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Original Article

Pathology Section

Placental Changes in Perinatal Death- An Observational Study from a Tertiary Care Centre in North Karnataka

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ABSTRACT

Introduction: Placenta is poetically described as a diary which bears the events of intrauterine life; hence examining them, especially in perinatal death can provide valuable information regarding the cause of death and sometimes gives an idea about recurrence of such events.

Aim: To describe the various placental lesions in perinatal death and compare them with equal number of normal placentae.

Materials and Methods: This prospective, comparative, cross-sectional study was conducted in tertiary care centre, Karnataka Institute of Medical Sciences, Hubballi, Karnataka, India. All placentae, irrespective of the gestational age, received in the Department of Pathology, from October 1st 2017 to March 31st 2019 were collected after taking an informed consent. A total of 539 cases were received in this time frame, of which 121 (22.45%) were dead and included in the study and were compared with 121 normal placentae (alive), without any maternal co-morbidities. The placentae were grossed and assessed according to Amsterdam guidelines. The significance of the difference observed was established by Chi-square test using Statistical Package for Social Sciences software (SPSS) version 21.0.

Results: Of these 121 cases, 89 (73.5%) cases had placental changes, whereas 32 (26.5%) cases were devoid of placental changes. Placental infarct and increased syncytial knots were seen contributing maximum to foetal death in 31 (25.6%) cases followed by chorioamnionitis. Rare cases like Twin Reversed Arterial Perfusion (TRAP) syndrome, Persistent Right Umbilical Vein (PRUV), maternal floor infarct were also reported.

Conclusion: Despite many antenatal imaging advances, placental examination still remains valuable in diagnosing cause of death and growth restriction in the foetus especially recurrent causes, favouring clinical intervention in those cases.

Keywords: Increased syncytial knots, Intrauterine death, Maternal floor infarct, Placental infarct

INTRODUCTION

Throughout the world there are more than 3 million perinatal deaths reported every year [1]. India, with perinatal mortality rate of 26 per 1000 live births, still struggles to end preventable still births and neonatal deaths, despite tremendous improvements in maternal and child health now-a-days. Besides, these deaths cause a significant negative psychological impact on the mother. Autopsy, by confirming the cause of death, helps to predict the recurrence risk and hence affects the future reproductive decision of the couple [2]. Placental causes of foetal death contribute to upto 33% of the various causes of still birth and can never be overlooked. This study, is done along with a bigger study to describe the various placental lesions in perinatal death, compare them with equal number of normal placentae and arrive at significant conclusion [3].

MATERIALS AND METHODS

This prospective, comparative, cross-sectional study was conducted in tertiary care centre, Karnataka Institute of Medical Sciences, Hubballi, Karnataka, India. All placenta specimens received in the Department of Pathology from October 2017 to March 2019 were collected after taking an informed consent. Of the 539 cases received in the Department, 121 (22.45%) cases were dead. Ethical clearance was obtained vide No. KIMS/PGS/SYN/447/2017-18 before starting the study, dated 21/11/2017.

Inclusion and Exclusion criteria: These dead cases, irrespective of cause of death- be it maternal/foetal or non obstetric causes were included in this study and were compared with 121 normal other placentae which were devoid of any significant maternal illness which could possibly contribute to placental changes. Unbooked cases without proper previous records were also excluded from the control group.

Study Procedure

The placenta specimens preserved in 10% formalin were received in the Department of Pathology. These predominantly included specimen were from the labour ward and Elective and Emergency Operation Theatres, Department of Obstetrics and Gynaecology of the Institute and the samples received from peripheral hospitals of the district. These specimens were subjected to thorough gross examination for the measurement of weight, diameter and thickness and cut open by bread-loafing it and examined for clots, infarcts and fibrin deposits. After adequate fixation over a minimum period of 24 hours, representative bits were taken for microscopic examination, processed and stained with Haematoxylin and Eosin (H&E) and studied. Special stains like Gomori methanamine silver (to confirm fungal infections), gram stain (Bacterial infection), Masson trichrome staining, Periodic Acid Schiff (PAS) stain were used.

Amsterdam guidelines were implemented for both gross and microscopic examination [4]. Sections from the placental parenchyma were examined for features of acute or chronic infarct, abnormal maturation, villitis, calcification, fibrin deposition (grading used from + to 4+), villous oedema, foetal vessel thrombosis, endarteritis of stem villi and the patency of vasculosyncytial membrane. Syncytial knots were counted in 100 tertiary villi and compared with the standards for corresponding gestational age. Umbilical cords were examined for signs of infection and thrombosis. Membranes were examined for signs of infection. The results of dead vs alive were statistically analysed for significance.

STATISTICAL ANALYSIS

Data was entered in Microsoft excel and analysed using Statistical Package for Social Sciences software (SPSS) version 21.0. The significance of the difference observed was established by Chi-square test. The p-value <0.05 was considered to be significant.

RESULTS

Of the 539 cases included in this study, 121 (22.45%) cases were dead. Of these 121 cases, 89 (73.5%) cases had placental changes, indicating the contribution of abnormal placenta in adverse foetal outcome, whereas 32 (26.5%) cases were devoid of placental changes. Among the placental changes, infarct and increased syncytial knots, which are features of hypoxia and malperfusion, were seen contributing maximum to foetal death in 31 (25.6%) cases followed by chorioamnionitis in 16 (13.3%) cases. The [Table/Fig-1] shows various histopathological and gross findings in the placentae of dead foetuses as compared to live foetuses.

Changes in placentae	Alive foetuses n (%)	Dead foetuses n (%)	p-value
Intrauterine growth restriction (IUGR)	37 (30.6%)	80 (66.1%)	0.0001*
Increased syncytial knots	29 (24%)	34 (28.1%)	0.089
Infarction	8 (6.6%)	29 (24%)	0.0001*
Poor vaculosyncytial membrane	5 (4.1%)	64 (52.9%)	0.0001*
Abnormal maturation	2 (1.65%)	9 (7.4%)	0.025*
Obliterated vessels	2 (1.65%)	2 (1.65%)	0.378
Increased fibrin	15 (12.4%)	16 (13.2%)	0.150
Calcification	10 (8.3%)	7 (5.8%)	0.151
Villitis	1 (0.8%)	4 (3.3%)	0.175
Villous oedema	-	9 (7.4%)	0.002*
Villous crowding	6 (5%)	7 (5.8%)	0.215
Abnormal placental shape	2 (1.65%)	3 (2.5%)	0.315
Abnormal umbilical cord insertion	4 (3.3%)	12 (9.9%)	0.025*
Abnormal umbilical cord vessels	0 (0%)	15 (12.4%)	0.0001*
Preterm	7 (5.8%)	107 (88.4%)	0.0001 *
Inflammation	18 (14.9%)	27 (22.3%)	0.137

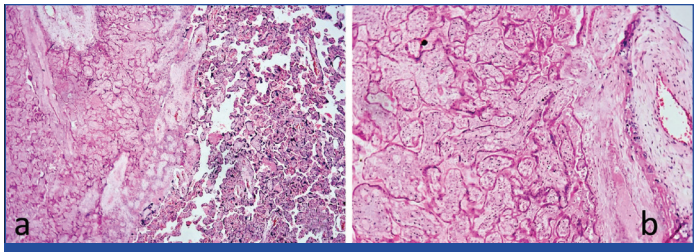
[Table/Fig-1]: Showing the gross and microscopic changes in placentae of dead foetuses as compared to placentae of live foetuses.
*Statistically Significant; p-value <0.05 was considered to be significant

DISCUSSION

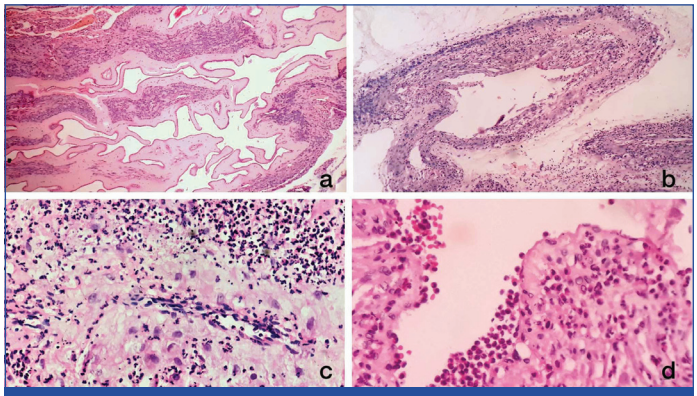
Placenta was often overlooked by surgical pathologists because of its complexity in histology which differs in different gestational age groups which makes it difficult to interpret without supporting data like Ultrasonography (USG) findings, confirming the gestational age. For instance, if the placenta of 28 weeks gestational age shows mature intermediate villi, it is normal, but the same in a 34-36 week gestational age should be interpreted as villous dysmaturity. If the gestational age is not accurate because of wrong dates, or irregular menstrual cycles, then the problem sets in.

Moreover, the placental changes are not specific for a particular disorder. A variety of disorders may show a similar change like infarct in the placenta. A maternal eclampsia may produce infarcts, but not all infarcts are produced by maternal pre-eclampsia/eclampsia. Besides, there might be multiple disorders in a single patient and the final picture is often very complicated. Some placental and decidual changes tend to recur in the subsequent pregnancies and cause recurrent foetal loss as well. Thus, studying the placentae in detail grossly and microscopically can give us a clear idea of the pathology in the foetus and mother in selected cases and may help face the recurrent conditions better by means of effective parental counselling. Villitis of unknown aetiology, maternal floor infarct, decidual angiopathy are some of the recurrent lesions in placentae and has to be looked for during the examination.

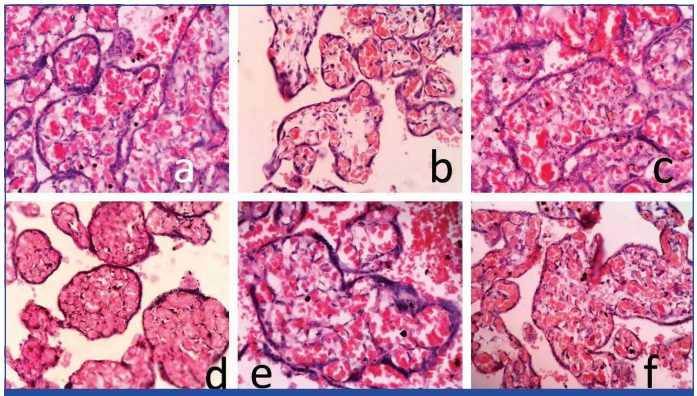
Placental changes in Intrauterine Death (IUD): Man J et al., studied 946 still birth cases and concluded that 32% cases had abnormalities of the placenta, cord or membranes which lead to the cause of death with one third of still births (≥24 weeks) presenting with isolated placental histological abnormality [5]. The cause of death was ascending infection in 176 (19%) cases. Maternal vascular malperfusion was the largest category among the placental abnormalities in still birth, especially in the early third trimester, which is consistent with our study. Tellefsen CH and Vogt C studied 104 cases and concluded that significant placental pathology was found in 69.2% of the perinatal deaths; as compared to 89 (73.5%) cases (% among the dead) in present study, 12 (9.6%) cases had small, possibly contributing changes; 14 (11.5%) cases did not show any pathology of interest; and there were changes of uncertain significance in 6 (4.9%) cases of the deaths in their study [6]. Their most frequently observed diagnoses were infection (22.1%), degenerative changes (13.5%), and abruptio placentae (12.5%). However, in present study infarcts and increased syncytial knots were the most common placental change [Table/Fig-2]. The [Table/Fig-3,4] shows chorioamnionitis and chorangiosis respectively and [Table/Fig-5] shows pale friable large placenta associated foetal cardiac illness.



[Table/Fig-2]: a,b) Showing microscopic images of remote infarct marked by ghost villi (H&E, 10X).

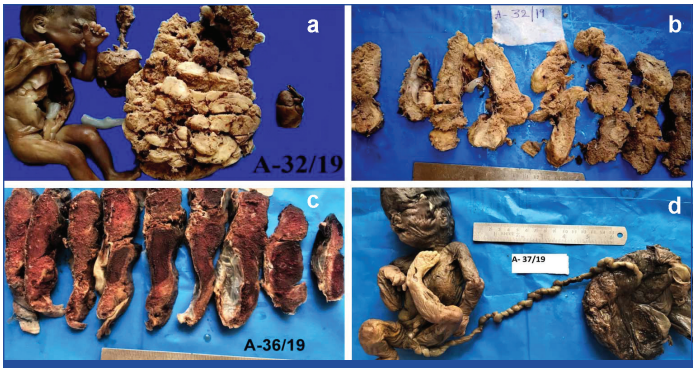


[Table/Fig-3]: Showing microscopic images of membrane roll showing amnion, amnionic and chorionic mesoderm and trophoblast layers; a) at magnification (H&E, 4X); b) Neutrophils infiltrating the different layers (H&E, 10X); c-d) Acute inflammatory infiltrates in the membranes (H&E, 200X).



[Table/Fig-4]: a-f) Showing chorangiotic foci in various cases in this study as a result of long standing low grade hypoxia, as defined by >10 capillaries in at least 10 terminal villi in 10 or more non infarcted areas in at least three low power field. Few nucleated RBCs are also seen in the capillaries (H&E, 400X).

Heazell AE and Martindale EA, concluded that placental examination contributed useful information to the classification of 47% of still births [7]. Kidron D et al., studied 120 cases and found that 88% of the underlying causes of death were related to the placental disc, umbilical cord or chorioamnionitis [8]. Bonetti LR et al., studied 124 cases and concluded that through analysis of the placenta, they

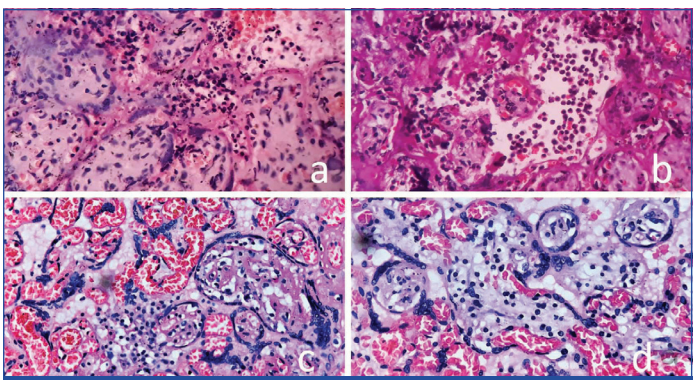


[Table/Fig-5]: a) Showing 18 week dead foetus, placenta with the dissected heart showing cardiomegaly. Further dissection of the foetal heart revealed dilated right atria and ventricle and poor AV canal. Placenta was large, pale and friable and weighed 450 grams; b) Showing cut section of the placenta which is friable, pale and large for 18 weeks gestational age. Microscopy showed edematous villi and chorioamnionitis; c) Placenta of 30 week IUD foetus, showing a well-defined indurated red area in cut section, occupying more than 30% of the surface area-acute Infarction of the placenta. Microscopy showed increased syncytial knots, crowded and congested, crowded chorionic villi; d) 32 week dead foetus with placenta and hypercoiled umbilical cord.

were able to reduce the unexplained still birth rate from 20.16% to 15% [9]. The major conditions associated to still births were fetoplacental infection, and placental insufficiency mainly associated with IUGR (<10th customised percentile).

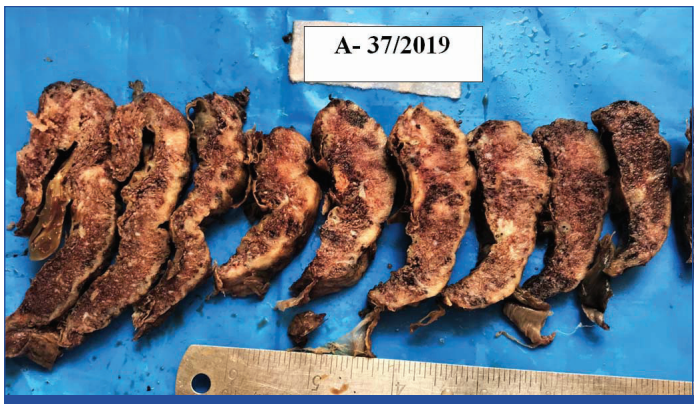
Pinar H et al., studied 518 still births and compared them with 1200 live births and concluded that among still births, inflammation and retroplacental hematoma were more common in placentas from early deliveries, while thrombotic lesions were more common in later gestation [10]. Ptacek I et al., did a systematic review of placental changes in still birth and concluded that the proportion of still births attributed to a placental cause ranged from 11-65%, based on the different classification system used, which affects the utility of histopathological examination of the placenta [11]. And he emphasised on the need of a common classification system which could rectify this problem.

Villitis of unknown aetiology: Two cases (1.65%) of villitis of unknown aetiology were seen in this study as shown in [Table/Fig-6]. Villitis of Unknown Aetiology (VUE), also known as chronic villitis, is an inflammation involving placental villi. VUE is a recurrent condition which is known to cause Intrauterine Growth Restriction (IUGR) resulting in the poor growth of the foetus, still birth, miscarriage and premature delivery [12,13]. VUE recurs in about 1/3 of subsequent pregnancies and is predominantly seen in term placentas (around 80%) [14]. Hence, VUE in a placenta less than 32 weeks old should be screened for infectious villitis [12]. Both the cases reported in this study were in the dead group and were preterm, suggesting a possible infective aetiology in these cases.

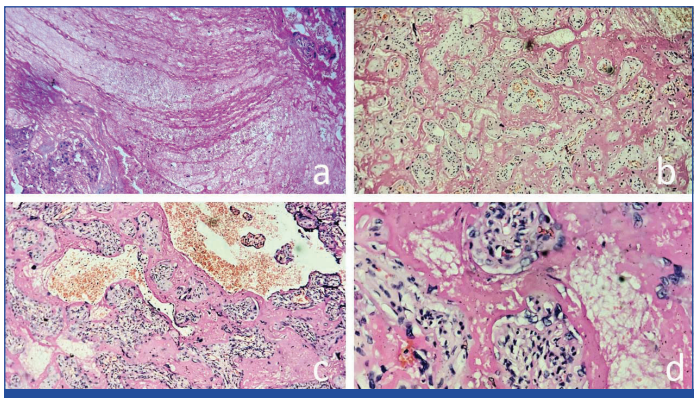


[Table/Fig-6]: a) Villitis of unknown aetiology showing villi with sclerosed blood vessels, surrounding fibrin and infiltration by lymphocytes, plasma cells and neutrophils causing destruction of the villi. Intervillous space also shows inflammatory cells (H&E, 200X); b) Acute inflammatory cells in the intervillous space with surrounding degenerating villi (H&E, 200X); c-d) extensive infiltration of chorionic villi by lymphocytes. Surrounding Villi show congested blood vessels (H&E, 200X).

Maternal floor infarct: There were two cases of maternal floor infarct in this study. A 20-year-old primi with 32 weeks gestational age presented with lack of foetal movements, USG revealed intrauterine foetal death. She was induced and the foetus and the placenta was delivered and sent for examination. The foetus weighed 550 grams, and the placenta weighed 80 grams. Foetal autopsy did not reveal any gross or microscopic changes but grossly, placenta had a thick layer of fibrin deposition 0.6 cm thick occupying the whole of maternal surface and had an area of remote infarct measuring 3×3×2 cm as shown in [Table/Fig-7]. Microscopically, the placenta showed areas of ghost villi which are crowded and back to back, surrounding viable areas showed increased syncytial knots of 47/100 mature tertiary villi, suggesting an ongoing hypoxic episode. Besides, there was accelerated villous maturation and areas of avascular villi as shown in [Table/Fig-8]. Moreover, the areas corresponding to maternal floor fibrin showed a layer of fibrin deposition in microscopy as well. All these features point to the diagnosis of maternal floor infarct.



[Table/Fig-7]: Showing cut section of the placenta showing maternal floor infarct/ massive perivillous fibrin deposition showing fibrin deposits along the entire length of the maternal surface of the placenta which <0.3 cm thick required for the diagnosis.



[Table/Fig-8]: Showing microscopic images of a case of maternal floor infarct; a) Large areas of fibrin deposition in the maternal aspect (H&E, 40X); b-d) Sclerosed villi encased by fibrin (H&E, 10X. 40X, 100X respectively).

There was another similar case in this study, a 22 year- G2P1L0D1- female with 35 weeks gestation presented with IUD. Autopsy of the foetus revealed no abnormality, on the contrary, placenta showed several significant changes, contributing to foetal death. Placental maternal surface showed a 0.4 cm thick layer of fibrin deposition, a remote peripheral wedge infarct measuring 2×2×2 cm as shown in [Table/Fig-9]. Umbilical cord revealed single umbilical artery. Microscopy confirmed the areas of maternal floor infarct and wedge infarct. Besides, they showed increased syncytial knots (28/100 terminal villi) and features of acute chorioamnionitis.

Benirschke K and Driscoll SG first described maternal floor infarction of the placenta [15]. Massive Perivillous Fibrin Deposition (MPFD) and Maternal Floor Infarction (MFI) are placental pathology of unknown aetiology characterised by extensive deposition of fibrinoid material in the intervillous space which appears as pinkish acellular areas microscopically. The surrounding villi are generally sclerosed and hypoplastic [15,16]. Fibrin and/or fibrinoid material deposition

[Table/Fig-9]: Showing placenta of 35 week dead foetus with hypercoiled umbilical cord single umbilical artery and Maternal Floor infarct (extensive fibrin deposition on the entire length of the maternal surface >0.3 cm thick.

interferes with perfusion and gas/nutrient exchange in the intervillous space, which results in chronic placental insufficiency [17-19]. Pregnancy with MPFD is associated with spontaneous abortion foetal growth restriction and foetal death [16,17,19-22]. Andres RL et al., reported 48 maternal floor infarcts with a mortality rate of 40% and a recurrence rate of 12% [17]. Hence, it is suggested to rule out maternal disease like MPFD when there are multiple abortions without any successful pregnancy [15].

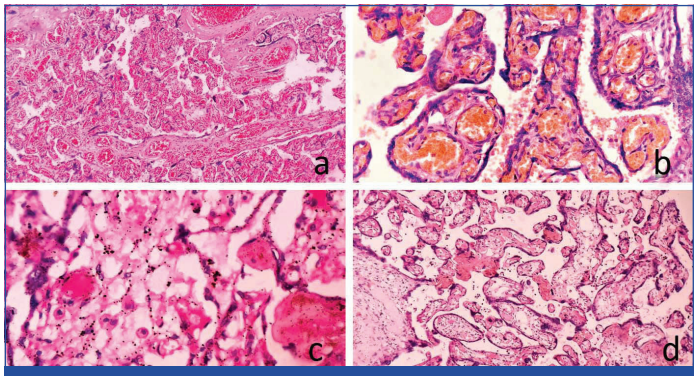
Romero R et al., found that plasma cell deciduitis, maternal anti-human leukocyte antigen (HLA) class I positivity, positive C4d deposition on umbilical vein endothelium were found to be significantly higher in cases with MPFD than in those with normal term deliveries. Besides, specific maternal antibody against foetal HLA antigen class I or II and maternal plasma concentration of C-X-C motif chemokine ligand 10 (CXCL10) were higher in patients with evidence of MPFD than in those without evidence of MFPD. Hence, it is postulated that maternal floor infarct could be a feature of maternal antifoetal rejection [23]. Other aetiologic hypotheses include infection cytotoxicity, and a final common pathway of other disorders [24-26].

Anti-phospholipid Antibody (APLA) syndrome: Three cases were positive for IgM APLA antibodies, one of these cases presented with recurrent second trimester abortions. The foetus growth was retarded, but placenta did not show any change grossly or microscopically as compared with normal placentae. But, considering the small sample size, further larger studies has to be done to exclude the role of placental pathology in recurrent abortions in these cases.

Umbilical vessel abnormalities- single umbilical artery: Abnormal vessels were reported in 15 cases, all of them falling in the dead group. Single Umbilical Artery (SUA) were reported in 14 (93.3%) cases and Supranumerary or PRUV is seen in 1 (6.6%) case. A SUA is found in about 1 in 200 deliveries [27]. Several studies have confirmed that SUA is associated with chromosomal abnormalities especially trisomy and multiple foetal defects [28,29]. Dagklis T et al., concluded that the finding of an SUA with co-existant foetal defects in USG were associated with chromosomal abnormalities [29]. However, he insisted that isolated SUA has little association with chromosomal abnormalities. Hua M et al., concluded that there was an increased risk of IUGR in foetuses with single umbilical artery is made and recommended serial growth monitoring in those cases [30]. Bombrys AE et al., performed a case-control study comparing 297 pregnancies with SUA to 297 pregnancies with DUA and concluded that there was not statistically significant increase in IUGR in SUA group (13.7% in SUA compared with 13.9% in DUA, p-value=0.93) [31]. In above mentioned study, omphalomesentric/allantoic duct remnant was seen in cases.

Persistence of right umbilical vein: This study included one case with supernumerary umbilical vessels. The mother was G3A2 with recurrent second trimester abortion. The child died in utero, and the autopsy revealed no obvious findings except for supernumerary umbilical vessels. Microscopically, the cord had two arteries and two veins. The condition in which the right vein remains patent is termed "Persistence of Right Umbilical Vein" (PRUV) [32], it is due to the maintenance of the patency of the normal left umbilical vein and persistence of the caudal part of the right umbilical vein [33]. Less than 15 such cases are being reported in the literature [34]. Several reports have insisted on foetal echocardiography in antenatally diagnosed cases of umbilical vein abnormalities to rule out foetal hydrops, as these cases are more prone for the same [32,35,36].

Twin arterial reverse perfusion syndrome: There were were three cases cases of twin to twin transfusion syndrome in this study; one of them was a case of TRAP syndrome. Incidence of acardiac twin resulting from TRAP is 1:34,600 births or 1% of all monozygotic twins [37], wherein the normal twin 'pumps' or 'donates' blood to the abnormal twin, which is called the 'recipient' or 'perfused' twin through abnormal artery-to-artery or venous-to-venous communications in the placenta [38]. In present case, the recipient twin had abnormal upper trunk with absent face, anophthalmia, absent ears and mouth. Internal examination showed absent bilateral lungs, heart and liver. It was associated with single umbilical artery, as seen in 75% of these cases and the umbilical cord diameter was small compared to the donor umbilical cord. Reduction of blood supply in early trimesters are known to cause reabsorption of the tissues affected, resulting in complete absence or atresia of organs [39]. Recurrence of TRAP syndrome is likely to be low and the couples can be counselled positively for future pregnancy [40]. The another case was that of twin to twin transfusion syndrome with monochorionic, monoamniotic placenta. One of the foetuses survived while the other was dead. Placenta towards the dead foetus showed areas of remote infarction and increased syncytial knots. Here, [Table/Fig-10] shows the microscopic features of placenta of both donor and recipient part of the placenta.



[Table/Fig-10]: Showing microscopic images of the congested (a,b) and pale (c,d) portion of the monochorionic diamniotic twin placentae of TRAP syndrome. a) Congested villi which are mature for age, from the recipient side of the placenta (H&E, 40X); b) Congested foetal vessels in the villi (H&E, 200X); c) Pale immature intermediate villi with chorangiotic change (H&E, 400X); d) Pale appearing villi from the donor region of the twin placenta (H&E, 100X).

Umbilical cord abnormalities: Abnormal umbilical cord insertion was associated with foetal death and was seen in 12 (9.9%) cases in the dead group as compared with 4 (3.3%) cases in alive group (p value-0.038). Brouillet S et al., studied the influence of abnormal cord insertion on optimal birth weight achievement and found that only 17/343 (5.0%) of infants with central cord insertion were growth restricted, as compared to 37/185 (20%) of the infants with a peripheral insertion and neonates with centrally inserted cord were found to be significantly heavier [41]. In present study, 14 (87.5%) cases with abnormal cord insertion showed growth restriction and 12 (75%) cases with abnormal cord insertion were appropriate for gestation. The [Table/Fig-5d] shows hypercoiled umbilical cord.

Limitation(s)

The comparison group is not matched with age, gestational age. However since the sample size is large, the findings can be generalised.

CONCLUSION(S)

Despite many antenatal imaging advances, postnatal placental examination still remains valuable in contributing to identifying cause of death and growth restriction in the foetus especially recurrent causes, favouring clinical intervention.

Further studies should be done on individual recurrent causes of foetal loss with larger sample size of individual entities to find specific characteristic findings in these entities.

Author declarations: Three other studies were done simulataneously (Reference number 3) and have overlapping methodology as the data were collected simultaneously though the objectives and the subjects of these studies are unique and unrelated.

REFERENCES

[1] Cousens S, Blencowe H, Stanton C, Chou D, Ahmed S, Steinhardt L, et al. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: A systematic analysis. The Lancet. 2011;377(9774):1319-30. Doi: 10.1016/S0140-6736(10)62310-0. PMID: 21496917.

[2] Sankar VH, Phadke SR. Clinical utility of fetal autopsy and comparison with prenatal ultrasound findings. Journal of Perinatology. 2006;26(4):224-29. Doi: 10.1038/sj.jp.7211482. PMID: 16541112.

[3] Bargunam P, Jigalur P, Reddy P. Proportionality of clinical outcome and placental changes to the increasing severity of maternal hypertension- An observational study. Turk Patoloji Derg. 2021;1(1). English. Doi: 10.5146/tjpath.2021.01563. PMID: 34854472.

[4] Khong TY, Mooney EE, Ariel I, Balmus NC, Boyd TK, Brundler MA, et al. Sampling and definitions of placental lesions: Amsterdam placental workshop group consensus statement. Archives of Pathology & Laboratory Medicine. 2016;140(7):698-713. Doi: 10.5858/arpa.2015-0225-CC. Epub 2016 May 25. PMID: 27223167.

[5] Man J, Hutchinson JC, Heazell AE, Ashworth M, Jeffrey I, Sebire NJ. Stillbirth and intrauterine fetal death: Role of routine histopathological placental findings to determine cause of death. Ultrasound in Obstetrics & Gynecology. 2016;48(5):579-84. Doi: 10.1002/uog.16019. Epub 2016 Oct 25. PMID: 27781319.

[6] Tellefsen CH, Vogt C. How important is placental examination in cases of perinatal deaths? Pediatric and Developmental Pathology. 2011;14(2):99-104. Doi: 10.2350/10-07-0870-OA.1. Epub 2010 Aug 18. PMID: 20718631.

[7] Heazell AE, Martindale EA. Can post-mortem examination of the placenta help determine the cause of stillbirth? Journal of Obstetrics and Gynaecology. 2009;29(3):225-28. Doi: 10.1080/01443610802716042. PMID: 19358031.

[8] Kidron D, Bernheim J, Aviram R. Placental findings contributing to fetal death, a study of 120 stillbirths between 23 and 40 weeks gestation. Placenta. 2009;30(8):700-04. Doi: 10.1016/j.placenta.2009.05.009. Epub 2009 Jun 16. PMID: 19535137.

[9] Bonetti LR, Ferrari P, Trani N, Maccio L, Laura S, Giuliana S, et al. The role of fetal autopsy and placental examination in the causes of fetal death: A retrospective study of 132 cases of stillbirths. Archives of Gynecology and Obstetrics. 2011;283(2):231-41. Doi: 10.1007/s00404-009-1317-4. Epub 2010 Jan 6. PMID: 20052483.

[10] Pinar H, Goldenberg RL, Koch MA, Heim-Hall J, Hawkins HK, Shehata B, et al. Placental findings in singleton stillbirths. Obstetrics and Gynecology. 2014;123(2 Pt 1):325. Doi: 10.1097/AOG.0000000000000100. PMID: 24402599; PMCID: PMC3948332.

[11] Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AE. Systematic review of placental pathology reported in association with stillbirth. Placenta. 2014;35(8):552-62. Doi: 10.1016/j.placenta. 2014.05.011. Epub 2014 Jun 6. PMID: 24953162.

[12] Redline RW. Villitis of unknown etiology: Noninfectious chronic villitis in the placenta. Human Pathology. 2007;38(10):1439-46. Doi: 10.1016/j.humpath.2007.05.025. PMID: 17889674.

[13] Tamblyn JA, Lissauer DM, Powell R, Cox P, Kilby MD. The immunological basis of villitis of unknown etiology–review. Placenta. 2013;34(10):846-55. Doi:10.1016/j.placenta.2013.07.002. PMID 23891153.

[14] Feeley L, Mooney EE. Villitis of unknown aetiology: Correlation of recurrence with clinical outcome. Journal of Obstetrics and Gynaecology. 2010;30(5):476-79. Doi: 10.3109/01443611003802339. PMID 20604650. S2CID 11473529.

[15] Benirschke K, Driscoll SG. Maternal floor infarction. In: Benirschke K, Driscoll SG, eds. Pathology of the Human Placenta. New York: Springer-Verlag; 1967: 328-30.

[16] Katzman PJ, Genest DR. Maternal floor infarction and massive perivillous fibrin deposition: Histological definitions, association with intrauterine fetal growth restriction, and risk of recurrence. Pediatric and Developmental Pathology. 2002;5(2):159-64. Doi: 10.1007/s10024001-0195-y. Erratum in: Pediatr Dev Pathol. 2003;6(1):102. PMID: 11910510.

[17] Andres RL, Kuyper W, Resnik R, Piacquadio KM, Benirschke K. The association of maternal floor infarction of the placenta with adverse perinatal outcome. American Journal of Obstetrics and Gynecology. 1990;163(3):935-38. Doi: 10.1016/0002-9378(90)91100-q. PMID: 2403172.

[18] Naeye RL. Maternal floor infarction. Human pathology. 1985;16(8):823-28. PMID: 4018779.

[19] Bendon RW, Hommel AB. Maternal floor infarction in autoimmune disease: Two cases. Pediatric Pathology & Laboratory Medicine. 1996;16(2):293-98. PMID: 9025835.

[20] Bane AL, Gillan JE. Massive perivillous fibrinoid causing recurrent placental failure. BJOG: An International Journal of Obstetrics and Gynaecology. 2003;110(3):292-95. PMID: 12628270.

[21] Clewell WH, Manchester DK. Recurrent maternal floor infarction: A preventable cause of fetal death. American Journal of Obstetrics and Gynecology. 1983;147(3):346-47. Doi: 10.1016/0002-9378(83)91130-4. PMID: 6624805.

[22] Sebire NJ, Backos M, El Gaddal S, Goldin RD, Regan L. Placental pathology, antiphospholipid antibodies, and pregnancy outcome in recurrent miscarriage patients. Obstetrics & Gynecology. 2003;101(2):258-63. Doi: 10.1016/s0029-7844(02)02385-2. PMID: 12576248.

[23] Romero R, Whitten A, Korzeniewski SJ, Than NG, Chaemsaithong P, Miranda J, Dong Z, Hassan SS, Chaiworapongsa T. Maternal floor infarction/massive perivillous fibrin deposition: A manifestation of maternal antifetal rejection? American Journal of Reproductive Immunology. 2013;70(4):285-98. Doi: 10.1111/aji.12143. Epub 2013 Aug 1. PMID: 23905710; PMCID: PMC4122226.

[24] Robb JA, Benirschke K, Mannino F, Voland J. Intrauterine latent herpes simplex virus infection: II. Latent neonatal infection. Human Pathology. 1986;17(12):1210-17. https://doi.org/10.1016/S0046-8177(86)80562-7.

[25] Gersell DJ. Chronic villitis, chronic chorioamnionitis, and maternal floor infarction. Semin Diagn Pathol. 1993;10(3):251-66. PMID: 8210775.

[26] Vernof KK, Benirschke K, Kephart GM, Wasmoen TL, Gleich GJ. Maternal floor infarction: Relationship to X cells, major basic protein, and adverse perinatal outcome. American Journal of Obstetrics and Gynecology. 1992;167(5):1355-63. https://doi.org/10.1016/S0002-9378(11)91716-5.

[27] Thummala MR, Raju TN, Langenberg P. Isolated single umbilical artery anomaly and the risk for congenital malformations: A meta-analysis. Journal of Pediatric Surgery. 1998;33(4):580-85. Doi: 10.1016/s0022-3468(98)90320-7. PMID: 9574755.

[28] Sepulveda W, Peek MJ, Hassan J, Hollingsworth J. Umbilical vein to artery ratio in fetuses with single umbilical artery. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 1996;8(1):23-26. Doi: 10.1046/j.1469-0705.1996.08010023.x. PMID: 8843614.

[29] Dagklis T, Defigueiredo D, Staboulidou I, Casagrandi D, Nicolaides KH. Isolated single umbilical artery and fetal karyotype. Ultrasound in Obstetrics and Gynecology. 2010;36(3):291-95. Doi: 10.1002/uog.7717. PMID: 20549772.

[30] Hua M, Odibo AO, Macones GA, Roehl KA, Crane JP, Cahill AG. Single umbilical artery and its associated findings. Obstetrics & Gynecology. 2010;115(5):930-34. Doi: 10.1097/AOG.0b013e3181da50ed. PMID: 20410765.

[31] Bombrys AE, Neiger R, Hawkins S, Sonek J, Croom C, McKenna D, et al. Pregnancy outcome in isolated single umbilical artery. American Journal of Perinatology. 2008;25(04):239-42. Doi: 10.1055/s-2008-1061504. PMID: 18548398.

[32] Viora E, Sciarrone A, Bastonero S, Errante G, Mortara G, Chiappa E, et al. Anomalies of the fetal venous system: A report of 26 cases and review of the literature. Fetal Diagnosis and Therapy. 2004;19(5):440-47. Doi: 10.1159/000078997. PMID: 15305101.

[33] Aoki S, Hata T, Ariyuki Y, Makihara K, Hata K, Kitao M. Antenatal diagnosis of aberrant umbilical vessels. Gynecol Obstet Invest. 1997;43(4):232-35. Doi: 10.1159/000291863. PMID: 9194620.

[34] Karatza A, Tsamandas A, Varvarigou A, Davlouros P, Pavlou V, Mantagos S. Supernumerary umbilical vein in a hydropic neonate with hypertrophic cardiomyopathy. Fetal and Pediatric Pathology. 2011;30(3):173-36. Doi: 10.3109/15513815.2010.547557. Epub 2011 Feb 28. PMID: 21355676.

[35] Wolman I, Gull I, Fait G, Amster R, Kupferminc MJ, Lessing JB, et al. Persistent right umbilical vein: Incidence and significance. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2002;19(6):562-64. Doi: 10.1046/j.1469-0705.2002.00678.x. PMID: 12047534.

[36] Gorincour G, Droullé P, Guibaud L. Prenatal diagnosis of umbilicoportosystemic shunts: report of 11 cases and review of the literature. American Journal of Roentgenology. 2005;184(1):163-68. Doi: 10.2214/ajr.184.1.01840163. PMID: 15615968.

[37] Gillim DL, Hendricks CH. Holoacardius; Review of the literature and case report. Obstet Gynecol. 1953;2(6):647-53. PMID: 13120037.

[38] Levi CS, Lyons EA, Martel MJ. Sonography of multifetal pregnancy. Diagnostic Ultrasound. 2005;2:1207-09.

[39] Hoyme HE, Higginbottom MC, Jones KL. Vascular etiology of disruptive structural defects in monozygotic twins. Pediatrics. 1981;67(2):288-91. PMID: 7243457.

[40] Steffensen TS, Gilbert-Barness E, Spellacy W, Quintero RA. Placental pathology in trap sequence: Clinical and pathogenetic implications. Fetal and Pediatric Pathology. 2008;27(1):13-29. Doi: 10.1080/15513810801893389. PMID: 18568986.

[41] Brouillet S, Dufour A, Prot F, Feige JJ, Equy V, Alfaidy N, et al. Influence of the umbilical cord insertion site on the optimal individual birth weight achievement. BioMed Research International. 2014;2014. https://doi.org/10.1155/2014/341251.

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