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PLACENTAL HISTOPATHOLOGY CORRELATION WITH ANTENATAL UMBILICAL AND UTERINE ARTERY DOPPLER

Pathology

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ABSTRACT

Defective placentation results in a host of pregnancy complications like fetal loss, preeclampsia, and fetal growth restriction and abruptio placentae. There have been recent major advances in obstetric ultrasound such as high-resolution antenatal structural imaging, determination of maternal and fetal blood flow parameters and 3D and 4D ultrasound, which have revolutionised the obstetric care by antenatal diagnosis of placental pathology and its effect on the fetuses. The aim of this study is to correlate placental pathology findings to antenatal Doppler and ultrasonogram and fetal outcome. **METHODS**: All placental specimens received in the department of Pathology, Karnataka Institute of Medical sciences, Hubballi from October 2017 to March 2019 were collected after taking an informed consent. **INCLUSION CRITERIA:** All the cases with antenatal Doppler and ultrasonogram details, irrespective of the gestational age and fetal outcome. **EXCLUSION CRITERIA:** Unbooked cases and cases without clinical history and image findings. **SAMPLE SIZE:** 115 cases Gross examination was done and sections were taken from parenchyma, umbilical cord and the membranes according to Amsterdam guidelines for microscopic examination. The resultant microscopic findings were correlated with antenatal Doppler and ultrasonogram. **RESULTS:** 115 of the 539 cases included in this study had Doppler data, among them, 19 cases showed abnormal Doppler. Placentae with abnormal Doppler findings showed increased syncytial knots, poor vasculo-syncytial membrane, villous crowding and infarct ($p<0.05$) and were associated with increased fetal death and growth restriction. **CONCLUSION:** Placental study correlated with the Doppler findings and was instrumental in reaching a specific diagnosis in inconclusive cases.

KEYWORDS

Doppler, Placental Histopathology, Fetal outcome, Placental insufficiency, IUGR

INTRODUCTION

Pathology of the placenta, cord, or membranes is attributed as a cause or contributor to stillbirth in 11% to 65% of cases, based on the classification used. [1] Uterine artery Doppler waveform as high impedance or abnormal waveforms in the first, and particularly, second trimesters are related to adverse pregnancy outcome. [2] But the uterine artery Doppler waveform can be normal in cases where pathology is evident and may be abnormal in the absence of placental and placental bed pathology. This is likely because of other influences like maternal vascular and endothelial function which act via Hagene Poiseuille law. [3]This study aims to correlate antenatal Doppler with the fetal outcome and placental histopathological changes.

MATERIALS AND METHODS

All placenta specimens received in the department of Pathology, Karnataka Institute of Medical sciences, Hubballi from October 2017 to March 2019 were collected after taking an informed consent. All cases with antenatal Doppler and ultrasonogram details, irrespective of the gestational age and fetal outcome were included in this study. Unbooked cases and cases without clinical history and imaging findings were excluded.

The collected placenta specimens were preserved in 10% formalin immediately after delivery. Intact specimen were subjected to thorough gross examination for measuring weight, diameter and thickness and cut open by loafing it. After adequate fixation over a period of 24-48 hours, representative bits were taken for microscopic examination, according to Amsterdam guidelines, [4] processed and stained with haematoxylin and eosin and studied. Special stains were used whenever required.

Parenchyma were examined for villitis, calcification, fibrin deposition (grading used), acute or chronic Infarct, abnormal maturation, villous edema, fetal vessel thrombosis, endarteritis of stem villi, crowding and the status of vasculo- syncytial membrane. Syncytial Knots were counted in 100 tertiary villi and compared with the standards. Umbilical cords were examined for signs of infection and umbilical artery thrombosis. Membranes were examined for signs of infection and amniotic fluid irritation.

IUGR was taken as baby weight less than 10th percentile of their gestational age standards. The microscopy was correlated with Doppler and fetal outcome. The results were analysed using SPSS v 21. A □ value < 0.05 was considered significant.

RESULTS

Doppler details were available for 115 of the 539 cases included in this study. 19 cases displayed abnormal Doppler findings which were ranging between shallow diastolic notching to absent and reversal of flow. Of the 19 cases, 9(47.4%) fetuses were dead, among the 10 live fetuses, 5 (50%) showed IUGR. The clinical outcome and placental changes of normal and abnormal Doppler group were compared and enumerated below in Table 1.

Placentae with abnormal Doppler findings showed increased syncytial knots, poor vasculo-syncytial membrane, villous crowding and infarct ($p<0.05$) and were associated with increased fetal death and growth restriction. Figure 1 shows a discordant case with normal Doppler findings wherein histopathological examination gave a definite diagnosis. Figure 2 shows a case with abnormal Doppler finding wherein autopsy and histopathological analysis confirmed the cause of the abnormality. Table 2 shows the clinical, radiological and histopathological data of the cases with abnormal Doppler findings.

Table 1- Showing comparison of fetal outcome and placental changes between Normal Doppler group and abnormal Doppler group

Outcome	Normal	Abnormal Doppler	p value
IUGR	39 (41.1%)	12 (66.7%)	0.029
Dead	3 (3.2%)	8 (44.4%)	0.0001
Increased syncytial knots	19 (20%)	9 (50%)	0.008
Infarction	9 (9.5%)	8 (44.4%)	0.001
Poor Vaculosyncytial Membrane	14 (14.7%)	8 (44.4%)	0.006
Abnormal Maturation	6 (6.3%)	2 (11.1%)	0.249
Obliterated Vessels	3 (3.2%)	0 (0%)	0.591
Increased Fibrin	8 (8.4%)	4 (22.2%)	0.075
Calcification	12 (12.6%)	3 (16.7%)	0.246

Villitis	4 (4.2%)	0 (0%)	0.494
Villous edema	0 (0%)	1 (5.6%)	0.159
Villous Crowding	14 (14.7%)	6 (33.3%)	0.048

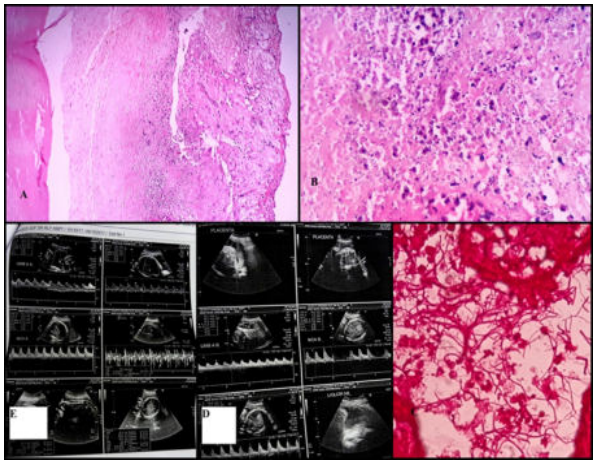

Figure 1- Elderly Primi (32 year) with preterm twin gestation, Gestational Diabetes, Pregnancy induced hypertension. Both the babies showed severe IUGR despite Normal Doppler. A- Section from membrane roll showing acute inflammatory infiltrates (H& E – 20x); B- High power view showing acute chorioamnionitis with neutrophilic infiltration, apoptotic bodies and Fungal spores (H& E-200x); C- PAS stain showing fungal pseudohyphae and neutrophils (400x); D, E- Normal Doppler images of both the babies

Figure 2- 18 week IUD fetus weighing 550 gms of a G2P1L1 21 year old mother without any co-morbidities. USG was suggestive of fetal Cardiomegaly, atrio-ventricular defect, 3.5 cm thick placenta with absent Stomach & ascitis. Doppler showed placental insufficiency. Fetal autopsy was done by removing the organ systems en masse. The heart was dissected by inflow- outflow method to reveal dilated right atria, right ventricle, atrial septal defect, tricuspid valve abnormality and a large, thick, pale friable placenta weighing 400gm & measuring 12x 8x 3 cm which is way too large for the age. Placental microscopy showed edematous immature villi.

Table 2- Clinical, radiological, gross and histopathological information of the 19 cases with Abnormal Doppler.

S NO	OBSTETRIC CODE	M AGE	G AGE	MATERNAL COMORBIDITIES	DOPPLER FINDINGS	BIRTH OUTCOME	FOETAL WT	CLINICAL & GROSS FINDINGS	PLACENTAL CHANGES
1	Primi	21	31w	-	Fetoplacental Insufficiency	Dead	SGA	Fetal cardiac anomaly, small Pulmonary artery	Increased SK
2	Primi	24	35w	Severe Pre eclampsia	UA PI Increased 2.1	Dead	SGA	-	-
3	G2P1L0	23	25w	-	Fetoplacental Insufficiency, Reverse flow in UA, Aortic Isthmus	Dead	SGA	Single Umbilical Artery	Increased SK
4	G3P2L1D1	24	36 w	-	No diastolic flow - UA	Dead	SGA	Hypercoiled umbilical cord	Increased SK
5	G3P1L0A1	21	28w	Chronic hypertension	Increased UA Resistance	Dead	SGA	-	Chronic Infarct, Increased SK
6	G2P1L1	21	18w	-	Placental Insufficiency	Dead	LGA	Cardiomegaly- RA, RV dilated, ASD, Tricuspid Valve Absent, Enlarged pale friable placenta 3.5 cms thick	Edematous villi
7	Primi	21	23w	-	Uteroplacental & Fetoplacental Insufficiency	Dead	SGA	-	Chronic Infarct, increased SK
8	Primi	21	32w	PIH	Uteroplacental & Fetoplacental Insufficiency	Dead	SGA	-	Chronic Infarct, increased SK
9	G2P1L1	26	21w	Hyperthyroidism Anti TPO Positive	Increased S/D Ratio of UA	Dead	AGA	Lumbar Meningomyelocoel, Gross Hydrocephalus, Chiari 2 Malformation	-
10	G3P1L1A1	31	35w	PIH, Anaemia	Placental Insufficiency and Resistance	Live	AGA	Massive Perivillous Fibrin Deposition	Chronic infarct, Distal villous Hypoplasia
11	G3P1L1A1	30	38w	Anaemia	Decreased Diastolic Flow in Right UA	Live	SGA	-	Distal Villous Hypoplasia, Thick Vasculo-syncytial Membrane

12	G3P2L2	35	37w	Hypothyroid, Rh negative	Uteroplacental Insufficiency	Live	SGA	-	-
						Live	SGA	-	-
13	G2P1L1	36	38w	-	Uteroplacental Insufficiency	Live	AGA	-	-
14	Primi	30	37w	PIH	Uteroplacental Insufficiency	Live	AGA	-	-
15	G3A2	30	36w	PIH, GDM	Uteroplacental Insufficiency at 36 w; Normal at 31st w	Cried after Resuscitation	AGA	Marginal insertion of Umbilical cord	-
16	Primi	23	38w	Hypothyroid, Rh negative	Early Uteroplacental Insufficiency- Notching of Bilateral UA	Live	SGA	-	Increased SK, Chronic Infarct
17	G2P1L0	26	35w	-	Fetoplacental Insufficiency	Live	SGA	-	-
19	Primi	21	39w	Mild Pre eclampsia, Anaemia	Uteroplacental Insufficiency	Live	SGA	-	Increased SK, Chronic Infarct

(M age- Maternal age; G age- Gestational age; G- Gravida; P- Para; L- Live; A- Abortion; w- week; UA- Umbilical artery; PI- Pulsatility Index; SGA- Small for gestational age; AGA- Appropriate for gestational age; LGA- Large for gestational age; PIH- Pregnancy induced Hypertension; GDM- Gestational Diabetes Mellitus; RA- Right Atria; RV- Right Ventricle; Rh- Rhesus factor; ASD- Atrial Septal defect; SK- Syncytial Knots)

DISCUSSION

There have been recent major advances in obstetric ultrasound which resulted in changes in antenatal obstetric management, thereby reducing maternal and perinatal mortality. Ultrasound examination is based on high-frequency, low-intensity sound waves being transmitted via an ultrasound transducer consisting of a curved array of piezoelectric crystals. The ultrasound pulses are transmitted and the reflected signals received, the composite signal being visualised as an image representing differing echo densities. Examination of blood flow requires use of techniques based on the Doppler frequency shift principle that for a moving structure, such as blood flowing through a vessel, the reflected wave will be at a different frequency from the transmitted wave depending on the direction and velocity of flow. The Doppler signals can be superimposed on the grey-scale image as coloured areas representing blood flow (colour Doppler imaging), while pulsed-wave Doppler of a specific vessel can determine its flow velocity waveform (FVW) from which both absolute velocities and impedance indices, such as the systolic to diastolic (S/D) ratio, resistance index (RI) and pulsatility index (PI), can be determined. In the present context, the main vessels relevant are uterine (UtA) and umbilical artery (UA) FVWs, representing blood flow and resistance in the uteroplacental and fetoplacental circulations, respectively. [5]

Doppler ultrasound enables the assessment of blood flow parameters for the adequate and reduced perfusion in vivo, for umbilical artery blood velocity waveform reflects function of the placental tertiary villous tree. [6] Reduced villous development correlates with abnormal umbilical artery Doppler velocimetry, being severe in cases of absent or reversed end-diastolic flow velocity. [7,8] Impaired trophoblastic invasion of the maternal spiral arteries is shown to be associated with increased impedance to flow in the waveforms obtained by Doppler ultrasound examination of the uterine arteries. [9,10]

In this study, 115 cases had Doppler findings, of which 19 cases had abnormal Doppler findings. The placentae with abnormal Doppler were compared with those with normal Doppler findings. In this study, placentae with abnormal Doppler findings showed increased syncytial knots, poor vasculo-syncytial membrane, villous crowding and infarct ($p<0.05$). This is in comparison with the study done by Madazli et al, [11] wherein they compared a group of 47 Intrauterine Growth Retardation (IUGR) placentae with 25 Appropriate for Gestational Age (AGA) placentae and found that placentae from IUGR cases with abnormal umbilical artery Doppler velocimetries had a significantly increased number of villous infarcts ($p=0.001$), cytotrophoblast proliferation ($p=0.038$) and thickening of the villous trophoblastic basal membrane ($P=0.02$). M. Parra-Saavedra et al [12] concluded that significant proportion of late-onset SGA births with normal umbilical artery Doppler may still be explained by placental insufficiency.

Dicke et al [13] concluded that placental abnormalities were significantly more common in cases with abnormal Doppler values (positive predictive value, 94%). C. Lacovella et al [14] concluded that high first-trimester uterine artery Doppler RI is associated with late stillbirth after 34 weeks' gestation which supersedes those of conventional risk factors such as maternal age, parity and Body Mass Index (BMI), implying that these factors result in an increased risk of stillbirth by causing placental dysfunction.

Salafia et al [15] concluded that absent end-diastolic flow cases had more occlusive lesions of the intraplacental vasculature, whereas in cases with reversed end-diastolic flow, lesions suggesting vascular remodeling predominated. A. Spinillo et al [16] found that there is increase of syncytial knots [odds ratio (OR) = 28.7; 95% confidence interval (CI) = 2.75–298.5], intervillous fibrin deposits (OR = 2.1; 95%CI = 1.04–4.28), placental site giant cells (OR = 3.0; 95%CI = 1.05–8.84), and patterns suggesting maternal under perfusion (OR = 2.9; 95%CI = 1.0–7.1) were independently associated with increased rates of absent/reversed UA end-diastolic flow. Vedmedovska N et al [17] compared placentae of control group with normal Doppler with placentae of 50 Fetal Growth Restriction (FGR) women with abnormal Doppler velocimetry of uterine and umbilical arteries and found that the abnormal group had statistically significant increase in intervillous thrombi and villous infarctions. Thickening of the basal membrane and villitis was clearly linked to the FGR ($p = 0.006$ and $p = 0.01$).

Redline et al studied 60 cases of severe early onset IUGR with absent or reversed end diastolic flow in the umbilical arteries and found that the majority cases with abnormal uterine artery Doppler was associated with decidual vasculopathy (sensitivity 91%, positive predictive value 51%.). Lesions in the parenchyma/villi were common (70% accelerated villous maturation, 40% excess perivillous fibrin deposition, 53% villous infarction, 7% intervillous thrombi, 5% fetal thrombotic vasculopathy) with 93% cases with one or more of these histopathologic abnormalities. [18]

CONCLUSION

Doppler is a good screening tool to assess feto-maternal circulaion. Abnormal Doppler is associated with poor fetal outcome, increased syncytial knots, placental infarction and abnormal vasculo-syncytial membrane and hence is a bleak prophecy indicating feto-maternal malperfusion. However, placental histopathological examination remains the gold standard as Doppler has scant use apart from vascular pathology especially in a country like India wherein infections are very common and severe enough to cause poor fetal outcome and hence should always be followed up with it.

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