of diastolic flow but predominant antegrade flow, it was considered as antegrade flow. If the flow was predominantly retrograde then it was considered as retrograde flow. Absence of flow in diastole was taken as absent diastolic flow in AoI.

FGR staging was done as per Gratacos et al. 2014 [12]. Doppler parameters and impedance indices were plotted against established centiles for gestation using Barcelona fetal medicine reference charts. Further follow up was done as per the staging based classification and management by Gratacos et al. 2014 [12].

Statistical analysis was performed using SPSS 23.0.Doppler variables and perinatal outcome were analyzed by Pearson's Chi-square or Fisher's exact test as indicated.

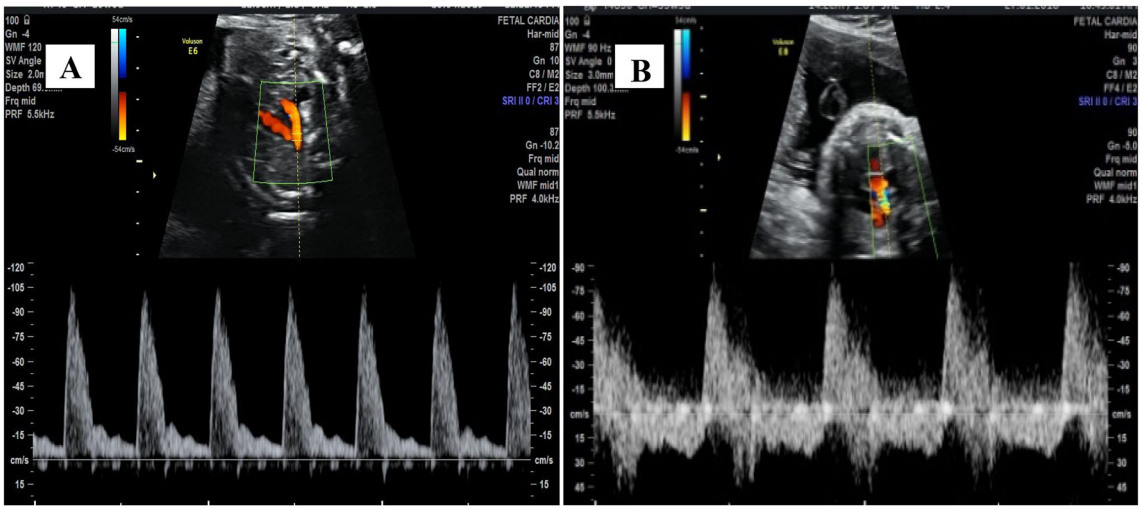

Fig. 1 **a** Normal antegrade diastolic flow in the aortic isthmus (AoI); **b** Retrograde flow in the AoI

Triggers for delivery were as follows: For < 30 weeks—reversal of flow in DV, for 30–32 weeks—REDF in UA, between 32 and 34 weeks—AEDF in UA or abnormal fetal heart rate trace, for > 34 weeks—Abnormal fetal heart rate trace by CTG. Mode of delivery was by Caesarean section irrespective of the stage of FGR as a routine institutional protocol.

Outcome

Outcome was analyzed as still birth, neonatal death, development of respiratory distress, bronchopulmonary dysplasia, intraventricular hemorrhage, Transient tachypnea of newborn (TTN), necrotizing enterocolitis (NEC), sepsis, and neonatal intensive care (NICU) stay longer than 7 days. Perinatal outcome was defined as adverse when any of these complications was present.

Results

Optimal aortic isthmus waveform assessment could be obtained in all cases. Out of 45 cases recruited, 7 cases were excluded from the study because 2 cases were lost to follow up and 5 cases delivered at other hospitals. Of the total analyzed 38 cases, 25 had antegrade and 13 had retrograde diastolic flow in the aortic isthmus. Demographic and obstetric data of the study population is mentioned in Table 1.

There was no significant difference in these two groups with respect to maternal age, type of conception and parity. There was a high incidence of preeclampsia in the retrograde group (46%) as compared to the antegrade group (24%). Gestational age at delivery ($p = 0.021$) and birth weights ($p = 0.022$) were significantly lower in fetuses with retrograde flow in the aortic isthmus. Distribution of complications in antegrade and retrograde flow in the aortic isthmus groups is given in Table 2 and Fig. 2.

Overall, adverse perinatal outcome includes intrauterine death and postnatal complications. The retrograde AoI group had higher rates of adverse perinatal outcome (92.3% vs. 72%). However, this was not statistically significant (p value − 0.222) but this might be attributed to insufficient sample size. Only 1/13 of the retrograde group did not have any adverse perinatal outcome. There was 1 intrauterine death and 2 neonatal deaths in the study population. All these cases were from the retrograde AoI group. Perinatal mortality was 3/13 (23%) in the retrograde flow in AoI group and there was no perinatal mortality in the antegrade AoI group.

Necrotizing enterocolitis was seen in one case. This was from the retrograde group. Respiratory distress syndrome was more common in the retrograde AoI group (69% vs. 36%) ($p = 0.052$). For the remaining complications, there was no difference in these two groups. The relationship between aortic isthmus Doppler flow and other Doppler parameters is given in Table 3.

There was a significant association of retrograde diastolic aortic isthmus flow with abnormal umbilical artery, abnormal MCA, and abnormal DVdoppler. Of the retrograde AoI group 3 (23%) cases had umbilical artery PI > 95th centile and 9 (69%) cases had AREDF. 12/13 (92.3%) cases had abnormal MCA Doppler flow (PI < 5th centile) and 5/13 cases had abnormal DV doppler (> 95th centile). 5/7 (71.4%) of abnormal DV had reverse diastolic flow in the aortic isthmus.

The predictive value of the AoI and other Doppler parameters for an adverse perinatal outcome is given in Table 4; An equation of multiple regression analysis was

Table 1 Demographic and obstetric data of the study group

	Antegrade (N = 25)	Retrograde (N = 13)	*p* value
Maternal age	27 ± 6.6	28 ± 5.4	0.68
Conception			
Natural	19 (76%)	9 (69.2%)	0.709
IVF	6 (24%)	4 (30.8%)	
Parity			
Primipara	14 (56%)	5 (38.5%)	0.305
Multipara	11 (44%)	8 (61.5%)	
Preeclampsia	6 (24%)	6 (46%)	0.163
Gestational age at delivery	34.5 ± 3.2	31.9 ± 2.8	0.021
Gestational age at delivery < 34 weeks	8 (32%)	10 (77%)	0.016
Mode of delivery			
Vaginal delivery	4 (16%)	1 (7.7%)	0.643
LS CS	21 (84%)	12 (92.3%)	
Indication for delivery			
Fetal	16 (64%0	12 (92.3%)	0.118
Maternal	9 (36%)	1 (7.7%)	
Gender			
Male	15 (60%)	7 (53.8%)	0.715
Female	10 (40%)	6 (46.2%)	
Birth weight	1697 ± 627	1215 ± 492	0.021

IVF in vitro fertilization, *LSCS* lower segment caesarean section

Table 2 Distribution of complications in antegrade and retrograde flow in the aortic isthmus groups

Complications	Antegrade (n = 25)	Retrograde (n = 13)	*p* value
Overall	18 (72%)	12 (92.3%)	0.222
Nicu stay	16.8 ± 16.2	9.2 ± 5.2	0.078
Nicu > 7 days	14/25 (56%)	7/10 (70%)	0.155
Respiratory distress syndrome	9 (36%)	9 (69%)	0.052
Nnj	15 (60%)	7 (54%)	0.715
Sepsis	6 (24%)	4 (30%)	0.709
Ttn	9 (36%)	3 (23%)	0.486
Nec	0	1 (8%)	0.342
Iud	0	1 (8%)	0.342
Nnd	0	2 (15%)	0.111
Perinatal mortality	0	3/13 (23%)	0.34

NICU neonatal intensive care unit; *TTN* transient tachypnea of newborn; *NEC* necrotising enterocolitis; *IUD* intrauterine death; *NND* neonatal death

used: Perinatal Outcome = 2.227 − (0.313 × UA PI > 95th) − (0.104 × UA AREDF) − (0.268 × MCA) − (0.125 × DV) + (0.011 × AOI) + (0.031 × WOG). Based on standardized coefficient, WOG (0.092) is the most important factor to extract perinatal outcome followed by AoI (0.013).

UA and AoI retrograde Doppler flow patterns and gestational age at delivery < 34 weeks of gestation had the highest positive likelihood ratios (5.3, 5.0 and 8.7 respectively). Abnormal AoI Doppler has 63% sensitivity, a specificity of 87.5%, a good positive predictive value (92.3%) and a positive likelihood ratio of 5.0 for the prediction of adverse perinatal outcome.

In the retrograde AOI group, outcome was assessed in two subgroups: one with normal DV Doppler and another with abnormal DV Doppler (Table S1). Perinatal mortality was higher (25%) in the retrograde AoI group with normal DV. This shows that the perinatal outcome can be adverse even when the DV flow is normal, especially in terms of perinatal mortality.

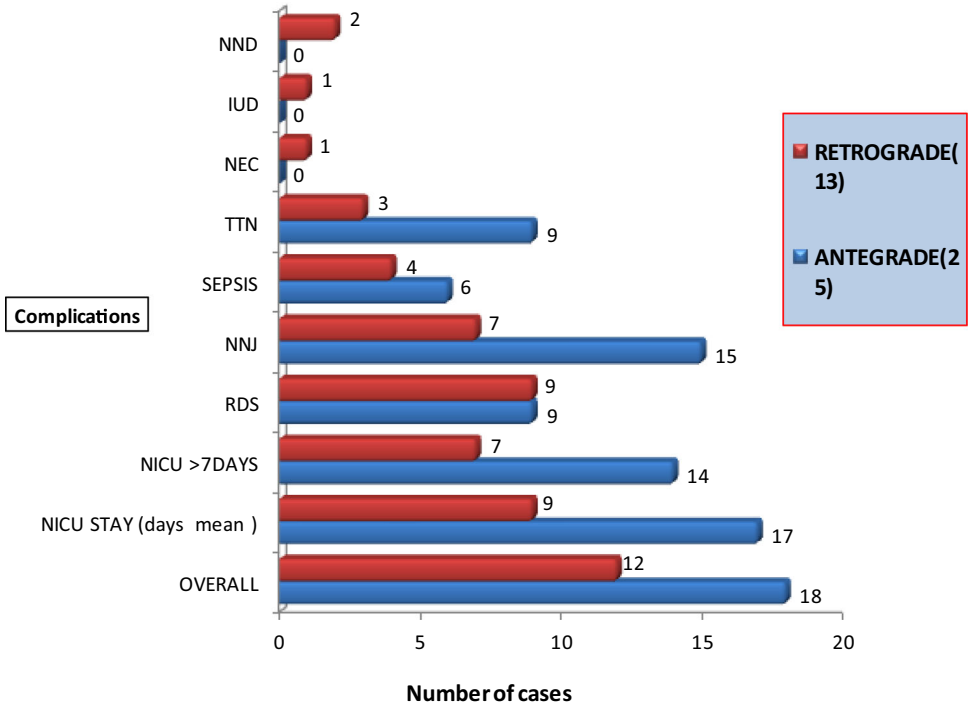

Fig. 2 Distribution of complications in antegrade and retrograde flow in AoI groups. NND—Neonatal death, IUD—Intrauterine death, NEC—Necrotising enterocolitis, TTN—Transient tachypnea of newborn, NNJ-Neonatal jaundice, RDS—respiratory distress syndrome, NICU—Neonatal intensive care unit

Table 3 Distribution of Doppler results in antegrade and retrograde flow in the aortic isthmus groups

Doppler parameter	Antegrade (n = 25)	Retrograde (n = 13)	*p* value
UA PI > 95th percentile	9 (36%)	3 (23%)	0.416
AREDF UA	0	9 (69%)	< 0.001
Abnormal MCA	12 (48%)	12 (92%)	0.012
Abnormal CPR	17 (68%)	13 (100%)	0.022
Abnormal DV	2 (8%)	05 (38%)	0.034

Abnormal UA (Umbilical artery)—Umbilical artery PI > 95th centile for gestational age or with AREDF (Absent or reverse diastolic flow),

Abnormal MCA (Middle cerebral artery)-MCA-PI (Pulsatality index) < 5th centile, ABNORMAL CPR (Cerebroplacental ratio)- < 5th centile

Abnormal DV (Ductus venosus)—PI > 95th percentile for gestational age or with absent or reversal of a wave

Table. 4 The predictive value of the AoI (Aortic isthmus) and other parameters for an adverse perinatal outcome

Parameter	Sensitivity	Specificity	PPV	NPV	+ LR	*p* value
Abnormal UA	66.6 (20/30)	87.5 (7/8)	95.2 (20/21)	41.1 (7/17)	5.3	0.013
Abnormal MCA	73.3 (22/30)	75 (6/8)	91.6 (22/24)	42.8 (6/14)	2.9	0.034
Abnormal DV	23.3 (7/30)	100 (8/8)	100 (7/7)	25.8 (8/31)	–	0.307
Abnormal AOI	63.1 (12/19)	87.5 (7/8)	92.3 (12/13)	28 (7/25)	5.0	0.222
< 34WOG	70 (17/24)	93 (13/14)	94 (17/18)	65 (13/20)	8.75	0.016

PPV positive predictive value, *NPV* negative predictive value, + *LR* positive likelihood ratio, *UA* umbilical artery, *MCA* middle cerebral artery, *DV* ductus venosus, *AoI* aortic isthmus, *WOG* weeks of gestation

Analysis of the fetuses with AEDF or REDF in UA with retrograde AoI by sub grouping in those having normal DV and those with Abnormal DV is shown in Table no. S2. There was 1 IUD and 1 NND from the group with normal DV and 1 NND from the DV abnormal group. Importantly, even with normal DV Doppler flow the perinatal mortality (40%) was found in AEDF/REDF with retrograde AOI group with normal DV flow: *p* value 0.638, 95% CI

(− 0.454 to 0.754). Longitudinal changes in Doppler parameters in these FGR fetuses are shown in Fig. 3.

The median values for umbilical artery PI > 95th centile, AEDF in UA, REDF in UA, MCA PI < 5th centile, retrograde flow in aortic isthmus and DV PI > 95th centile were 8,1,0,7,2 and 0.5 respectively.

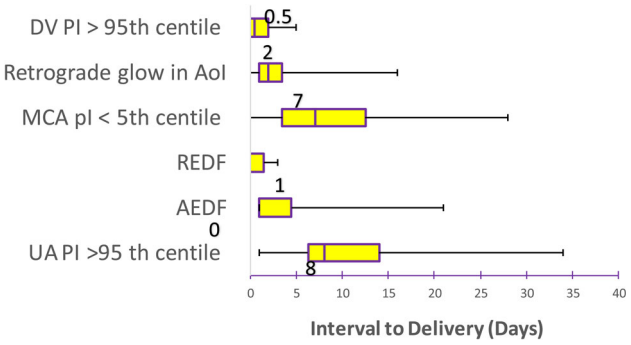

Fig. 3 Longitudinal Doppler changes in Doppler in FGR fetuses. DV (Ductus venosus), AoI (aortic isthmus), MCA (Middle cerebral artery), REDF-Reverse end diastolic flow, AEDF—Absent end diastolic flow; UA—Umbilical artery, PI (Pulsatality index)

Discussion

There is a diversity and lack of a uniform model that reflects hemodynamic changes in pregnancy with FGR. The major concern is surveillance of these FGR cases and taking a decision whether to deliver or not weighing the risk of intrauterine death by prolonging the gestation versus delivering the fetus prematurely.

This study supports the association of retrograde flow in the aortic isthmus with adverse perinatal outcome as suggested by Del Rio et al. [13] and Hidar et al. [14]. In our study, the retrograde AoI group had higher rates of adverse perinatal outcome (92.3% vs. 72%). However, this was not statistically significant (p value − 0.222), but may be attributed to insufficient samople size. Abnormal AoI had a sensitivity of 63.1%, a high specificity (87.5%) and a PPV (92.3%) and a likelihood ratio of 5 for prediction of adverse perinatal outcome. Overall perinatal mortality (intrauterine death and neonatal death) was higher in the retrograde group 3/13 (23%) (p value 0.34). There was no perinatal mortality in the antegrade flow in the AoI group. This suggests a potential role for Doppler imaging of the AoI in the clinical surveillance of severe FGR fetuses.

There was a highly significant association of retrograde diastolic flow in the AoI with AREDF UA 9 (69%) ($p < 0.001$) suggesting more severe and earlier onset of placental insufficiency and with abnormal DV flow (38% vs. 8%) ($p = 0.034$) suggesting an association of these parameters with progressive deterioration of cardiac function occurring in FGR similar to Del Rio et al. [13].

AoI PI and DV PI independently predict adverse outcome and in preterm growth restricted fetuses, AoI blood flow becomes abnormal on an average 1 week before DV blood flow does [13]. In our study, retrograde flow in the AoI was seen on an average 2 days before delivery and abnormal DV PI was seen 1 day before delivery.

Fetuses with AEDF or REDF in the UA with retrograde AoI were analyzed by sub grouping as those with normal DV and those with abnormal DV. There were 2 perinatal deaths in the normal DV group and 1 NND in the abnormal DV group. Even with normal DV Doppler flow, perinatal mortality (40%) was found in AEDF/REDF with retrograde AOI group. Thus, even though the DV flow is normal, adverse outcome might be suspected in fetuses with AEDF/REDF in UA and retrograde flow in the AoI. This finding has to be taken into considerartion as at present we do not have a clear cut trigger to deliver these FGR fetuses between 30 and 34 weeks and we are using REDF in the UA as a trigger to deliver between 30 and 32 weeks and AEDF in the UA between 32 and 34 weeks. Our study highlights the importance of retrograde flow in the AoI in such cases as an additional trigger for delivering FGR fetuses between 30 and 34 weeks with AREDF in the UA. This provides a better window for delivering the FGR fetuses before failure of fetal compensatory mechanisms to hypoxia.

Our study confirms previous observations that retrograde blood flow in the AoI is associated with adverse perinatal outcome, particularly intrauterine demise, neonatal death and respiratory distress syndrome. It correlates significantly with abnormal flow in the UA, MCA and DV and is seen prior to abnormal changes in DV Doppler flow.

Clinical Implications

Even when DV flow is normal, adverse outcome might be suspected in fetuses with AEDF/REDF in the UA and retrograde flow in the AoI. This provides a better window for delivering the FGR fetus before failure of fetal compensatory mechanisms to hypoxia. Retrograde flow in the AoI might be considered as an additional trigger for delivering FGR fetuses between 30 and 34 weeks with AREDF in the UA and might be considered as an additional clinical parameter in the routine assessment of hemodynamically compromised growth-restricted fetuses. We suggest combing UA, AoI and DV Doppler flows in minimizing adverse perinatal outcomes. Before 26 weeks and after 28 weeks, gestational age alone is the strongest predictor of perinatal mortality in early-onset FGR. However, in the group between 26 and 28 weeks of gestation, the DV may provide useful information and allow stratification between high and low risks of perinatal mortality

[15]. AEDF in the UA and reversal in the AoI suggests severe placental insufficiency while REDF in the UA and abnormal DV PI suggest fetal acidosis [12]. Suboptimal neurological development has been found among children who had net reversed diastolic flow in the AoI antenatally [8], Considering all this it might be better to consider AEDF/REDF in UA and reversal of flow in AoI as a sensible marker for delivering the FGR fetus especially between 30 and 34 weeks of gestation before the fetal compensatory mechanisms to hypoxia fail.

Strengths and Limitations

The prospective nature of this study and simplified subjective approach of AoI waveform analysis are the merits of our study.

This study has limitations of a small sample size and prematurity. The important role of prematurity in the prediction of perinatal outcome cannot be neglected. Notably, retrograde flow in the aortic isthmus was not used as trigger for delivery.

Conclusion

This study confirms previous observations that retrograde blood flow in the AoI is associated with adverse perinatal outcome, particularly intrauterine demise, neonatal death and RDS. Retrograde flow in the AoI correlates significantly with abnormal flow in the Umbilical artery, Middle cerebral artery and Ductus venosus. Moreover, even though DV flow is normal, adverse outcome might be suspected in fetuses with AEDF/REDF in the UA and retrograde flow in the AoI. Currently, we lack a clear cut trigger to deliver FGR fetuses between 30 and 34 weeks and are using REDF in the UA as a trigger to deliver between 30 and 32 weeks and AEDF in the UA between 32 and 34 weeks. It might be better to consider addition of retrograde flow in the AoI with AEDF/REDF in the UA as a sensible marker for delivering the FGR fetus especially between 30 and 34 weeks of gestation before fetal compensatory mechanisms to hypoxia fail. Large prospective studies and a randomized controlled trial using retrograde flow in the aortic isthmus along with AREDF in the UA as a trigger to deliver are required for evaluating immediate perinatal as well as long term neurological outcome. This might help to improve surveillance protocols and perinatal as well as long term neurodevelopemental outcome in FGR fetuses.

Compliance with Ethical Standards

Conflict of interest The authors report no conflict of interest.

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