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Umbilical Cord Abnormalities in Fetal Autopsies: A Six Year Study

Shailaja Prabhala[1], Padmaja Korti[2], Ramamurti Tanikella[3], Ashok Kumar Deshpande[4]

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Abstract

Introduction: The role of umbilical cord abnormalities has seldom received attention as a cause of intrauterine fetal demise (IUFD). Umbilical cord anomalies are of various types ranging from clinically inconsequential anomalies to those which can result in fetal demise. There can be numerical abnormalities or non-numerical abnormalities or both within the same cord. In this study, we attempted to focus on the abnormalities of the umbilical cord. *Aim of the study:* To study the various types of abnormalities in umbilical cords in fetal autopsy specimens.

Materials and Methods: This was a prospective study done in the department of Pathology at Kamineni Academy of Medical Sciences and Research Centre, Hyderabad, India, over a period of six years. A total of 83 fetal autopsy specimens were received and studied grossly and microscopically. Autopsies were performed as per standard protocol and included complete anthropometry, external examination, gross and microscopic evaluation of different organs and placenta. Both numerical and non-numerical abnormalities were recorded.

Observations and Results: There were total 83 fetal autopsy specimens with umbilical cords. Primigravida accounted for 53% cases. MTP accounted for 45.7% cases and 54.2% cases were intrauterine deaths. Numerical abnormality of umbilical cord vessels was seen in 16.8% cases and all had single or multiple developmental anomalies. There were 20.4% cases of cord having normal or abnormal number of vessels along with additional other abnormalities. There were 18% cases with numerically normal vessels but with other abnormalities. The commonest numerical abnormality was of two vessels; single umbilical artery and single vein. Hypercoiling of cord and stenosis of cord were the common non-numerical abnormalities.

Conclusion: Ultrasound examination is recommended in all antenatal cases and definite guidelines are required for reporting cord abnormalities on ultrasound. In cases of MTP and/or IUD, a complete autopsy study should be done to detect cord anomalies. Irrespective of pregnancy outcome, examination of all umbilical cords from the labour room or operation theater will be helpful in determining whether further evaluation of the neonates is required or not.

Key Words: Cord abnormalities; Cord accidents; Fetal autopsy; Ultrasound of umbilical cords.

Authors Affiliation: [1,3]Professor, [2]Associate Professor, [4]Professor and Head, Department of Pathology, Kamineni Academy of Medical Sciences, Nalgonda Road, Suryodaya Colony, Hyderabad, Telangana 500068, India.

Corresponding Author: Shailaja Prabhala, Professor, Department of Pathology, Kamineni Academy of Medical Sciences, Nalgonda Road, Suryodaya Colony, Hyderabad, Telangana 500068, India.

E-mail: shailajaprabhala@yahoo.co.in

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Introduction

The role of umbilical cord abnormalities has seldom received attention as a cause of intrauterine fetal demise (IUFD). There are many studies on fetal autopsies but literature on cord anomalies is sparse. This may be due to the fact that intact entire cords are rarely received in Pathology for examination. More than 80% of all abortions occur in the first trimester, and 53% of these are attributable to chromosomal

abnormalities.[1] The etiology of fetal loss in 45% of cases is unknown. Similarly, the exact cause of abortions in the early second trimester is often unknown.Umbilical cord anomalies are of various types ranging from clinically inconsequential anomalies to those that can result in fetal demise. Due to advances in prenatal ultrasound, many such anomalies can be detected in utero in present days. However, in low resource settings or in predominantly rural population where specialist services of a sonologist may not be available, or where population in general lacks awareness about antenatal care, such problems may go undetected. Cord anomalies can result in fetal loss and intrauterine deaths (IUD). Many such cases will go unnoticed due to resistance on the part of the couple for fetal autopsy due to various factors. If fetal autopsy is performed in all such cases, more information can be brought to light regarding the association between cord anomalies and fetal demise.

In the present paper we have attempted to study the prevalence of various cord anomalies in fetal autopsies in our local population. All the cord anomalies were noted only during fetal autopsy, and were not reported on antenatal ultrasound scan.

Aim of the Study

To study various types of abnormalities in umbilical cords in fetal autopsy specimens.

Materials and Methods

The present study was a prospective study carried out in the department of Pathology at Kamineni Academy of Medical Sciences and Research Centre, Hyderabad, India, over a period of six years from January 2013 to December 2018. A total of 83 fetal autopsies were done in this period. The clinical details were collected from the request forms which included demographics, obstetrics history, history of consanguinity, gestational age of fetus, nature of fetal death i.e., whether it was a medical termination of pregnancy (MTP), spontaneous abortion, missed abortion, intrauterine death or stillbirth. All the cases had prenatal ultrasound scan reports done at varying stages of gestation and these reports accompanied the pathology requests for fetal autopsy.

After fixation of the fetal specimen in 10% neutral buffered formalin, autopsy was carried out in the following order:

(a) external examination,
(b) anthropometric measurements
(c) presence of effusions
(d) in situ examination of organs
(e) en bloc dissection, and
(f) examination of individual organs.

Whether the location of the organs was normal or abnormal and whether they were of appropriate size for the gestational age was noted. The placenta, membranes and umbilical cord were examined in detail.

On gross examination the following points were looked for in the umbilical cord: the length of the cord, presence of true or false knots, the adequacy of Whartons jelly, presence of any strictures or stenosis, hypercoiling of the cord, evidence of funisitis, and type of insertion of cord into the placenta, number of vessels on cut surface of cord, presence of any cystic areas.

For microscopic examination, all the fetal organs were sampled. The cord was sampled as transverse bits at two different levels in all cases and additional tissue bits were taken from areas suspected of having some abnormality. The tissue bits were submitted for routine histopathological processing. The sections were cut at five micron thickness, stained with hematoxylin and eosin staining, and were examined under light microscope.

Results

In the present study there were 81 women, 83 fetal autopsies and 83 umbilical cords. Of the 81 cases, there were 2 cases of twin pregnancies, both having single placenta. Placenta was received in 58 (71.6%) cases only (58 of 81 pregnancies, as two twin gestation cases had single placenta).

Of the 81 cases, 27 (33.3%) cases were referral cases which came from outside peripheral smaller hospitals and 54 (66.6%) cases from our own hospital. Ours is a tertiary care centre with fully equipped department of Obstetrics and Gynecology and department of Radiodiagnosis. As fetal echocardiography and fetal Doppler studies are available with us, most of the cases detected as abnormal TIFFA scans in smaller hospitals are referred to us for second opinion and if any abnormality is detected the parents are given thorough counselling after which they decide on the option of medical termination of pregnancy (MTP).

Table 1: Parity of patients (n = 81)

Parity	No. of cases	Percentage (%)
Primipara	43	53.0
Gravida 2	25	30.8
Gravida 3	11	13.5
Gravida 4	01	1.2
Gravida 5	01	1.2

Spontaneous IUD versus MTP: Of the total 83 fetal autopsies, 38 (45.7%) were medical termination of pregnancies and 45 (54.2%) were intrauterine deaths, still births, spontaneous abortions or inevitable abortions.

Numerical abnormality of umbilical cord vessels was seen in 16.8% cases. There were 19 cases (20.4%) cases where the cord had normal or abnormal number of vessels and in addition also had some other abnormalities. There were 18% cases with numerically normal vessels but with other abnormalities.

The commonest numerical abnormality in cord vessels was of two vessels ie single umbilical artery and single vein. Hypercoiling of cord and stenosis of cord were the common non-numerical abnormalities.

Spontaneous IUD versus MTP in cases of cord abnormalities: Total cases with abnormal umbilical cords were 29. Some of the cords had more than one abnormality like numerical abnormality of cord vessels, with/without hypercoiling, stenosis or reduced quantity of Wharton's jelly. All the fetuses with cord abnormalities that had MTP had congenital malformations that were detected on ultrasound scan.

Table 2: Features of umbilical cord (n = 83)

Cord features	No. of cases	Percentage (%)
Normal vessels and normal cords	69	83.1
Numerical abnormality of vessels	14	16.8
*Numerically normal vessels but having other cord abnormalities	17	18.0
*Numerically abnormal vessels with other changes	02	2.4

*The above groups are not mutually exclusive

Table 3: Features of umbilical cord abnormalities* (n = 83)

Cord anomaly	No. of cases	Percentage (%)
Two vessels (single artery and single vein)	12	14.4
Two vessels (two arteries, no vein)	01	1.2
Four vessels (three arteries, one vein)	01	1.2
Twisting/Hypercoiling of cord	08	9.6
Stenosis of cord	05	6.0
True knots	01	1.2
False knots	01	1.2
Wharton's jelly cystic changes	01	1.2
Reduced Wharton's jelly	02	2.4
Velamentous insertion of cord	01	1.2

*The above groups are not mutually exclusive

All the 14 cases with vessel abnormalities had single or multiple developmental anomalies that were detected on prenatal ultrasound and were confirmed on autopsy. In all these cases, the vessel abnormalities were picked up on autopsy only and not on ultrasound.

Table 4: Autopsy findings of vessel abnormalities of cord and fetal anomalies (n = 14)

Vessel abnormality in cord	MTP/IUD	Fetal anomaly	No. of cases
One artery, one vein	MTP	Absent skull bones	1
One artery, one vein	IUD	Absent right middle finger	1
One artery, one vein	IUD	Multiple anomalies, Potter's sequence, Bilateral renal agenesis	1
One artery, one vein	MTP	Truncus arteriosus, VSD	1
One artery, one vein	MTP	Bilateral cystic kidneys, imperforate anus	1
One artery, one vein	IUD	Bilateral cystic kidneys, pericardial effusion	1
One artery, one vein	MTP	Fused kidneys, bilateral lower limbs absent, imperforate anus	1
One artery, one vein	MTP	Skull bones absent, defective anterior abdominal wall	1
One artery, one vein	MTP	Hydrops fetalis	1
One artery, one vein	MTP	SGA, Dilated brain ventricles	1
One artery, one vein	MTP	Multicystic kidney right side	1
One artery, one vein	MTP	Defective anterior abdominal wall, amniotic band syndrome	1
Two arteries, no vein	MTP	Atretic intestine, absent pancreas, imperforate anus	1
Three arteries, one vein	MTP	Bilateral polycystic kidneys, Hydrops, absent bladder	1
Total	MTP(11)/IUD(3)	–	14

MTP: medical termination of pregnancy, IUD: intrauterine death, SGA: small for gestational age, VSD: Venticular septal defect

Table 5: Other abnormalities in cord and fetal anomalies (n = 19)

Other cord anomalies	MTP/IUD	Fetal anomaly	No. of cases
True knots	IUD	SGA	1
False knots	IUD	Nil	1
Hypercoiling of cord	IUD	No anomalies	2
		IUGR	2
		Anomalies present	2
Hypercoiling of cord (with fetal anomalies)	MTP	Present	2
Cord stenosis	IUD	SGA	3
Cord stenosis (with fetal anomalies)	MTP	Present	2
Reduced Wharton's jelly	IUD	–	2
Cystic changes in Wharton's jelly	IUD	Absent distal gut and imperforate anus. Omphalomesenteric cyst	1
Velamentous insertion	IUD due to Antepartum hemorrhage	Nil	1
Total	MTP(4) / IUD(15)	–	19

Discussion

Detecting umbilical cord anomalies in first trimester is extremely difficult. However, second trimester scan can assess some of the characteristics of the umbilical cord like measurement of the cord area, number of vessels, placental site where the cord inserts, and coiling pattern.[2] The color Doppler examination can establish the umbilical blood flow patterns.

The length of the human umbilical cord varies from no cord (achordia) to 300 cm, with diameters up to 3 cm. Umbilical cords are helical in nature, with as many as 380 helices. An average umbilical

cord is 55 cm long, with a diameter of 1–2 cm and 11 helices.[3] 5% of cords are shorter than 35 cm, and another 5% are longer than 80 cm.[4]

Causes of differences in cord length are unknown. Shorter cords are more susceptible to abruptio placentae with antepartum hemorrhage, cord rupture and vaginal delivery is usually difficult.[5] On the other hand, extra long cords commonly cause fetal entanglement, true knots and thrombi.[3,6] Despite these associations, assessing cord length prenatally is not possible. Hyper or hypo-coiling of the cord detected on ultrasound is associated with an increased risk for preterm delivery, however the association is not strong enough to be clinically useful.[7, 8] Its important to note the cord length in cases of placental abruption, oligohydramnios, or breech presentation, as abnormal cord length suggests a long-term fetal condition. In our study, the total cord length could not be measured in all cases as in some cases the placenta with attached part of cord was not submitted for examination.

Numerical abnormalities of the cord vessels: In the present study, the prevalence of numerical abnormality of umbilical cord vessels was seen in 14 (16.8%) cases (Table 2).

Single umbilical artery: In our study, the most common abnormality seen was of single umbilical artery with single umbilical vein (14.4% cases).

Vesalius described the single umbilical artery for the first time in 1543.[9] The cord cross section shows only two vessels in such cases. Single umbilical artery syndrome is seen when the other umbilical artery undergoes atresia, aplasia or agenesis.[10] Single umbilical artery (SUA) is the most common abnormality of the umbilical cord. Among pregnancies with single umbilical artery associated with various malformations, twothirds of fetal deaths occur before birth. The remaining one third encounter postnatal death, fetal growth restriction and small sized placentae.[11] In absence of chromosomal or structural abnormalities in such fetuses, a single umbilical artery is defined as an 'isolated SUA (iSUA)'[12] and more than 90% of cases with SUA exhibit an isolated anomaly but without increased risk of chromosomal abnormalities.[13] Regarding adverse pregnancy outcomes and perinatal complications, studies show discordant results. A meta-analysis suggests that there is no significant association between iSUA and pregnancy outcomes.[14] Another study suggests that iSUA is associated with a significant increase in adverse perinatal outcomes.[15]

There are no specific fetal abnormalities associated with the single umbilical artery. However, the most common fetal anomalies associated with SUA are ventricular septal defects, renal anomalies, hydronephrosis, cleft lip, ventral wall defects, esophageal atresia, spina bifida, hydrocephaly, holoprosencephaly, diaphragmatic hernia, cystic hygromas, and polydactyly or syndactyly. Whenever concomitant anomalies are detected on ultrasound, fetal echocardiography and karyotype analysis are recommended. In our study, 5 out of 12 (41.6%) cases of single umbilical artery had renal system abnormalities on autopsy. (Table 4). Single umbilical artery occurs in less than 1% of cords in singletons and 5% of cords in at least one twin. Single umbilical artery also occurs more often in fetal demise than in live births,[16] and there appears to be an association between isolated single umbilical artery and an increased risk for small-for-gestational-age (SGA) infants and pregnancy-induced hypertension.[17] With single umbilical arteries, a 5–20% perinatal mortality rate has been reported,[18] although this includes fetuses with severe congenital anomalies and chromosomal defects. So it cannot be said with certainty how much exactly is the contribution of SUA in fetal deaths.

Not all single umbilical arteries lead to fetal demise and despite the SUA, a pregnancy can progress to full-term and have a healthy neonate with normal size and development. However, a complete detailed physical examination by a paediatrician is required to exclude any hidden anomalies. Ultrasound views of the heart can detect 66% of the heart malformations associated with single umbilical artery. The undiagnosed ones are minor and have a favorable outcome.[19] Hence, examination of the cut section of the umbilical cord should become a routine practice in the labour room itself.

In cases of non-isolated SUA, chromosomal microarray testing is recommended because the risk of syndromes and chromosomal anomalies is increased. Isolated SUA with a normal insertion of the cord does not require special precautions during labor. In these cases, the long-term outcome for children is the same as for children born with three vessels in the umbilical cord.[20] Also, 13% cases of single umbilical artery are associated with velamentous insertion.[16] In our study, we didn't find any velamentous insertion in cases with single umbilical artery.

Four-vessel umbilical cord: Four vesselsare seen in almost 5% of the cords and the extra vessel is usually

a persistent small vitelline artery.[21] Four vessels are frequently associated with major congenital anomalies. In our study also there was one case of four- vessels with three arteries and one vein which also had multiple other anomalies (Table 4).

Non-numerical abnormalities: In our study, there were 19 cases (20.4%) cases where the cord had normal or abnormal number of vessels and in addition also had some other abnormalities. There were 18% cases with numerically normal vessels that had other abnormalities which is quite a high percentage. None of these other abnormalities were reported on the ultrasound and were noted only during the autopsy examination. Hypercoiling of the cord, cord stenosis, reduced Wharton's jelly, cystic changes in Wharton's jelly, etc. (Table 5). Most of them were intrauterine deaths and the others were MTP due to presence of concomitant fetal anomalies.

Cysts are found in 0.4% of pregnancies.[22] Of cord cysts of any type, 20% are associated with structural or chromosomal anomalies. During fetal anatomy scans, the abdominal wall near the cord insertion is the most likely location to detect a cyst. Cysts can be visualized most easily with color Doppler studies during the first trimester, when the umbilical vessels are small.

Most often cysts in the cord are clinically insignificant and are remnants of the allantois or theomphalomesenteric duct. Such finding warrants further detailed sonographic evaluation and karyotype testing when IUGR or other anomalies are also found.[23] Most often first-trimester cysts are transient with normal pregnancy outcome. The prognosis of persistent cysts is similar to that of second-trimester cysts.

Umbilical cord cysts are classified as true cysts or pseudocysts. True cysts have an incidence of 3.4% in first trimester of pregnancy and have no clinical significance.[23] They are derived from the embryological remnants of either the allantois or the omphalomesenteric duct, are located typically toward the fetal insertion of the cord and range from 4 to 60 mm in size.[24] Increased hydrostatic pressure in the umbilical vessels is thought to give rise to such cysts. Morphologic features of cord cyst (single, multiple) correlate with fetal abnormalities of abdominal wall defects and patent urachus.

Pseudocysts are more common than true cysts and can be located anywhere along the cord; they are devoid of epithelial lining and represent localized edema and liquefaction of Wharton's jellyand are known as Wharton jelly cysts. Ultrasound cannot distinguish between true cysts and pseudocysts.[25] Anomalies can be seen in both type of cysts. Pseudocysts are more common than true cysts and they are strongly associated with chromosomal defects and other congenital anomalies, especially omphalocele, hydrops, and trisomy. Usually, ultrasonography monitoring is sufficient, invasive tests not being typically needed. A higher risk of fetal anomalies is associated with the following: detection of cysts in the second or third trimester, persistence after the first trimester, large size, and location near fetal or placental end. Also, trisomy 18, 13, and 21 are known to be associated, in such cases, chromosomal analysis may be warranted.[26] They might be associated with omphalocele, Meckel's diverticulum, patent urachus, and hydronephrosis. False cysts are most commonly found at the fetal end of the cord, do not have an epithelial lining and might be associated with omphalocele, patent urachus, and chromosomal anomalies. Twenty percent of cord cysts are associated with structural or chromosomal anomalies. When the umbilical cyst is detected antenatally, especially in second or third trimesters, it is recommended to have a detailed ultrasonographic examination of the fetus, and to look for any associated defects. In case of any suspicion, karyotyping study should be done.

Velamentous insertion: One percent of singletons have velamentous insertion. However, this condition occurs in almost 15% of monochorionic twins.[27] In our study, we observed one case (1.2%) of velamentous insertion that led to antepartum hemorrhage and IUD.

True and false knots: True knots and false knots can form in the umbilical cord. True knots occur in approximately 1% of pregnancies, with the highest rate occurring in monoamnionic twins. False knots are kinks in the umbilical cord vessels and are more common than true knots and have no known clinical significance. True knots arise from fetal movements and are more likely to develop during early pregnancy, when relatively more amniotic fluid is present and greater fetal movement occurs. True knots are also associated with advanced maternal age, multiparity, and long umbilical cords. In our study, there was one case each (1.2%) of true and false knots. True knots have been reported to lead to a 4-fold increase in fetal loss, presumably because of compression of the cord vessels when the knot tightens. Weiner et al.[5] noted that umbilical cord entanglements, true knots, and short cords were more common in emergent cesarean deliveries (ECDs) than in vaginal deliveries.

Cord Coiling: In our study, there were 8/83 (9.6%) cases of hypercoiling of cord. The normal cord shows 1 coil per 5 cm, and the coiling is established as early as 9 weeks of gestation. The generally accepted method of assessing the degree of the umbilical cord coiling is by calculation of the umbilical coiling index (UCI), defined as the number of complete coils per centimeter length of cord. The normal UCI is around 0.2 in the postpartum setting based on examination of the delivered placenta and umbilical cord (pUCI) and it is 0.4 on antenatal sonographic examination (aUCI). Hypercoiling may be associated with constriction and long cords. Frequently the hypercoiled cord becomes thin and whip-like, or sometimes the torsion is focal. Many studies have shown that hypercoiling can lead to adverse pregnancy outcome and/or fetal death.[28] Achirality is absence of the coiling of cord.

Cord stricture: Cord stricture is constriction or occlusion of the cord. This condition is found in 19% of fetal demises. Familial recurrence of umbilical cord strictures has been described.[29] Umbilical cord stricture is a recognized cause of fetal demise, but the exact etiology remains unknown. The risk of recurrence has generally been thought to be low. French et al[29] described demise of three of 4 fetuses of a single patient between 28 and 30 weeks of gestation. They recommended that patients with fetal demise attributed to umbilical cord stricture should be counseled and that the risk of recurrent cord stricture is undetermined. The etiology of umbilical cord stricture is unknown. There is a deficiency in Wharton jelly in the umbilical cord in the area of stricture, however this could be a postmorbid change.

This condition cannot be diagnosed prenatally. Most infants with cord stricture are stillborn.

Malformations among fetuses with single umbilical artery have been reported to be as high as 46%.[30] In a meta-analysis of 37 studies related to single umbilical artery, the mean association with structural anomalies was 27% in live-born, while in specimens obtained from early abortions, fetal deaths and autopsies it raised up to 66,3%.[16] The mechanism of death is postulated to be chronic ischemia superimposed by a catastrophic acute vascular event.[1]

Cord varix: Cord varix is a cystic dilatation that can occur in any portion of the umbilical vein. It is a rare entity and is of unknown etiology. Reports have documented poor fetal outcomes in the presence of varices and an association with fetal anomalies. Cord ulceration, cord hematoma, cord hemangioma, cord teratoma are other conditions. In our study, we did not observe any cord varix, cord ulceration or cord hematoma.

Usually there is a good correlation between prenatal ultrasound scanning and autopsy findings for congenital anomalies.[31] But same is not true for umbilical cord anomalies. In our study, none of the cysts or other cord abnormalities were reported antenatally. This could be due to difficulties encountered by the radiologist. Also, as antenatal cases have ultrasound examination carried out in different places with radiologists having variable degree of expertise, who may not be well-versed in reporting cord abnormalities. Especially where resources are low, antenatal ultrasound may not be done in the recommended period or it may not be done at all due to lack of access to health care.

Conclusion

Ultrasound examination is recommended in all antenatal cases, with definite guide lines for reporting cord abnormalities. Fetal autopsy and evaluation of placenta, membranes and cord are mandatory, and must be accompanied by cytogenetic studies, if required. Also, when documented on large scale, a database for cord abnormalities and associated fetal anomalies can be created for further scientific studies and research.

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