CLINICAL SIGNIFICANCE OF INTERMITTENTLY ABSENT END-DIASTOLIC FLOW OF THE FETAL UMBILICAL ARTERY ON PERINATAL AND NEONATAL OUTCOMES

Başakşehir Çam ve Sakura City Hospital Clinical Research Ethics Committee (ethics no.2023-561, date 08/11/2023)

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Clinical Significance Of Intermittently Absent End-Diastolic Flow Of The Fetal Umbilical Artery On Perinatal And Neonatal Outcomes

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Abstract

Objective: This study aimed to estimate the risk of adverse perinatal outcomes among pregnant patients with intermittently absent (iAEDF) and persistently absent end-diastolic umbilical artery flow (pAEDF).

Study design: We performed a retrospective cohort study of patients diagnosed with the iAEDF or pAEDF at our institution from 2020 to 2023. Fetuses were classified under two categories: iAEDF group and pAEDF group.

Results: Of the 137 patients included, 38 had iAEDF and 99 had pAEDF. In terms of pregnancy outcomes, the duration from diagnosis to birth was significantly shorter for women diagnosed with pAEDF compared to women diagnosed with iAEDF. Additionally, pregnancies with iAEDF were associated with a later gestational age at delivery.

In terms of pregnancy complications, there were no statistically significant differences between the two groups. But all four stillborn patients were in the pAEDF group and the percentage of fetal distress in women diagnosed with pAEDF was noticeably greater than the percentage of fetal distress in women diagnosed with iAEDF. A comparison of the two groups revealed that concerning neoatal outcomes, in the iAEDF group, the Apgar score was significantly greater and the percentage of women with an Apgar score in the fifth minute less than seven was lower.

Conclusion: For fetuses with absent end-diastolic flow-related UA, the absence of flow was associated with pregnancy outcome. There was no significant difference between the groups in terms of stillbirth, however, all 4 stillborns were in the pAEDF group, which suggested that inpatient follow-up of pregnancies with iAEDF allows early intervention. However, the average time from diagnosis to delivery in women with an iAEDF was 15.6 days, which extended latency from diagnosis to delivery may favor outpatient management of iAEDF. These outcomes should be considered when creating an antenatal surveillance plan and discussing the potential for outpatient management.

Key Points

-Doppler velocity measurements have excellent benefits in the surveillance of risky fetuses.

-Absent umbilical artery end-diastolic flow is associated with adverse perinatal outcomes.

- Patterns of end-diastolic flow may inform management and decision-making for high-risk pregnancies

Keyword: absent end-diastolic flow, Doppler, gestational age, intrauterine growth restriction, pregnancy outcome, neonatal outcomes, ultrasound, umbilical artery

Introduction

Doppler velocity measurement of the umbilical artery (UA) serves as a crucial clinical tool for monitoring feto-placental hemodynamics and assessing fetal well-being in high-risk pregnancies[1-3]. This technique has demonstrated notable advantages in monitoring potentially

risky fetuses, particularly in pregnancies complicated by placental disorders, such as fetal growth restriction (FGR)[4,5]. Since UA Doppler (UAD) results can deteriorate over the course of pregnancy, regular assessments are recommended[6,7]. However, the frequency of these assessments, management protocols, and delivery timing recommendations vary among major national obstetric societies[7].

The UA blood velocity waveform is typically characterized by the pulsatility index (PI)[8] and qualitative information concerning the potential absence or reversal of end-diastolic flow (EDF)[9]. Absent end-diastolic flow (AEDF) signifies increased resistance to flow in the placental vascular bed[10,11] and is associated with elevated risks of intrauterine death and adverse perinatal outcomes[12-14]. AEDF in the UA can be either persistent (pAEDF), occurring in most or all fetal cardiac cycles, or intermittent (iAEDF), manifesting in only some of the cardiac cycles. However, standardized definitions for these terms lack and the clinical implications of the iAEDF versus the pAEDF remain unclear.

A previous study indicated that, compared to fetuses with pAEDF, those with iAEDF are diagnosed with UAD abnormalities later in pregnancy and are delivered at a later gestational age (GA) with higher birth weights[15]. Consequently, it is plausible that some fetuses with an iAEDF may remain in utero for an extended duration without facing an immediate risk of death. Identifying this specific subgroup might allow the avoidance of some neonatal risks associated with extremely preterm birth.

In this study, we aimed to assess the risk of adverse perinatal outcomes among pregnant patients with intermittently absent and persistently absent end-diastolic umbilical artery flow. This investigation seeks to contribute to a better understanding of the fetal risks associated with different patterns of absent end-diastolic flow, thereby informing clinical management and decision-making for high-risk pregnancies.

Materials and Methods

We performed a retrospective cohort study of patients with non-anomalous, singleton pregnancies diagnosed with intermittent absence of end-diastolic umbilical artery Doppler flow or persistent absence of end-diastolic flow at our institution from 2020 to 2023. The study was approved by the Başakşehir Çam ve Sakura City Hospital Clinical Research Ethics Committee (ethics no.2023-561, date 08/11/2023) and was conducted in accordance with the latest version of the Declaration of Helsinki (2019/92). Fetuses were classified into two categories: intermittent absent end-diastolic flow and persistent absent end-diastolic flow.

Patients were excluded if they had major fetal anomalies or aneuploidy diagnosed prenatally or if they lacked delivery or neonatal outcome data. Patients were also excluded if they were intermittently elevated or if they showed REDF syndrome during pregnancy. All ultrasounds were performed and interpreted by a maternal-fetal medicine fellowship-trained obstetrician. UAD waveforms were obtained through transabdominal imaging from a free-floating loop of the umbilical cord on a Hitachi machine. To improve the accuracy of the measurements, waveforms were obtained during a brief pause during maternal breathing. At least three separate UAD assessments were performed for each fetus. Doppler waveforms were defined as iAEDF if diastolic flow was absent in one or more waveforms during a cycle of images. Doppler waveforms were defined as persistently absent if the absence of diastolic flow was observed in all waveforms. The REDF was defined as the reversal of flow in the UA in at least one fetal cardiac cycle. The patients defined as having an iAEDF were not subdivided based on the percentage of patients with no waveforms. The most recent guidelines for the management of FGR from the Society for Maternal-Fetal Medicine and American College of Obstetricians and Gynecologists (ACOG) were released in 2020. We recommend that pregnant patients with AEDF undergo UAD surveillance two to three times weekly and delivery by 33 to 34 weeks of gestation [6,16]. Inpatient management is suggested as an option for AEDF. In our

study, the management of AEDF included admission of pregnant patients for antenatal corticosteroid administration and inpatient monitoring, including daily UAD assessment and antenatal testing twice a day. Although previous studies have shown that improvements in UAD abnormalities can be observed with the application of corticosteroids to stimulate fetal lung maturity[17,18], we did not find it necessary to study it since corticosteroids were already administered to all patients whose AEDF was detected. Delivery was recommended at the GA of 34 weeks following the recommendations of ACOG, or if another indication arose[19]. If a diagnosis of AEDF or REDF was made after the recommended GA for delivery, it was advised to proceed with delivery at the time of diagnosis.

Maternal demographic information, medical complications, prenatal history (including additional ultrasound studies), and delivery and neonatal outcomes were taken from medical records.

The primary outcome was a composite of neonatal outcomes, including birth weight, Z-score for standardized birth weight, Apgar score in the first minute, Apgar score in the fifth minute, Apgar score in the fifth minute lower than seven, admission to the ICU, and the need for intubation.

The secondary outcomes included demographic information, time of AEDF diagnosis, latency from the time of AEDF diagnosis to delivery, and pregnancy complications (IUMF, ablatio placenta, fetal distress, IUGR, amniotic fluid abnormalities).

These outcomes were compared between patients with iAEDF and those with pAEDF.

Statistical Analysis

Statistical analysis was performed using R statistical software (R Core Team 2021). A score of $P<0.05$ was considered to indicate statistical significance. The normality of the distribution of the variables was assessed using quantile–quantile plots and the Shapiro–Wilk test. Continuous variables were evaluated using the unpaired student's t test or Mann–Whitney U test (for two

groups), depending on the normality of the distribution. Categorical variables were analyzed using the $\chi 2$ test or Fisher's exact test, depending on the variable count[20].

Results

Our cohort included 137 pregnancies in the final analysis. A total of 99 (33.0%) patients were classified as pAEDF, while 38 (16.0%) were classified as iAEDF. The sociodemographic and obstetrical characteristics of the patients in both groups are shown in Tables 1 and 2.

Table 1 shows the comparisons of age, parity, and gravidity between the groups. There were no significant differences in age, parity, or gravidity between the persistent dak group and the intermittent dak group. Table 2 shows the results of the comparison of the two groups in terms of pregnancy outcomes, including the week of AEDF diagnosis, gestational age at birth, birth weight, Z-score for standardized birth weight and the time elapsed from diagnosis to birth. There were significant differences between the two groups in terms of gestational age at birth and the time elapsed from diagnosis to birth. The mean gestational age at birth among women who were diagnosed with persistent dak was 29.6 ± 2.8 years, while the mean gestational age at birth was 30.9 ± 2.6 years (p=0.03). The time from diagnosis to birth was significantly shorter for women who were diagnosed with persistent dak (mean=7.88, sd=9.99) compared to women who were diagnosed with intermittent dak (mean=15.6, sd=11.5) (p=<.0001).

Table 3 shows the results of the comparison of the two groups in terms of pregnancy complications, including AFI abnormalities, stillbirth, ablatio placenta, and fetal distress. There were no significant differences between the two groups in terms of pregnancy complications. However, the percentage of fetal distress in women who were diagnosed with persistent dak (56.6%) was noticeably greater than the percentage of fetal distress in women who were diagnosed with intermittent dak (39.5%). Although there was no significant difference between the groups in terms of stillbirths, all four stillborns were in the pAEDF group.

Table 4 shows a comparison of the two groups in terms of adverse neonatal outcomes. There were significant differences between the two groups in terms of the Apgar score at the first minute and the Apgar score at the fifth minute. Among women who were in the persistent dak group, the mean Apgar score in the first minute was 4.2 ± 2.2, while the mean Apgar score in the first minute among women in the intermittent dak group was 5.4 ± 1.9 (p=0.004). Similarly, the mean Apgar score at the fifth minute was lower in the persistent dak group than in the intermittent dak group (6.4 ± 2.2 and 7.6 ± 1.0, respectively).

We also evaluated the Apgar score at the fifth minute by categorizing patients as being less than or more than seven. However, there was a significant difference between the two groups. The percentage of women with Apgar scores less than seven in the dak group (33.3%) was much greater than the percentage of women with Apgar scores less than seven in the fifth minute in the intermittent dak group (13.2%) (p=0.02).

The significant difference between the two groups in terms of Apgar score was due to higher mean gestational age at birth of women diagnosed with pAEDF compared to the mean gestational age at birth of women diagnosed with iAEDF.

There were no significant differences between the two groups in terms of admission to the ICU or intubation.

Discussion

An improvement in UAD has been associated with longer latency, later GA at delivery, and lower rates of acidosis at delivery[21,22].

In the current study conducted on pregnancies with AEDV, pregnancies with iAEDF had longer latency from diagnosis to delivery, were delivered at a later gestational age (GA) and were less likely to be delivered because of fetal distress. Based on the data that pregnant women with iAEDF have a longer latency from diagnosis to delivery and require delivery later in

gestation, iAEDF is a stage of placental insufficiency progression and likely represents less severe UAD abnormality than pAEDVF

Rosner et al. compared outcomes among 109 pregnancies with an iAEDF or pA/REDF from 19 to 39 weeks (15). Like our study, they reported that pregnancies with an iAEDF were delivered at a later gestational age and were less likely to have a fetal indication for delivery. In contrast, they found no difference in latency from AEDV diagnosis to delivery and did not observe changes in UAD velocimetry. This may be attributed to the low percentage of pregnancies complicated by FGR in this study. Their study included all pregnancies with UAD abnormalities, as did ours and only 83% of the subjects had FGR. In our study, 94% of patients had UAD abnormalities complicated with FGR.

Like our study, a recent retrospective study of singletons with fetal growth restriction and absent end-diastolic velocity conducted by Katherine H. Bligard et al. has reported that the latency to delivery was longer in the iAEDF group than in the pAEDF group and the nonreassuring fetal status indication for delivery was greater in the pAEDF group. In that study, when the two groups were compared in terms of Apgar scores and birth weights, the Apgar scores and birth weights were greater for fetuses complicated with iAEDF[23]. Our study supported these data with approximately twice the number of patients.

Sophie Green et al. compared outcomes among three Doppler groups (persistently elevated, intermittently absent, and persistently absent end-diastolic flow) of growth-restricted fetuses[24]. According to our study, there was no difference in composite neonatal morbidity among the three groups. Although the Apgar score was lower in the pAEDF group, there were no significant differences between the two groups in terms of admission to the ICU or intubation. Our study is limited because subsequent neonatal outcomes are unknown. It is important to acknowledge that UAD is a dynamic measurement that changes over time. Green's study and

our study could be more powerful if they included data from pregnancies with an iAEDF that subsequently progressed to an AEDF in the outcome analyses.

Conclusion

In fetuses with AEDF in the UA, the severity of flow absence was associated with pregnancy outcomes (gestational age at birth, time elapsed from diagnosis to birth, fetal distress, and Apgar scores). Although there was no significant difference between the groups in terms of stillbirth, all four stillborns being in the pAEDF group suggested that inpatient follow-up of pregnancies with iAEDF allows early intervention in these patients. However, the mean time from diagnosis to delivery in women with an iAEDF was 15.6 days, which extended latency from diagnosis to delivery may favor outpatient management of iAEDF. However, considering the lack of available clinical data on the iAEDF population, we believe that our study contributes to the current data as a descriptive study because it involves the largest number of patients with AEDF, and the multiple parameters evaluated.

Conflict of Interest

None declared.

Acknowledgments

The authors would like to thank the staff of the Başakşehir Çam ve Sakura City Hospital for their help and support.

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Tables

Table 1. Demographic information

	iAEDF (n=38)	pAEDF (n=99)	p-value
Age	29.5 (6.1)	29.5 (6.6)	0.96*
Parity			0.78**
0	19 (50.0)	48 (48.5)	
1	12 (31.6)	26 (26.3)	

2	4 (10.5)	18 (18.2)	
3	2 (5.3)	5 (5.1)	
4	0 (0.0)	1 (1.0)	
5	1 (2.6)	1 (1.0)	
Gravidity			0.69**
1	15 (39.5)	43. (43.4)	
2	8 (21.1)	24 (24.2)	
3	9 (23.7)	15 (15.2)	
4	2 (5.3)	6 (6.1)	
5+	4 (10.5)	11 (11.1)	

*The Mann-Whitney U, **Fisher's Exact test, ***Chi-square test, [a] Independent Sample T-test

Table 1 represents the comparison of age, parity, and gravidity between two groups. There were no significant differences in age, parity and gravidity between pAEDF and iAEDF group.

Table 2. Pregnancy outcomes

	iAEDF (n=38)	pAEDF (n=99)	p-value
The week of AEDF diagnosis	28.6 (2.8)	28.5 (2.9)	0.84[a]
Gestational age at birth	30.9 (2.6)	29.6 (2.8)	0.03*
Birthweight	1067 (450)	929 (441)	0.09*
z score for standardized birthweight	(-3.05) (1.1)	(-3.0) (1.6)	0.73*
The time passed from the diagnosis to the birth	15.6 (11.5)	7.88 (9.99)	<.0001*

*The Mann-Whitney U, **Fisher's Exact test, ***Chi-square test, [a] Independent Sample T-test

Table 2 represents results from the comparison of the two groups in terms pregnancy outcomes including the week of AEDF diagnosis, gestational age at birth, birthweight, z score for standardized birthweight and the time passed from the diagnosis to the birth. Mean gestational age at birth in women who diagnosed with pAEDF was 29.6 ± 2.8 while mean gestational age at birth in women who diagnosed with iAEDF 30.9 ± 2.6 (p-value=0.03). The time passed from the diagnosis to the birth was much shorter for women who diagnosed with pAEDF (mean=7.88, sd=9.99) than for women who diagnosed with iAEDF (mean=15.6, sd=11.5) (p-value=<.0001).

Table 3. Pregnancy complications

	iAEDF (n=38)	pAEDF (n=99)	p-value
AFV			0.57**
A	4 (10.5)	9 (9.1)	
N	29 (76.3)	66 (66.7)	
O	5 (13.2)	21 (21.2)	
P	0 (0.0)	3 (3.0)	
IUFD			0.57**
+	0 (0.0)	4 (4.0)	
-	38 (100.0)	95 (96.0)	
Placentel Ablatio			1.00**
+	1 (2.6)	5 (5.1)	
-	37 (97.4)	94 (94.9)	
Fetal Distress			0.07***
+	15 (39.5)	56 (56.6)	

-	23 (60.5)	43 (43.4)	
IUGR			1.00**
+	36 (94.7)	93 (93.9)	
-	2 (5.3)	6 (6.1)	

*The Mann-Whitney U, **Fisher's Exact test, ***Chi-square test, [a] Independent Sample T-test

Table 3 represents results from the comparison of the two groups in terms pregnancy complications including AFV abnormalities (A: anhydramnios O: oligohydramnios, P: polyhydramnios), IUFD (intrauterine fetal demise), placental ablation, fetal distress. There were no statistically significant differences between two groups in terms of pregnancy complications. However, the percentage of fetal distress in women who diagnosed with pAEDF (56.6%) was noticeably higher than the percentage of fetal distress in women who diagnosed with iAEDF (39.5%).

Table 4. Adverse neonatal outcomes

	iAEDF (n=38)	pAEDF (n=99)	p-value
Apgar score in the first minute	5.4 (1.9)	4.2 (2.2)	0.004*
Apgar score in the fifth minute	7.6 (1.0)	6.4 (2.2)	0.002*
Apgar score in the fifth minute			0.02***
<7	5 (13.2)	33 (33.3)	
>=7	33 (86.8)	66 (66.7)	
admission to the ICU			0.58**
+	0 (0.0)	4 (4.0)	
-	38 (100.0)	95 (96.0)	

to be intubated.			0.08***
+	20 (52.6)	68 (68.7)	
-	18 (47.4)	31 (31.3)	

*The Mann-Whitney U, **Fisher's Exact test, ***Chi-square test, [a] Independent Sample T-test

The comparison of the two groups in terms adverse neoatal outcomes is given in Table 4. Among women who were in the pAEDF group, mean Apgar score in the first minute was 4.2 ± 2.2, while the mean Apgar score in the first minute among women who were in the iAEDF group was 5.4 ± 1.9 (p-value=0.004). Similarly, the mean Apgar score in the fifth minute was lower for the pAEDF group than the iAEDF group (6.4 ±2.2, 7.6 ±1.0 respectively).

The percentage of women with Apgar score in the fifth minute less than 7 in the dak group (33.3%) was much higher than the percentage the percentage of women with Apgar score in the fifth minute less than 7 in the intermittent dak group (13.2%) (p-value=0.02).