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DISSERTATION

Furcate cord insertion of the umbilical cord: Pathological and clinical
characteristics in 132 cases and a review of the literature

zur Erlangung des akademischen Grades
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1. Abstract

1.1. Abstract in english

Introduction

The furcate cord insertion with a prevalence of 0.1% is extremely rare and has only been reported in the literature in 18 cases. It is defined by a separation of the umbilical vessels prior to inserting at the placenta centrally, eccentrically or marginally. In the literature, an association with stillbirth, fetal hemorrhage, intrauterine growth restriction and varices and thrombosis of fetal vessels is described (1). The aim of this thesis is to evaluate the clinical and pathological characteristics of the furcate cord insertion of the umbilical cord in 132 cases and a review of the literature.

Methods

A retrospective study of the cases with a furcate cord insertion of the umbilical cord found in the pathological database of the Charité between 1993 and 2016 was performed and 132 cases were identified. A statistical analysis with SPSS of the pathological features and the perinatal outcome was done after the extraction of the data from the pathological database and the electronic medical records. A review of the literature and a comparison to our patient collective was done.

Results

The prevalence for the furcate cord insertion in our patient collective lies at 0.17% with a risk for intrauterine fetal death of 1.0% within the Charité. In seven cases in our analysis, intrauterine fetal death was observed. Three of those cases can be linked to the furcate cord insertion. In two out of these three cases, a rupture of the umbilical vessels was identified as the cause of death. The furcate cord insertion is not associated with an intrauterine growth restriction but with a higher rate of HELLP syndrome, retention of placenta and lower five-minute APGAR scores. Risk factors for an adverse outcome after analyzing our data are an above average long furcate cord insertion and additional abnormal findings of the umbilical cord such as thrombosis or ectasia of the umbilical vessels.

Conclusion

The furcate cord insertion is a very rare anomaly of the umbilical cord occurring in approximately 0.17% of all pregnancies. In most cases, the outcome is good but in around 1% of the cases intrauterine fetal death is observed. In case of identifying a furcate cord insertion prenatally, delivery should be planned after completed 37 weeks of gestation to avoid prematurity but also to reduce the risk for sudden intrauterine fetal death. In cases of additional abnormalities of the umbilical cord, the patient should be counseled on delivery before 37 weeks of gestation.

1.2. Abstract in german

Einleitung

Bei der sehr seltenen Insertio furcata funiculi umbilicalis teilen sich die Nabelschnurgefäße wenige Zentimeter vor der Plazenta auf, verlieren ihr Whartonsche Sulze und inserieren zentral, exzentrisch oder marginal an der Plazenta. Die Autoren der 18 in der Literatur beschriebene Fälle beschreiben einen Zusammenhang der Insertio furcata funiculi umbilicalis mit fetaler Wachstumsretardierung, intrauterinem Fruchttod sowie der Ruptur, Thrombose und Varizen von Nabelschnurgefäßen (1). In dieser retrospektiven Studie wurden 132 Fälle dieser Insertionsanomalie aus der pathologischen Datenbank der Charité erhoben, um anschließend sowohl die pathologischen Charakteristika als auch den perinatalen Ausgang zu untersuchen. Zudem wurde eine Literaturrecherche durchgeführt.

Methodik

Eine Datenerhebung aus der Datenbank der Pathologie, gefolgt von einer Auswertung der perinatalen Daten mittels der Viewpoint und KIM Datenbank wurden durchgeführt. Nach Übertragung der Daten in das SPSS wurde die deskriptive Statistik erstellt. Es erfolgte eine Literaturrecherche gefolgt von einem Vergleich mit dem Patientenkollektiv dieser Arbeit.

Ergebnisse

Die Prävalenz der Insertio furcata funiculi umbilicalis liegt in unserem Kollektiv bei 0.17% mit einem Risiko für einen intrauterinen Fruchttod von 1.0% innerhalb der Charité. Von den 132 Fällen gab es sieben intrauterine Fruchttode bei denen in drei Fällen die Insertio furcata funiculi umbilicalis eine wesentliche Rolle spielte. In zwei von diesen drei Fällen wurde als Ursache des intrauterinen Fruchttodes die Ruptur der Nabelschnurgefäße festgestellt. Die Insertio furcata funiculi umbilicalis korreliert nicht wie in der Literatur angenommen mit einer fetalen Wachstumsrestriktion ist aber mit einer höheren Rate an HELLP Syndrom, Plazentaretention und niedrigeren APGAR Werten nach fünf Minuten assoziiert. Risikofaktoren für einen schlechten Ausgang der Schwangerschaft im Sinne eines intrauterinen Fruchttodes sind eine überdurchschnittlich lange Insertio furcata funiculi umbilicalis und zusätzliche Auffälligkeiten im Bereich der Nabelschnur wie zum Beispiel eine Ektasie oder Thrombose der Nabelschnurgefäße.

Schlussfolgerung

Die Insertio furcata funiculi umbilicalis ist mit einer Prävalenz von 0.17% eine sehr seltene Insertionsanomalie der Nabelschnur, die mit einem erhöhten Risiko für einen IUFT assoziiert ist. In den meisten Fällen ist der perinatale Ausgang sehr gut, aber in zirka 1% der Fälle wird ein intrauteriner Fruchttod beobachtet. Im Falle einer pränatalen Diagnose einer möglichen Insertio furcata funiculi umbilicalis mittels Ultraschall und Doppler Sonographie, sollte nach Auswertung unserer Daten eine Geburt nach abgeschlossenen 37 Schwangerschaftswochen erfolgen. Im Falle zusätzlicher Auffälligkeiten im Bereich der Nabelschnur, wie bereits weiter oben beschrieben, muss auch eine Entbindung zu einem früheren Zeitpunkt mit der Patientin diskutiert werden.

2. Introduction

A **Furcate cord insertion** is a rare abnormality affecting around 0.1% of all pregnancies. The umbilical vessels separate before reaching the placenta, inserting centrally, eccentrically or marginally. They lose their Wharton's jelly which provides a great level of protection to the umbilical vessels and thus are more vulnerable to be affected by aneurysm, thrombosis or injury. All these findings can consequently lead to a rupture of the umbilical vessels and intrauterine fetal death. In the literature, adverse outcomes like stillbirth, fetal hemorrhage, varices, thrombosis of fetal vessels, and intrauterine growth restriction are associated with furcate cord insertion (1).

2.1. Development of the umbilical cord

Between the fourth and eight weeks of gestation, the amnion spreads and covers the ductus omphalo-entericus and the umbilical coelom. The movements of the embryo cause the amnion to spread over the ductus omphalo-entericus, the body stalk and the umbilical vessels describing the parts of the umbilical cord. The membranes of the chorionic cavity and the amniotic cavity meet and the extra-embryogenic mesoderm layers fuse (2).

Around eight weeks of gestation, the umbilical cord is comparatively short and thick containing the **ductus omphalo-entericus** that attaches the primitive intestines with the umbilical vesicle and the two vitelline vessels. Another part of the umbilical cord is the **body stalk** with the **allantois** and the **umbilical vessels** that move ventrally during the development to finally connect with the umbilical vesicle. The **umbilical coelom** connects the intra-embryonic coelom with the extra-embryonic coelom (2).

Fig. 51 - Umbilical vesicle in the chorionic cavity
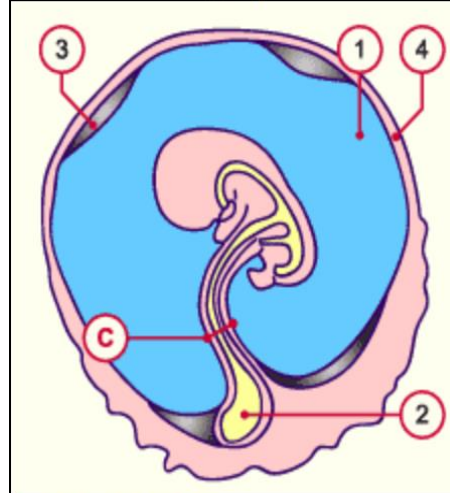
1　Amniotic cavity
2　Umbilical vesicle
3　Chorionic cavity
4　Chorion laeve

Fig. 2.1. Umbilical vesicle in the chorionic cavity in the eight week of gestation (2)

Fig. 52a - Development

1　Ductus omphalo-entericus
3　Allantois
4　Umbilical vein
5　Umbilical arteries
6　Amnion

Fig. 2.2. Development of the umbilical cord in the eighth week of gestation (2)

Fig. 52b - Development
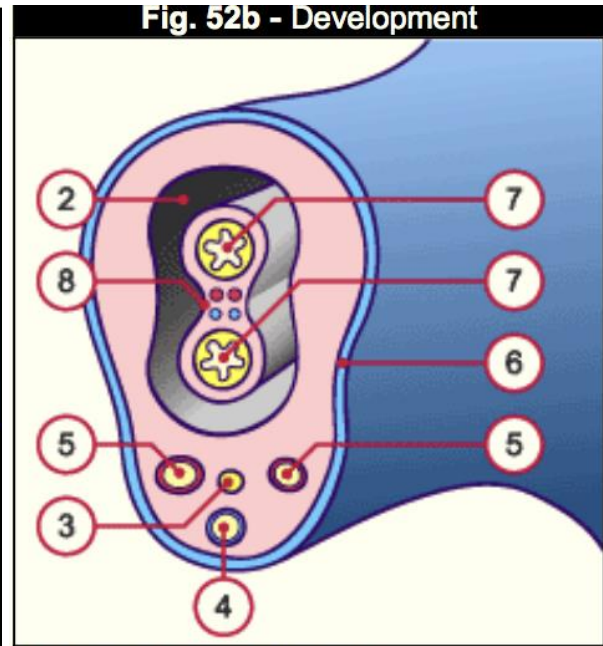
2　Extra-embryonic coelom (umbilcal coelom)
7　Intestinal tube (physiologic umbilical hernia)
8　Vasa omphalomesenterica

Fig. 2.3. Development of the umbilical cord in the third month of gestation (2)

The next steps include **lengthening** and **reduction** of some of the structures: The covering around the ductus omphalo-entericus and the body stalk that is formed by the amniotic cavity, elongates. This process makes fetal movements and coils in the amniotic cavity possible (2). The omphalo-enteric duct (it might continue existing in the form of a Meckel's diverticulum), the umbilical vesicle of the allantois, the vitelline circulation system in the extra-embryonic region and the umbilical coelom degrade in the third month of gestation.

In the end, the body stalk endures along with its umbilical vessels (two arteries, one vein), which are covered by an amniotic epithelial layer. The so-called Wharton's jelly, the connective tissue of the umbilical cord that protects the umbilical vessels, consists of the connective tissue from the body stalk and the amnion (2).

2.2. Anatomy of the umbilical cord and its insertion

2.2.1. Amnionic epithelium

Amnionic epithelium covers the umbilical cord. The area of the umbilical cord close to the abdominal wall consists of mostly unkeratinized stratified squamous epithelium. The further away from the umbilicus, the more the epithelium changes from a stratified columnar epithelium with two to eight layers into a simple columnar epithelium. The amnion of the cord is structurally much the same as one seen in membranes. In comparison to the amnion of the chorionic surface of the placenta, where it can be easily detached, the amnion of the cord grows deeply into the central connective tissue (1).

2.2.2. Wharton's jelly

The connective tissue of the cord, also called the Wharton's jelly is derived from the extraembryonic mesoblast. This mesenchymal part of the umbilical cord makes it a quite solid structure, changing its form depending on the contraction of the vasculature. It consists of open-chain polysaccharides and if an immunohistochemistry is performed, collagens types I, III, IV and VI are found, as well as laminin and heparan sulfate. In addition, spindle-shaped fibroblasts and mast cells are seen. With growing distance from the amnionic surface, stromal cells acquire cytoskeletal features of contractile cells consisting of desmin. In proximity to the umbilical vessels, myofibroblasts that additionally express the smooth muscle protein myosin are present (1).

Among the open-chain polysaccharides, hyaluronic acid is the most represented in the Wharton's jelly. The amount is one the highest in the human body and plays an important role in protecting the umbilical vessels from compression and bending. It decreases with gestational age and the content and composition of the hyaluronic acid can vary, like observed in fetusus with Down Syndrom (3).

A normogram of the Wharton's jelly for gestational weeks 15 to 41 was published. The amount of Wharton's jelly increases throughout pregnancy and correlates with fetal biometric parameters until 32 weeks of gestation, representing the largest part of the umbilical cord in the second and third trimester of pregnancy. From this point on, the amount slightly decreases until the end of pregnancy (4). In regard to the tensile properties of the umbilical cord, no significant differences in the parameters with reference to the sex of the fetus are found. A significant positive correlation is observed though between the breaking load and the birth weight of the newborn, being 2.49 times the newborn's birth weight (1).

In pregnancies complicated by diabetes a larger umbilical cord is observed. The diameter of the vein and the artery is the same as in pregnant patients without diabetes, but the amount of Wharton's jelly is significantly increased. This is also observed in patients who give birth to normosom newborns and have controlled diabetes during pregnancy (5, 6). It therefore has been postulated, that other factors such as microscopic alterations to the Wharton's jelly and the umbilical vessels, that are also observed in well controlled gestational diabetes, play an important role (7).

In intrauterine growth restricted fetusus the size of all parts of the umbilical cord, including the one of the Wharton's jelly are significantly smaller than in normosom fetusus (8).

Also in patients with early-onset of preeclampsia a significant reduced amount of Wharton's jelly is observed, possibly as a result of reduced hydration (9).

2.2.3. Structure of the umbilical vessels

Usually, there are two arteries and one vein found in the umbilical cord which size increase with gestational age and plateau at around 30 weeks of gestation (10). In approximately 1% of the pregnancies, a single umbilical artery is observed which correlates with a higher risk of different fetal malformations. The diameter of the arteries increases until 30 weeks of gestation and then plateaus at around 3mm. The one of the veins follows the same growth pattern but at around twice the size (11). There is a general understanding that there are no nerves along the umbilical cord.

An important part of the umbilical cord arteries is an anastomosis between the two arteries close to the placental surface, called the Hyrtl's anastomosis. It exists in around 90% of pregnancies, whereas in some cases, a fusion of the arteries, an absence or a single umbilical artery is observed (1). The blood flow in the anastomosis can be visualized by color Doppler and its median diameter was measured at 2.3mm. It is located around three centimeters from the placental insertion. In a series of 41 pregnancies a fusion of the umbilical arteries was observed in five cases and in three of those a marginal or velamentous cord insertion was detected. The Hyrtl's anastomosis is thought to balance the pressure between the two umbilical arteries that may supply different sized areas of the placenta (12).

2.2.4. Contractility of the umbilical vessels

The umbilical vessels are very susceptible to endocrine mediators such as serotonin, angiotensin and oxytocin (1). The activity of the smooth muscle cells is regulated by substances in paracrine loops seen in the neighborhood of endothelial cells. Important mediators in this respect are the prostaglandines that are produced more in the venous endothelium than in the arterial endothelium. In smoking or diabetic mothers, there is a reduced synthesis of prostaglandins (PGI_2/PGE_2) that play an important role as vasodilators and platelet aggregation inhibitors. This might explain the flawed placental perfusion in these pregnancies. Other important vasodilators are nitric oxide and atrial natriuretic peptide (ANP) (1).

In addition, vasoconstrictor substances are found in the endothelium consisting of angiotensin II, 5-hydroxytryptamine (5-HT), thromboxane, neuropeptide Y (NPY) and endothelin-1 (1).

Together with the vasodilators, a not yet fully understood autoregulation of the circulation of the umbilical cord is in place (1).

2.2.5. Spiral turns of the cord

The spiraling of the umbilical cord is physiological and in some cases can been seen in an ultrasound examination as early as in the first trimester. It usually is a left spiral (counterclockwise) with a ratio of 7:1 (1).

Strong et al. found that in 4.3% of the newborns, no spiraling exists which represents a higher risk for perinatal mortality.

In addition they could show that a low coiling index (number of coils divided by length of the cord; average 0.21/cm) below the 10th percentile is more often found in newborns with chromosomal aberrations, central nervous system disturbances, fetal distress and meconium staining and therefore goes hand in hand with a possible poor outcome (13, 14).

On the other hand Rana et al. could demonstrate that an excessive coiling is associated with cocaine substance abuse and correlates with premature labor (15). Also, umbilical cords of black fetuses have significantly less coiling than umbilical cords of white fetuses (16).

Cromi et al. investigated the coiling of 758 pregnancies and found atypical coiling (supercoiling and aperiodic coiling) in three percent of the cases. This correlated with intrauterine growth restriction and preterm delivery. Intrauterine fetal death occurred in three cases (17).

If the fetus is fixed to the surface of the placenta, a short umbilical cord with only a few or no coiling is seen. This postulates that the moving of the fetus might play an important role in this regard (18).

2.2.6. Length of the umbilical cord, cord entanglement

There have been numerous studies investigating the cord length showing that very short umbilical cords as well as very long ones correlate with a poor fetal outcome (1).

Also the amount of fetal movement in early pregnancy seems to play a role in regulating the length of the umbilical cord, as short cords are seen more frequently in fetuses that cannot move for example due to amnionic adhesions (1).

Naeya et al. show with the data from the Collaborative Perinatal Study published in 1972 that the umbilical cord in pregnancy grows steadily from around 32cm in the 20th week of gestation to around 60cm at term (19).

Regarding the lenght of the umbilical cord, one author investigating 8000 pregnancies found that the average lenght lies at 59.44cm whereas another author investigating 12000 pregnancies stated that the average lenght lies at 66.54cm (1). If the cord is circled around the neck of the newborn once the average lenght increases to 76,5cm and if circled twice it was 93,5cm long (1).

A short umbilical cord correlates with a lower intelligence quotient. Some conditions that also describe a short umbilical cord are the fetal alcohol syndrome, trisomy 21 and lethal bony malformations (1). Very long cords go hand in hand with excessive spiraling, true knots, thrombosis in fetal vessels and meconium staining (1).

Nuchal cords or looping of the umbilical cord around extremities occurs in around 23% of cases and correlates with excessively long cords (20).

The occurence of nuchal cords is significantly more likely after 38 weeks of gestation, possibly due to less amniotic fluid or more fetal activity (21). With the data from the Collaborative Perinatal Study in 1966, Spellacy et al. showed that a compromised cord perfusion might lead to a depressed one-minute Apgar score, though not affecting the longtern outcome. True knots and nuchal cords together represent ten percent of fetal deaths in fetuses weighing over 2500g (22).

2.2.7. Sonographic assessment of the umbilical cord

Usually, the umbilical cord in prenatal ultrasound scan is not described in a very detailed way. The focus lies on the number of umbilical vessels and the insertion of the umbilical cord.

Vasa praevia, if not diagnosed prenatally, increases the risk for fetal death due to a rupture of the umbilical vessels. A retrospective study investigating 14 cases of prenatally diagnosed vasa praevia showed that with an adapted clinical management, outcome is very good and fetal death can be avoided (23).

Recently, studies have been evaluating the diameter of the umbilical cord, the amount of the Wharton`s jelly and the umbilical vein flow. With this data, the size of the umbilical cord area and the diameter of its vessels for each gestational week were calculated. It was shown that the diameter of the umbilical vein and artery increase until around 32 weeks of gestation and that this size then does not change until the end of the pregnancy (24).

According to these results, reduced amounts of Wharton`s jelly, a reduced diameter of the umbilical cord or a reduced flow in the umbilical vein are associated with adverse perinatal outcomes such as hypertensive disease (9) , intrauterine growth restriction (25), lower fetal birth weight (26) and fetal distress during labor (27).

An increased diameter of the umbilical cord with an increased amount of Wharton`s jelly is observed in pregnancies with gestational diabetes and fetal macrosomia (5).

2.3. Pathology of the umbilical cord

Lethal complications involving the umbilical cord are found in 7.7–11.4% of stillbirths and 0.06% of all pregnancies (28-30). The most important pathologies of the umbilical cord are mentioned and briefly described below.

2.3.1. Cysts and edema of the umbilical cord

It is possible to differentiate between a true cyst of the umbilical cord which has an epithel and derives from embryological remanants and pseudocysts that have their origin in degenerative processes of the Wharton's jelly. Pseudocysts are more common than true cyst and both tend to be located close to the insertion of the umbilical cord. To prenatally diagnose which subtype is present is not possible and histological confirmation is only available in a few cases. This makes it difficult to determine the clinical significance of these two subtypes (31).

The incidence of umbilical cysts found between 7 and 14 weeks of gestation lies at 2.1% in a series of 1159 screened patients. In 18 cases a single cyst was observed and in six cases multiple cysts were seen. In newborns with a single umbilical cyst observed in the first trimester, perinatal outcome was good and no malformations or chromosomal aberrations were observed. Multiple umbilical cysts were associated with misscarriage, fetal malformation and aneuploidy. It is speculated that single umbilical cysts can occur physiologically in the course of the mechanical development of the umbilical cord, whereas multiple cysts might be a sign of an alteration in the composition of the Wharton's jelly (32).

In a different case series published by L. Ruiz Campo et al. 27 cases of umbilical cysts regardless of gestational age were analyzed. A single umbilical cyst diagnosed between twelve and 35 weeks of gestation was associated with a good perinatal outcome. In six cases multiple cysts were diagnosed between 12 and 29 weeks of gestation and this was associated with fetal malformations and aneuploidy (31).

Sepulveda et al. published 13 cases of umbilical pseudocysts (one double cyst, eight single cysts, and four cases with small cystic masses) diagnosed in the second and third trimester with a median of 27 weeks of gestation and found an association with chromosomal aberrations and/or malformations of the fetus in 11 cases (33).

Zangen et al. published ten cases of umbilical cysts diagnosed in the second and third trimester.

In eight cases no other fetal abnormalities were found in the anomaly scan and healthy neonates were born. One case was associated with intrauterine growth restriction and polyhydramnion but outcome was good. Umbilical cysts in the second and third trimester are associated with fetal anomalies but the prevalence in this publication is lower and outcome usually is good. A possible explanation for the difference in fetal outcome could be the tendency to report abnormal cases. Another reason might be that in fetusus with structural defects a very detailed scan is performed, whereas in fetusus without pathological findings, these cysts might be overlooked. In case of fetal anomalies karyotyping is recommended (34).

10% of newborns according to Coulter et al. have edema of the umbilical cord, being more common in prematurely born infants and caused by reduced oncotic pressure (35). Other authors like Rolschau et al., on the contrary, postulate no influence of umbilical cord edema on fetal outcome. It probably occurs without any correlation to gestational week or other factors (36).

2.3.2. Single umbilical artery

A single umbilical artery (SUA) is the most common congenital anomaly occurring in around 1% of the pregnancies. A large prospective trial investigating the single umbilical artery found an associated rate of anomalies in 30% of the cases and a correlation with an intrauterine growth restriction in 8% of the cases (37). It is now known that no specific malformation is associated with a SUA and that in the absence of other sonographic malformations, the outcome is not negatively influenced. In isolated SUA, there is no need to change routine obstetrical management (38). If a single umbilical artery is diagnosed, in the majority of the cases, the left artery is absent. Aneuploidy and structural abnormalities were associated with the missing of the left umbilical artery (39). In a series of 159 cases of a single umbilical artery an association with other placental anomalies such as velamentous cord insertion (four cases), placenta praevia (three cases) and a circumvallate placenta (two cases) was observed. In total in 16.4% of the cases another placental abnormality was seen (37) . An association with the velamentous cord insertion was also described by Suzuki et al (40).

2.3.3. Rupture of the umbilical cord

A rupture of the umbilical cord may occur in shorter umbilical cords during spontaneous or instrument assisted birth.

A rupture can be complete or partial, leading to bleeding or hematoma (1). Following these reports the breaking weight of umbilical cords was investigated and showed the average breaking point to be at 5.4kg with a range from 1.8kg to 10.9kg.

No correlation with other pathological parameters could be found (41). There are also case reports describing a bleeding of the umbilical cord after amniocentesis (42) and a cord hematoma after a fetal blood transfusion (43). The most common site of rupture is at the placental attachment (22.5%). In most of the cases, only a partial rupture occurs, leading to local hematomas (44).

In three cases in the literature, a rupture of the umbilical vessels is described as a complication of the furcate cord insertion (45-47) .

2.3.4. Varices and aneurysms of the umbilical cord

Aneurysms of the umbilical cord are the least common anomaly of the umbilical cord. They are associated with an increased risk for aneuploidy, IUGR and fetal death. The vein is more affected than the artery (1). In 75% of the cases, they are located close to the placenta where sometimes the vessels lack Wharton's jelly. This anomaly is more often seen in fetuses with trisomy 18, probably due to the abnormal placental vasculature in this aneuploidy (1). In an umbilical cord aneurysm with normal karyotype and no other malformations, close fetal surveillance and the earliest possible delivery is recommended. It is not clear at what time in pregnancy the risk for rupture or thrombosis of the aneurysmatic umbilical cord is the highest (1). The rate of fetal demise can be explained by the formation of a thrombus, compression of the dilated artery or the umbilical vein, rupture of the aneurysm or due to an additionally diagnosed fetal syndrome like trisomy 18 (1). The most detailed study of placental aneurysms based on the examination of 1000 consecutive placentas was reported by Lemtis in 1968, whose article was accompanied by exemplary photographs. Lemtis found these lesions in 24 cases and classified the anomalies into several types. The aneurysms were usually associated with an atypical insertion of the cord, SUA, fetal growth restriction or other placental anomalies (48).

2.3.5. Thrombosis of the umbilical cord

Thrombosis of the umbilical cord is frequently seen and mostly located in the surface veins. Thrombosis may occur in the first trimenon, leading to a single umbilical artery but is more often observed near term. It is associated with a velamentous cord insertion.

Due to the absence of Wharton's jelly, trauma to the umbilical cord is more likely to cause tears in the umbilical vessels leading to thrombosis. Thrombosis of cord vessels might also be seen in varices of the umbilical cord and can occur in looped and knotted cords as well.

It is also associated with the entangling of the umbilical cords in monoamnionic twins and with vascular obstruction for mechanical reasons such as amnionic bands. Part of the thrombus can break off and can lead to myocardial infarction or amputations. They can cause disseminated intravascular coagulation (DIC) or consumption coagulopathy followed by bleeding. The factor V Leiden mutation found in a dying neonate with aortic thrombosis also played a role in the forming of thrombi (1).

Thromboses of the placenta vascular tree are seen in placentas of trisomy 18 and are associated with cytomegalovirus infection, excessively long cords, knotting, velamentous cord insertion, severe chorioamnionitis, neonatal purpura, generalized fetal thrombosis and many other conditions. If the major ramifications of villous vessels are affected, an association with intrauterine fetal growth restriction and intrauterine fetal death is observed (1).

Due to the vulnerability of the umbilical vessels in furcate cord insertion, recurrent smaller injuries can lead to formation of multiple thrombi (46).

2.4. Insertion of the umbilical cord and outcome

The umbilical cord can insert at the placenta in different ways:

central, eccentric, marginal, velamentous, interpositional or with a furcate cord insertion (1). Central and eccentric insertions are not associated with adverse outcomes and are considered physiological. They are not discussed further.
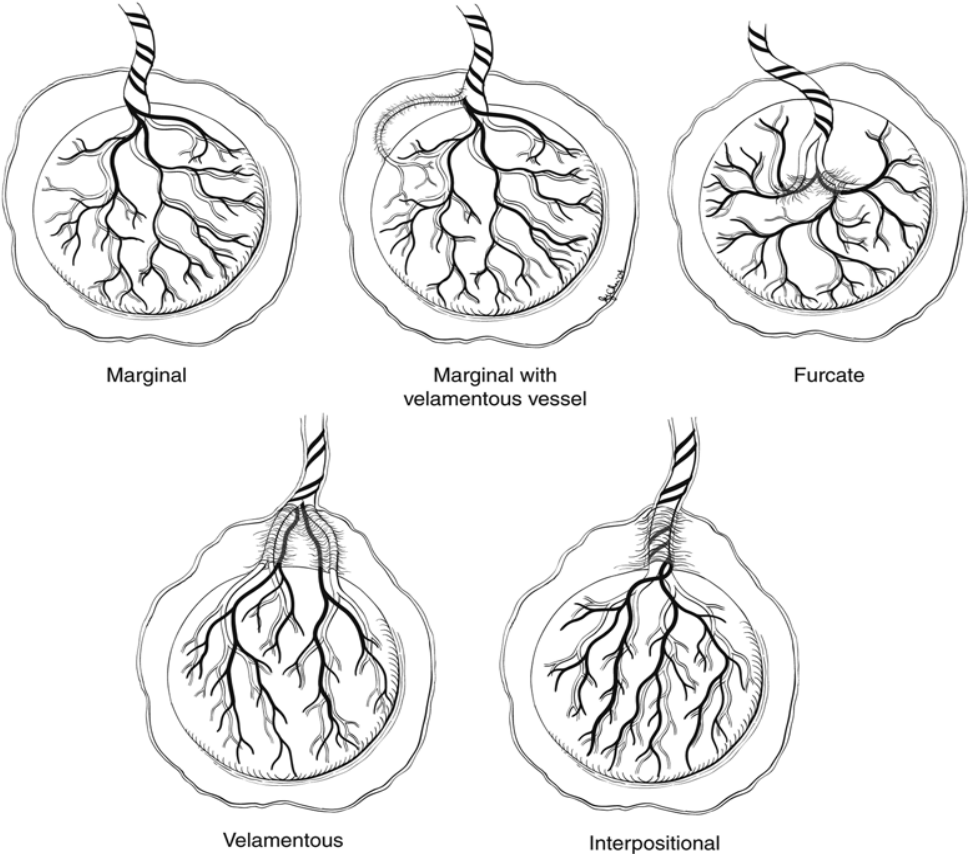

Fig. 2.4. Drawing of umbilical cord insertion patterns (49)

2.4.1. Velamentous and marginal cord insertion

In a **velamentous insertion of the umbilical cord,** the umbilical vessels separate and end up on the placental surface only covered with amnion and without the protection of the Wharton's jelly. It is found in 1% of singleton pregnancies (50) but is seen in up to 15 percent of monochorionic twin pregnancies. It is also described to be more frequently present in placenta praevia than in normally located placentas (51-53). Because the vessels are covered by the amnion, rupture of the membranes during birth may also rupture the vessels, which can rapidly result in fetal hemorrhage. This typically takes place when the membranous vessels are close to or cover the cervix. Rarely have membranous vessels ruptured without the rupture of membranes (54). The length of the normal cord and the membranous part varies. These vessels can also originate as aberrant vessels from a marginal cord insertion or can connect a bilobed or succenturiate placenta.

In the bilobed placenta the two lobes of the placenta are approximately the same size and the insertion of the umbilical cord is located in between the two lobes (55). This type of velamentous cord insertion has an incidence of 4,2% in a series of 8505 placentas (56). In the succenturiate placenta the accessory lobe is significantly smaller than the main part of the placenta. These two parts are connected with umbilical vessels and the insertion of the umbilical cord is found on the main part of the placenta in most of the cases (55).

The **marginal insertion of the umbilical cord** is described when the umbilical cord inserts at the edge of the placenta, lying within 2cm of the placental edge. It is found in around 7% of pregnancies. Ebbing et al. investigated in two separated population-based studies the risk factors for velamentous and marginal cord insertion at the placenta, reporting that both types of insertions share similar risks. Although the odds ratios for the different perinatal outcomes favor the marginal cord insertion, they are both associated with an increased risk for hemorrhage during the third stage of labor, consisting of manual removal of the placenta in 2.4% of the cases with a marginal cord insertion and 5.5% of the cases with a velamentous cord insertion. Curettage in marginal cord insertion was performed in 0,8% and in velamentous cord insertion in 2.2% of the cases (57, 58). It is also known that the velamentous cord insertion and to a lesser extent the marginal cord insertion are associated with a higher risk for prelabor ruptures of membranes and spontaneous preterm birth (59).

The pathogenesis of these umbilical cord insertions is not clear.

One hypothesis suggests that the cord in the beginning of the pregnancy inserts centrally, but its location continuously becomes peripheral as one half of the placenta actively grows towards the fundus of the uterus (trophotropism) while the other part involutes; the umbilical cord cannot follow this migration (60). The theory of trophotropism was first described by Strassmann (1902) in his large series of placenta praevia (1). In 1098 patients Rizos et al. observed placenta praevia in 5.3% of the cases at 16 to 18 weeks of gestation. At delivery the incidence dropped to 0.58% proving that the placenta can migrate during pregnancy, also called dynamic placentation. Unfortunately, neither the prenatal nor the postnatal location of the umbilical cord insertion in these cases is mentioned (61, 62). This process can be visualized by ultrasound and is explained by atrophy on one side of the placenta and growth on the other side, combined with the thinning of the lower uterine segment in the course of pregnancy (1). An important factor in the pathogenesis of the above-mentioned processes, is an unbalanced trophoblast expansion in early pregnancy. A hypothesis by Vogel M. states that this is caused by a suboptimal supply of the blastocyst with nutrients, which then leads to different types of umbilical cord insertions ranging from eccentric to velamentous (63).

2.4.2. Interpositional Cord insertion

Interpositional cord insertion is a type of membrane insertion. The vessels of the umbilical cord are covered by Wharton's jelly but also insert in the membranes like in the velamentous cord insertion. It therefore does not carry the risks associated with a velamentous insertion (1).

2.4.3. Vasa praevia

A further clinically relevant insertion anomaly is the vasa praevia. In this condition, blood vessels of the fetus cross the internal cervical os. In type 1 vasa praevia the velamentous placenta has one lobe, with the umbilical vessels crossing the cervix. In type 2 a bilobed or succenturiate placenta is observed with the fetal blood vessels connecting these two lobes and crossing the internal cervical os (64). The prevalence of vasa praevia is approximately 1 in 2500 deliveries (65), but in pregnancies conceived after the use of assisted reproductive technologies, the prevalence is higher (1 in 202) (66). Pathogenesis is unknown, but is probably similar to that of the velamentous cord insertion.

A higher risk for vasa praevia is seen in velamentous cord insertion, in umbilical cord insertion in the lower part of the uterus at first-trimester ultrasound, in placenta praevia or low-lying placenta at the second-trimester ultrasound scan, in a succenturiate placental lobe or bilobed placenta, after in vitro fertilization and in multiple gestation (67, 68).

A systematic review of predictive indicators of vasa praevia showed that around 83 percent of cases had risk factors, mostly placenta praevia followed by assisted conception, velamentous cord insertion and bilobed placenta (69).

Golic et al. evaluated 18 cases of vasa praevia and its clinical management. As early as 23 weeks of gestation, the patient should be seen regularly once a week to determine the cervical length and to assess the risk for preterm labor. Without a history of vaginal bleeding, preterm birth, shortening of the cervical length or contractions, the patient should be admitted to the prenatal ward between 32 and 34 weeks of gestation until the planned cesarean section between 35 and 37 weeks of gestation. In these cases, antenatal corticosteroids should be avoided. With this adapted management, no fetal deaths occurred. This is a deviation from the conventional management recommended by the International Vasa Praevia Foundation that suggests the administration of antenatal corticosteroids and elective cesarean section at 35 weeks of gestation in all cases. This increases the risks for complications associated with preterm birth and exposes the fetus to corticosteroids whose long-term side effects have not been investigated intensively so far (23).

2.4.4. Furcate cord insertion

Fig 2.5. Vogel M.: Furcate cord insertion (70)

Furcate cord insertion of the umbilical cord is an extremely rare anomaly affecting around 0.1% of pregnancies. Furcate cord insertion describes the separation of umbilical vessels prior to their attachment at the placenta without the protective Wharton's jelly making it very vulnerable. The insertion at the placenta can be central, eccentric or marginal representing the only difference to the velamentous cord insertion. A velamentous insertion of the furcate cord insertion therefore does not exist as this would have the same characteristics as a velamentous cord insertion. Adverse outcomes such as stillbirth, fetal hemorrhage, varices, thrombosis of fetal vessels, and intrauterine growth restriction have all been described in association with a furcate cord insertion (1). In the literature though, there are only 18 cases of a furcate cord insertion reported, leading to an intrauterine fetal death in six of these cases (71-76).

The first description of the furcate cord insertion goes back to 1870 described by an anatomist originally from Prague working later in Vienna named **Hyrtl** in the book "Blutgefäße der menschlichen Nachgeburt" (Blood vessels of the human placenta). He describes three cases but regarding the pathogenesis or morphology of the furcate cord insertion only imprecise facts are presented (76). In 1923 **Ottow B.** published a paper about the furcate cord insertion. He describes a hypothesis regarding the pathogenesis: if the body stalk that represents the connection between the embryo and the trophoblast is for unknown reasons broader than usual, the umbilical vessels do not grow close together leading to a broader and triangular shaped insertion at the placenta (71). This is seen more commonly and represents a pre-stage of the furcate cord insertion, according to Ottow. For unknown reasons, the mesoderm layer between the vessels does not develop or later degenerates. In the course of pregnancy, the placenta grows and these separated vessels can grow even more apart. It is rarely reported, that due to the big gap between the vessels one part has a marginal insertion as the other one has a velamentous one (71).

In the subsequent section of the thesis, cases reported in the literature and their outcomes are presented, ranging from prenatally diagnosed ones with a good fetal outcome to ones not seen prenatally and with a fatal outcome.

In summary, there are in total 18 cases described in the literature. More detailed information is available in 14 cases that are further described below. The cases are presented in chronological order.

In 1923 Oscar Herberz published six cases:

Case 1: 33-year-old, gravida 1 para 0 is admitted to the labor ward with contractions that had started five days earlier and with a rupture of membranes that had occurred four days before admission. Pushing contractions started shortly after admission. Before the last push contractions, heart tones of the fetus could not be heard and an asphyctic girl was born that could not be resuscitated. The cause of the asphyxia could not be linked to the furcate cord insertion but to an intrauterine infection. The pathological exam of the placenta showed a furcate cord insertion with a length of ten centimeters and an eccentric insertion. Seen were two umbilical arteries and one umbilical vein with no sign of rupture, aneurysm or thrombosis (74).

Case 2: A 27-year-old gravida 1 para 0 had presented at the labor ward with contractions, followed by a rupture of the membranes. A healthy boy was born after an uneventful physiological birth process.

The pathological examination of the placenta revealed a furcate cord insertion with a length of four centimeters and an eccentric insertion, two umbilical arteries and one umbilical vein with no sign of rupture, aneurysm or thrombosis (74).

Case 3: 26-year-old gravida 1 para 0 was admitted to the labor ward with contractions and a rupture of membranes. A healthy girl was born after an uneventful physiological birth process. The pathological examination of the placenta showed a furcate cord insertion with a length of three to four centimeters and a marginal cord insertion (74).

Case 4: 27-year-old gravida 1 para 0, presented at the labor ward with irregular contractions. When the fetal heart rate stayed at 180 beats per minute asphyxia was suspected and a vaginal exam was performed. After that event, the birth process was completely physiological and a healthy boy was born. In the pathological report of the placenta a furcate cord insertion of four centimeters was reported with a central cord insertion. Two umbilical arteries and one umbilical vein with no sign of rupture, aneurysm or thrombosis. A possible cause for the asphyxia during birth was the compression of the furcate cord insertion which was reversed once the head of the fetus descended (74).

Case 5: 32-year-old gravida 1 para 0 presented with contractions at the labor ward. After the rupture of membranes, regular contractions started and after an uneventful physiological birth process a healthy girl was born. In the pathological report of the placenta, a furcate cord insertion is described four centimeters in length with an eccentric insertion at the placenta. Two umbilical arteries and one umbilical vein with no sign of rupture, aneurysm or thrombosis were reported (74).

Case 6: 30-year-old gravida 1 para 0 presented with contractions at the labor ward. Fetal heart tones were physiological. Later in the birth process, the fetal heart tones could not be heard anymore and a vaginal exam was performed causing a rupture of membranes. Thick green amniotic fluid was seen and later a girl was stillborn. Cause of death was asphyxia. The furcate cord insertion had not contributed to the fetal death. The furcate cord insertion was a velamentous one, diverging in the amnion three to four centimeters before the placenta (74).

In 1939, one case was published by **Rüther H.**: 19-year-old patient presented at the labor ward at term with a lack of fetal movement for 17 hours, regular contractions and strong vaginal bleeding. Later, an avital girl was born. The pathological report revealed a furcate cord insertion with a central insertion at the placenta and a rupture of one of the umbilical arteries. Microscopically a tear in the umbilical artery with deficient elastic tissue fibers was observed (77).

Swanberg et al. published one case of a furcate cord insertion in 1951 of a 39-year-old para 3 who presented at the labor ward in 42 gestational weeks with a sudden reduction of fetal movements. The fetus was in vertex position but no heart tones could be heard. Then a rupture of the membranes with bloody amniotic fluid occurred and regular contractions started. Later a macerated fetus of 5000g was born. The placenta was expelled spontaneously with a marginal umbilical cord insertion and a furcate cord insertion over a length of four centimeters, shown in the Figure 2.6.. A rupture of the umbilical vein was seen explaining the intrauterine fetal death (45).
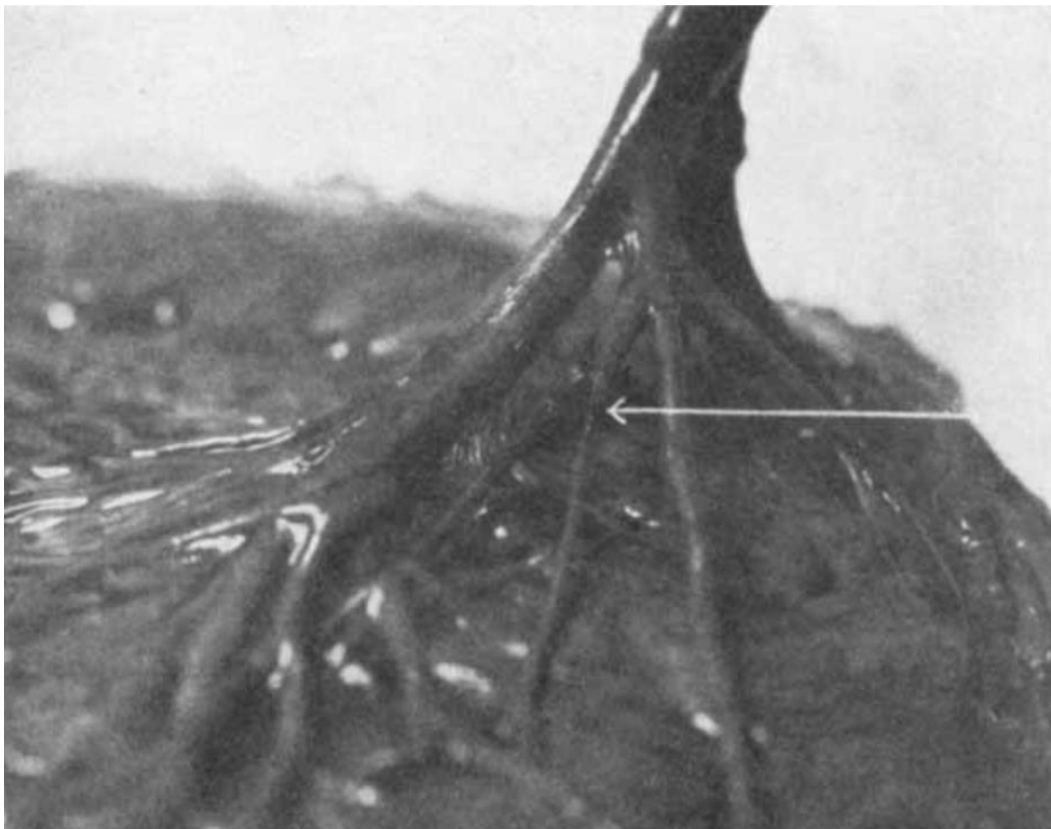

Fig. 2.6. Swanberg et al.: Furcate cord insertion (34)

In another publication from **1960, Kessler et al.** describes cases of hemorrhage from the umbilical cord including one with a furcate cord insertion. The gravida 3 para 0 presented at the labor ward with a rupture of membranes with bloody amniotic fluid. The fetal heart tones were uneventful and after 3.5 hours a healthy girl was born. In the pathological report of the placenta a furcate cord insertion with a singular umbilical artery was described. In the course of the pregnancy, multiple ruptures of the anastomosis between the two umbilical arteries had occurred. Due to the furcate cord insertion, this part was not covered by the Wharton's jelly and therefore was very vulnerable. A spontaneous formation of a thrombosis had recurrently stopped the bleeding and the newborn had a normal level of hemoglobin (46).

Laberke PJ et al. published a case of fetal death diagnosed at 40 weeks of gestation caused by hemorrhage into the amniotic fluid after rupture of the umbilical vein. An uneventful pregnancy of a 22-year-old woman is described. No apparent risk factors were known. It is not specified in the paper if a first and second trimester prenatal ultrasound examination was performed. The paper published in 2009 also determined that it cannot be expected that a furcate cord insertion can be seen prenatally. The autopsy of the fetus discovered a hypovolaemic shock due to rupture of the umbilical vein probably triggered by fetal movements. The fetus did not show any signs of malformations or syndromes (47).

In another case published by **Tashkova D et al.**, an intrauterine fetal death in a case with a furcate cord insertion is described in the English abstract. Unfortunately the article is only in Bulgarian (75).

In two cases, the furcate cord insertion was suspected prenatally and subsequently confirmed after birth:

The first case was published by **Fujita et al.** in 2017. The patient was admitted to the hospital with a suspected abnormal cord insertion and a furcate cord insertion was suspected. After counselling the patient on the increased risk for intrauterine fetal death, labor was induced at 37 weeks and a healthy neonate was born. It is suggested that prenatal visualization of the furcate cord insertion through Doppler sonography is possible and precautions can be taken (72).
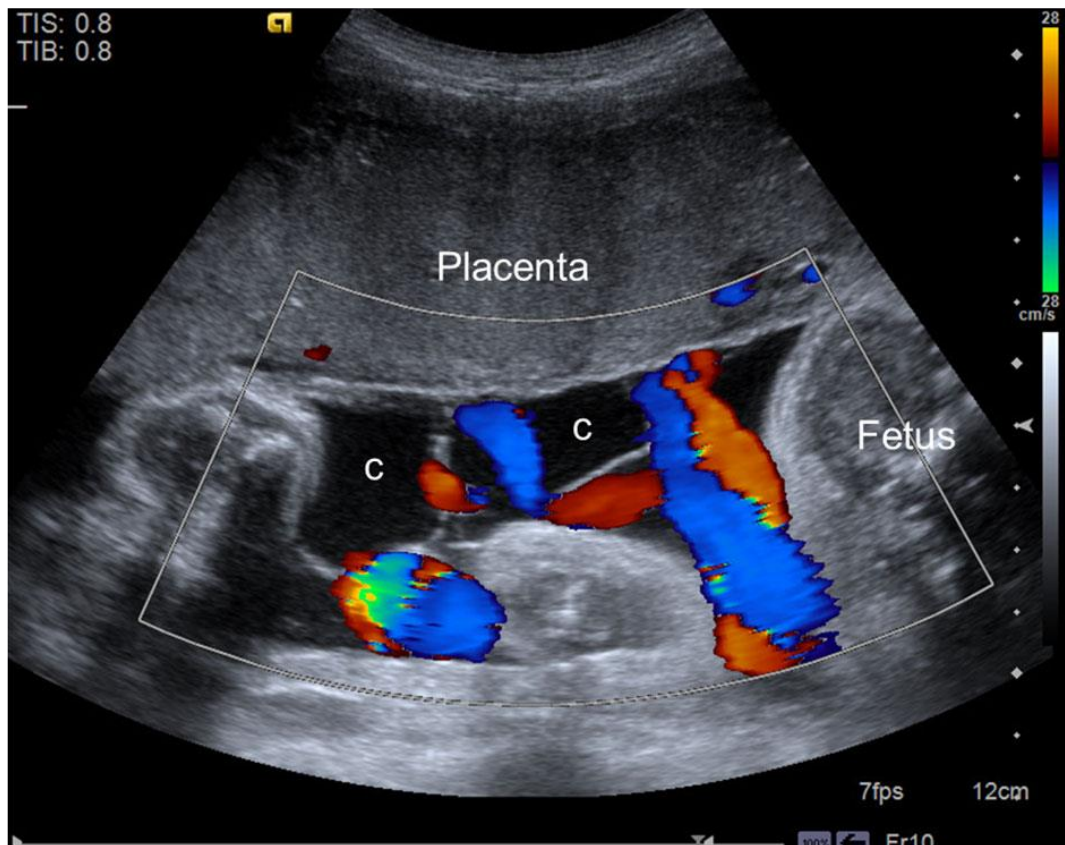
Fig. 2.7. Fujita et al.: Doppler sonography of the umbilical cord demonstrating the separation of the vessels. C=cystic lesion on the base of cord insertion (72)

The second publication is by **Lamale-Smith LM et al.** and describes two cases of a furcate cord insertion. One case was diagnosed antenatally via detailed prenatal ultrasound.

The outcome of the newborn was very good and no malformations were associated. Postpartum, a retention of the placenta occured leading to a manual extraction of the placenta and curettage.

In the second case, the furcate cord insertion was diagnosed only on postpartum evaluation after emergent delivery. It was found in conjunction with a VACTERL association of the fetus (73).

2.5. Research questions and the aims of this study

The furcate cord insertion of the umbilical cord is a very rare anomaly of the umbilical cord. Only a small number of case series and reports are available. So far, only 18 cases in total have been reported. Therefore, the true prevalence, the risks associated and the management of these pregnancies are still difficult to determine. We investigated 132 cases occuring in singleton pregnancies from 1993 to 2016 that were diagnosed in the pathological department of the Charité. The aim is to determine the prevalence of this anomaly on the basis of the largest series so far and in addition, to evaluate the pathological characteristics and perinatal outcomes trying to answer the following research questions:

Is the furcate cord insertion associated with intrauterine growth restriction?

Is the furcate cord insertion associated with an adverse perinatal outcome and if so, how likely is it?

If suspected prenatally, can an adapted management of the pregnancy avoid or reduce the risk for the fetus?

Is the furcate cord insertion associated with pregnancy-related diseases?

What are the pathological characteristics of the furcate cord insertion?

Does the length of the furcate cord insertion influence the outcome?

3. Materials and methods

The terms "Insertio furcata" and "Insertio furcuata" were searched in the database of the pathological department, retrieving results for the years 1993-2016. Overall 151 cases with this insertion anomaly were identified. Multiples and furcate cord insertions described with a velamentous cord insertion were excluded from further evaluation, leaving 132 cases for pathological and 98 cases for the perinatal analysis within the Charité.

The following pathological parameters were analyzed: site of insertion of the furcate cord insertion, number of umbilical arteries, length of the furcate cord insertion, weight of placenta, length of umbilical cord, cause of adverse fetal outcome or demise and origin of the pathological specimen. The site of insertion was categorized into normal insertion including central and eccentric insertions and pathological insertion including the marginal insertion which is defined as an insertion within 2cm of the placental edge.

Cases from the Charité were extracted from the KIM database (Nexus KIM GebDok 5.10.0.8) analyzing the outcome of each delivery with a furcate cord insertion until 2014. After 2014 births were documented in the Viewpoint database (Viewpoint GE Version 5.6.26.148). Perinatal data of external cases was evaluated if the intrauterine fetal death was supposedly caused by the furcate cord insertion. The following clinical parameters were evaluated: maternal age at birth, gestational week at birth, birth weight, Apgar scores, pH level of the umbilical artery after birth as well as mode of delivery. Furthermore, complications during pregnancy including pregnancy induced hypertension, preeclampsia or superimposed preeclampsia, HELLP syndrome, gestational diabetes, fetal malformation, and birth characteristics including blood loss, shoulder dystocia, green stained amniotic fluid, uterine rupture, pathological non stress test (NST) and retention of placenta were evaluated. Starting with 2001, prenatal ultrasound has been documented in the Viewpoint database. Cases were searched for abnormalities regarding the umbilical cord insertion, the umbilical vessels itself and fetal malformations. The perinatal data was then compared with the analysis of the data from all births from 1993 until 2014 at the department of obstetrics.

Until 2010, every placenta was sent for pathological examination, so that the prevalence of the furcate cord insertion was calculated from the 56374 singleton pregnancies from 1993 to 2010.

After searching the term "furcate cord insertion" on pubmed and searching the literature for cases of furcate cord insertion, further data from these cases such as the age at birth, gestational week, site of insertion, outcome and, if applicable, cause of death were extracted. This data was then compared with our analysis.

The data was then transferred to the SPSS statistical program (Version 24) and descriptive analysis was performed.

4. Results

4.1. Descriptive analysis

We observe a prevalence of the furcate cord insertion in our collective at 0.17%.

Out of the 132 cases, we observed seven cases of intrauterine fetal death (IUFD) representing 5.3%. The risk for intrauterine death within the Charité was 1.0%.

99 cases are from the Charité from the years 1993-2016. In 32 cases, external hospitals sent their specimen to the pathological department at the Charité for further examination. In one case the origin of the specimen could not be evaluated.

In two cases (one within the Charité and the second one from an external hospital), a termination of the pregnancy was performed. The reason in both cases was a severe malformation and not the furcate cord insertion.

The age of the mother at the time of birth ranged between 20 and 46 with the median at 30 years (SD=5.52; 95% CI 29.25;31.51).

The week of gestation at birth, excluding terminations of pregnancies, was between 20 and 43 with the median at 40 weeks (SD=2.99; 95% CI 39.12;40.33). In two cases, this information is missing. In 67.4% the mode of birth was a spontaneous vaginal delivery and in 9.5% a vaginal operative delivery. In 10.5%, a planned and in 12.6% a second-stage cesarean delivery was performed. In three cases, this information is missing.

The median blood loss for spontaneous vaginal delivery lay at 250ml (SD=252.48), for vaginal operative delivery at 300ml (SD=270.93), for planned cesarean delivery at 500ml (SD=271.3) and in the case of a second-stage cesarean delivery at 500ml (SD=1300.93). In six cases, this information is missing.

The gender distribution in newborns with a furcate cord insertion is 44,2% male and 55,8% female. In three cases this information is missing.

4.2. Prenatal diagnostics of suspicious umbilical findings in furcate cord insertion

In two cases, an abnormality regarding the umbilical cord was seen prenatally in the ultrasound.

4.2.1. Subject ID Number 76

38-year-old patient, gravida 1 para 1

In the first trimenon, a strong bleeding occurred. With 24+0 the patient was admitted due to premature contractions, vaginal bleeding and suspected preterm rupture of membranes. In the ultrasound performed in our clinic, a very thin umbilical cord with a marginal umbilical cord insertion and a retrochorial hematoma of 72x18mm was observed. Apart from a white spot in the left ventricle, no irregularities or other soft markers were seen. The estimated fetal weight at this point was 820g (95th percentile). The fetus was in breech position, with an anterior wall placenta. The length of the cervix was 40mm. Doppler sonography showed a normal umbilical image but a pathological Doppler finding in the uterine artery.
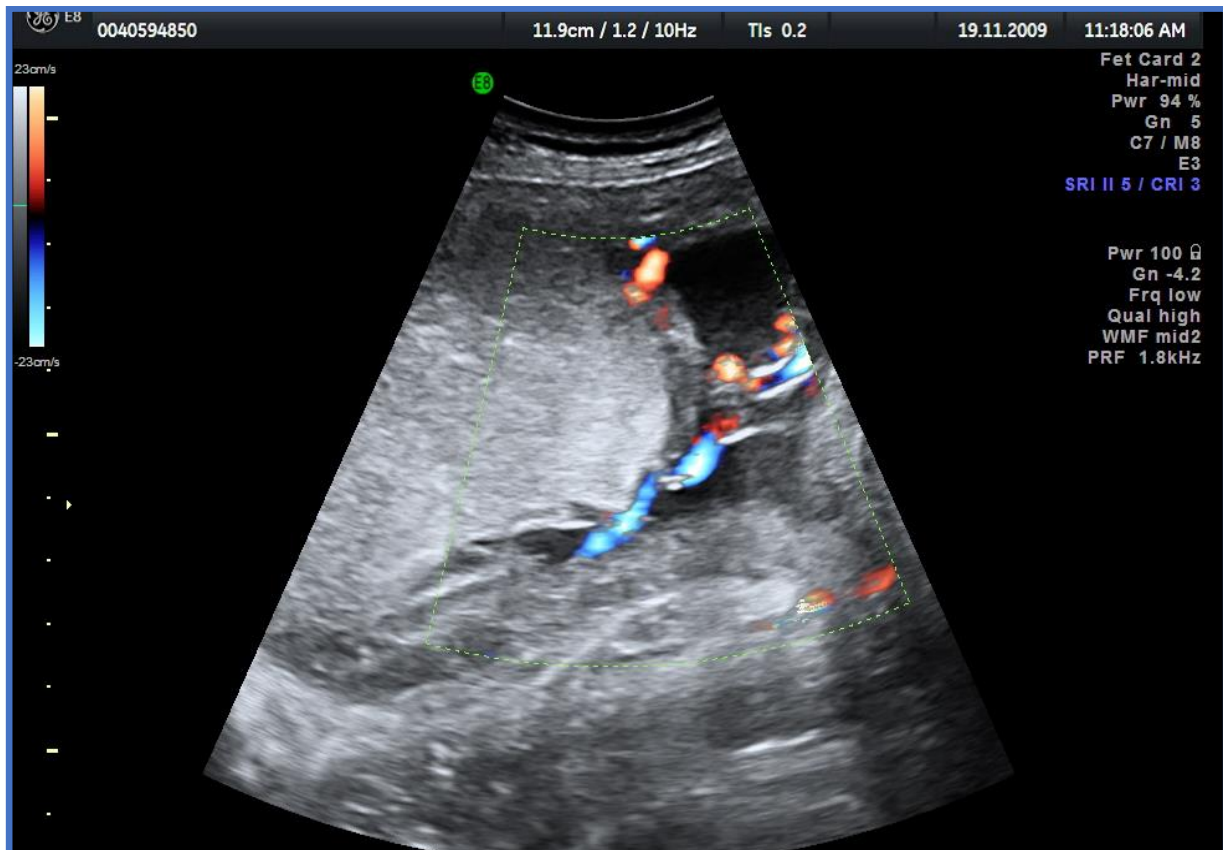

Fig. 4.1. Suspicious findings of a thin umbilical cord in furcate cord insertion with separating umbilical vessels at the insertion site

Antenatal corticosteroid treatment with two courses of betamethasone was completed. Due to several risk factors, the patient stayed hospitalized. At 28 weeks of gestation, a caesarean section was performed due to a recurring pathological NST as shown below.
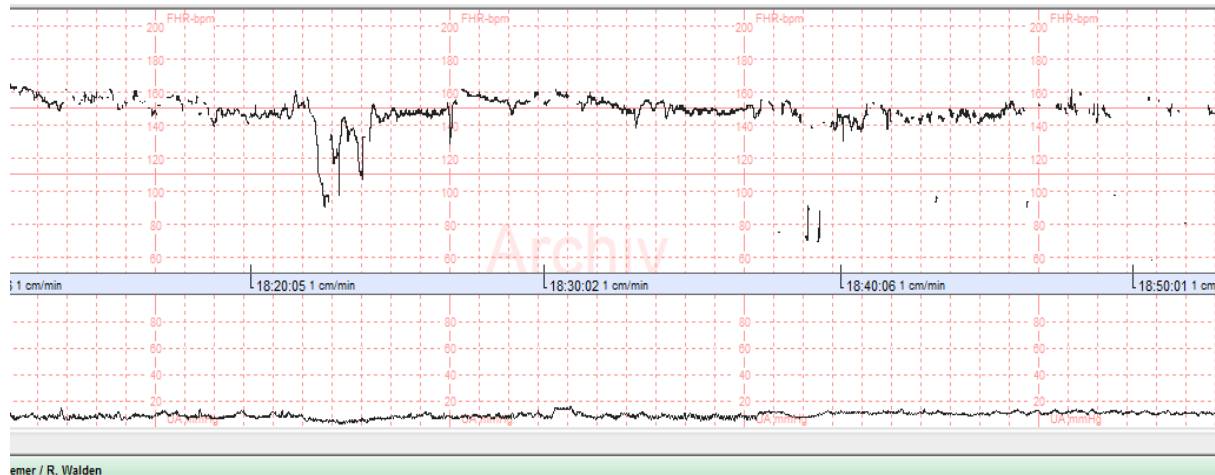

Fig. 4.2. NST of Subject ID Number 76

Bloody amniotic fluid was observed and the newborn was admitted to the NICU due to preterm birth with a low birth weight of just 998g. The Apgar score was 7/8/9 and the pH from the umbilical artery was 7.31.

The pathological report showed an extremely eccentric furcate cord insertion over a length of four to six centimeters, three umbilical vessels, meconium and signs of recurring bleedings from the chorionic plate of the placenta.

4.2.2. Subject ID number 141

37-year-old gravida 2 para 1 with an intrauterine fetal death in 36 weeks of gestation with an ectasia of the umbilical vein with partial thrombosis caused by a furcate cord insertion.

In the figure 4.3. below, the umbilical cord with a venous ectasia of the umbilical cord with partial thrombosis is seen. For details of the case see chapter 4.7.1.: Case Series: IUFD caused by the furcate cord insertion.
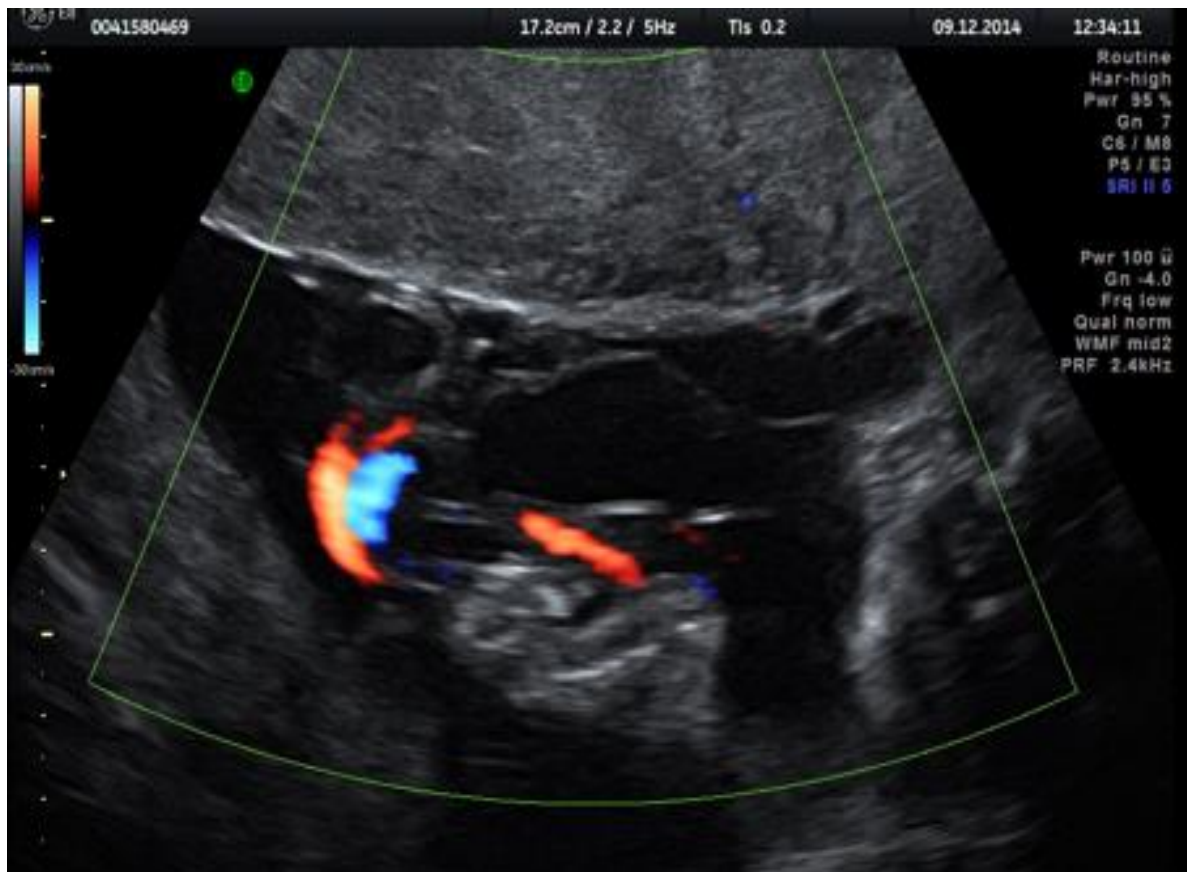
Fig 4.3. Umbilical cord with suspected venous ectasia of the umbilical vein

4.3. Pregnancy-related diseases

We observed one case of preeclampsia and HELLP syndrome. Preeclampsia and HELLP syndrome therefore both occur at 1.0% in these patients.

Four cases of gestational diabetes were detected as well (4.08%).

4.4. Perinatal complications

Nonreassuring fetal heart rate	Green amniotic fluid	Shoulder dystocia	Chorioamnionitis	Admitted to NICU
N26 (26.5%)	N16 (16.3%)	N2 (2.0%)	N1 (1.0%)	N17 (17.4%)
Retained placenta	**Placental abruption**	**Placenta praevia**	**Uterine rupture**	**Atony**
N5 (5.1%)	N1 (1.0%)	N3 (3.1%)	N2 (2.0%)	N2 (2.0%)

Tab. 4.1. Perinatal complications in furcate cord insertion

4.5. Neonatal outcome

Birth weights were analyzed week by week from 39+0-41+6 gestational weeks showing the median birthweight and percentiles for each week of gestation and gender in the tables below.
The average percentile of the birthweights of all newborns lies at 38 with the median at 3390g (SD=659.82; 95% CI 3242.81;3511.64). In three cases this information is missing.

39+0-39+6	40+0-40+6	41+0-41+6
3440g (SD=486.33) (39th percentile)	3920g (SD=609.85) (70th percentile	4045g (SD=493.67) (73rd percentile)

Tab 4.2. Birthweight of male newborns with a furcate cord insertion

39+0-39+6	40+0-40+6	41+0-41+6
3400g (SD=534.14) (48th percentile)	3500g (SD=346.48) (47th percentile)	3320g (SD=501.47) (25th percentile)

Tab. 4.3. Birthweight of female newborns with a furcate cord insertion
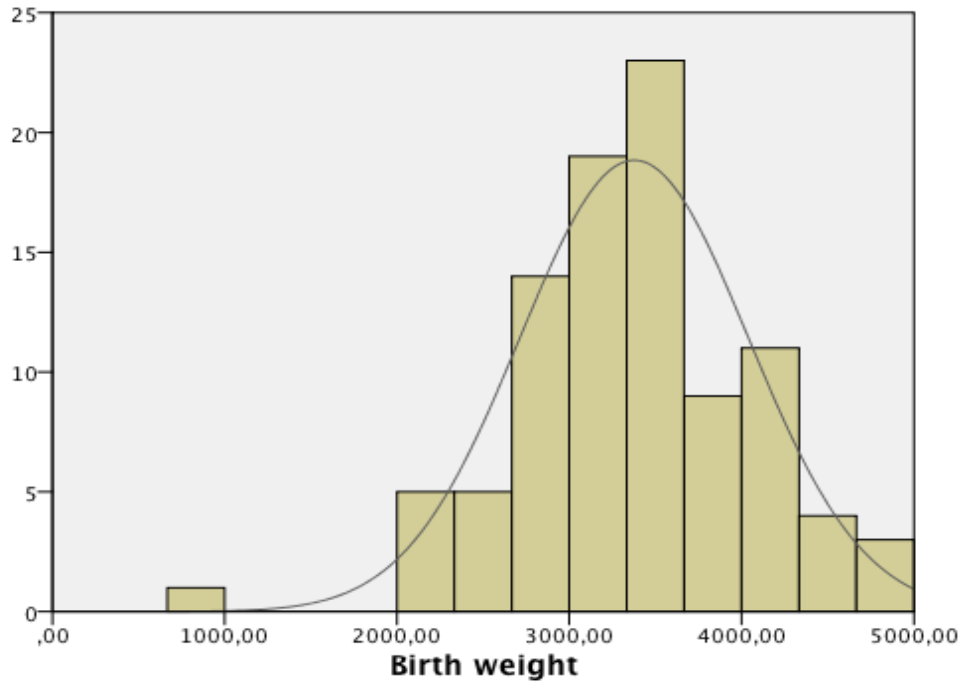
Fig. 4.4. Distribution of birth weights in furcate cord insertion

In addition to the Apgar score, the pH level measured from the umbilical artery after birth is an important instrument for evaluating adverse outcome in newborns, especially in high risk pregnancies. The Apgar scores as well as the data regarding the pH of the umbilical artery are shown in the table 4.4. and figure 4.5. below. In three cases, the Apgar score is missing.

APGAR Score	N with 1min	N with 5min	N with 10min
0	1	1	1
1	0	0	0
2	2	0	0
3	0	0	0
4	1	1	0
5	0	0	0
6	2	1	1
7	8	3	0
8	13	9	3
9	61	19	12
10	7	61	78

Tab. 4.4. Distribution of APGAR scores in pregnancies with a furcate cord insertion

The minimum pH measured was 7.08 and the highest 7.42, with the median at 7.27 (SD=0.065; 95% CI 7.25;7.27). In six cases, this information is missing.
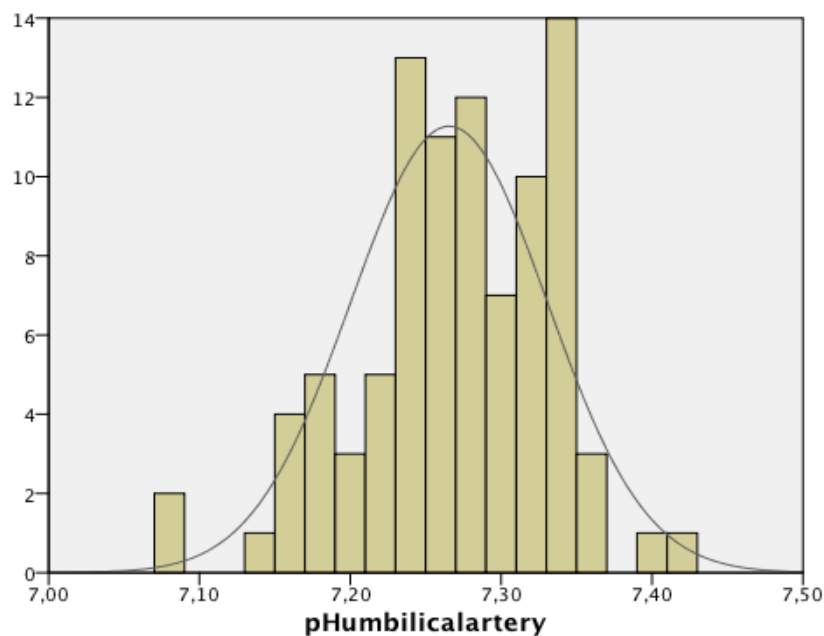

Fig. 4.5. Distribution of the levels of pH in the umbilical artery after birth

In 17 cases (17.35 %), the newborn had to be admitted to the NICU for further observation and treatment. Specifics are presented in the following table.

Subj. ID	Gestational week	Birth weight	Reason	Apgar 1	Apgar 5	Apgar 10	PH
8	40	3000g	Respiratory distress	7	8	9	7.17
23	41	2865g	Icterus, Hypotrophy	7	8	9	7.34
26	40	2830g	Aortopulmonary septal defect	9	10	10	n.a.
27	38	3100g	Respiratory distress	8	9	10	7.17
30	39	3460g	Respiratory distress	8	7	9	7.24
50	38	2850g	Hematological disorder	9	10	10	7.28
51	40	2975g	Drug withdrawal	8	9	9	7.33
58	36	2005g	Gastroschisis	9	9	10	7.34
63	39	3130	Icterus (rhesus isoimmunisation)	10	10	10	7.27
76	28	998g	Respiratory distress, Birthweight	7	8	9	7.31
96	34	2140g	Asphyxia, Birth weight	4	7	8	7.33
106	n.a.	2660g	Seizures, Enzephalopathy	8	9	10	7.15
113	37	2945g	Respiratory distress	7	6	9	7.26
115	41	3590g	Respiratory distress, Rhesus isoimmunisation	2	4	6	7.25

129	34	2560g	Immaturity	9	9	10	7.42
134	40	3350g	Hypoglycemia	7	7	9	7.33
135	38	2650g	Respiratory distress	9	8	9	7.31

Tab 4.5. Newborns admitted to the NICU

Fetal malformations

In six out of the 99 pregnancies within the Charité, a fetal malformation was observed (6.1%). In four of these cases, this was already diagnosed prenatally: an aortopulmonary septal defect, a right-sided aortic arch, a gastroschisis and one caudal regression syndrome.

In one case, a club foot was diagnosed at birth. As well as one newborn with a malformation of the ear which had not been detected prenatally either.

4.6. Pathological parameters

The pathological parameters were evaluated starting with the site of insertion.
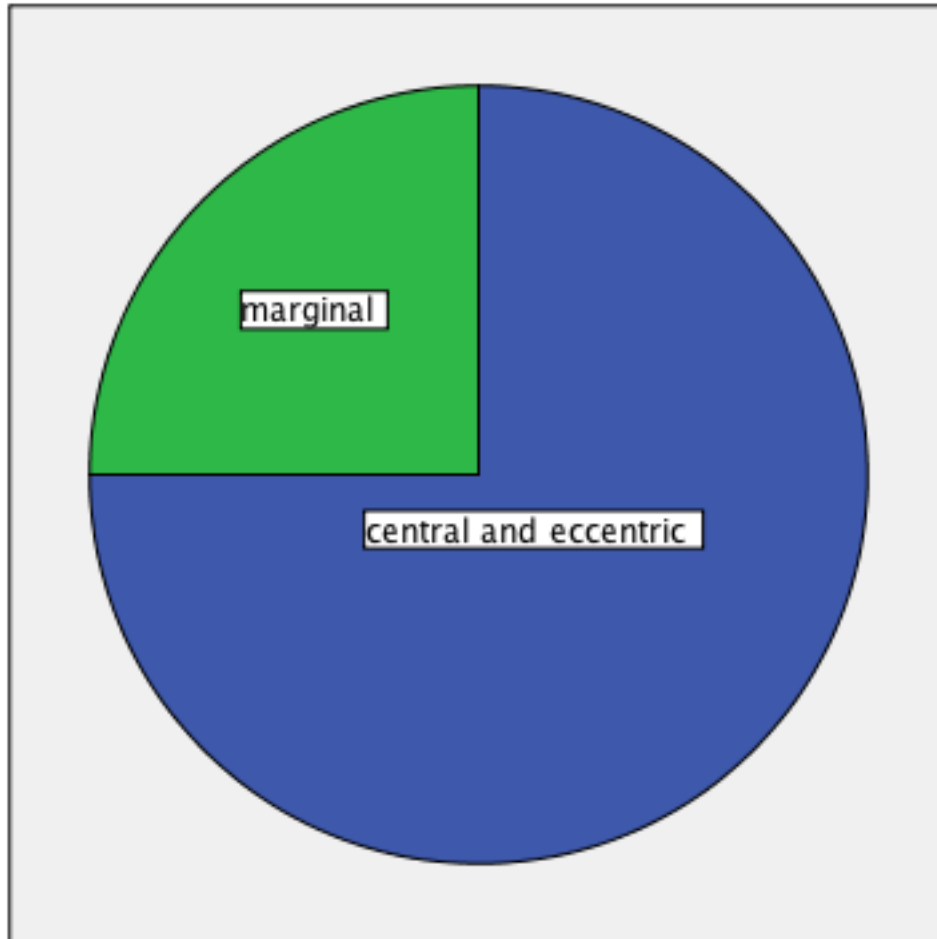

Fig. 4.6. Insertion site of the umbilical cord in furcate cord insertion

The types of insertion were divided into two groups: normal including the central and eccentric insertions (99 cases representing 75%) and marginal, defined as an insertion within 2cm of the placental edge (33 cases representing 25%).

Out of our three cases involving intrauterine fetal death due to a complication of the furcate cord insertion, two were categorized as a marginal and the third as an eccentric insertion, with the lengths of the furcate cord insertions at four centimeters and 18cm. Concerning the third case, the length of the furcate cord insertion is missing.

The length of the furcate cord insertion ranges in our cases from 0.5cm to 18cm, with the median at 3cm (SD=2.09; 95% CI 2.50;3.44). In 53, cases this information is missing.

In cases of intrauterine demise, the median length of the furcate cord insertions was 4cm (SD=6.27), with the minimum at 2cm and the maximum at 18cm. In three cases, it was an eccentric and in four cases a marginal insertion.

The percentage of a single umbilical artery in placentas with furcate cord insertion in our patient population lies at 3.1%. In 46 cases, this information is missing.

Varices in the umbilical cord and/or in the basal plate of the placenta were observed in four cases (3.03%) and in 16 cases a thrombosis in the placenta or the fetal vessels was seen (12.12%).

In one case, a chorangioma in the area of the furcate cord insertion is described.

Length of the umbilical cord

The length of the umbilical cords with a furcate cord insertion in our patient population ranges from 3cm to 95cm, with a median of 45cm (SD=16.58; 95% CI 41.62;48.69). The table below shows the umbilical cord lengths from the gestational weeks 39 to 42. In 45 cases, this information is missing.

Gestational week/gender	Median length umbilical cord in centimeter	SD
42/Male	52	7.88
42/Female	44	12.05
41/Male	62	25.45
41/Female	59.5	21.83
40/Male	47	16.35
40/Female	50.5	12.89
39/Male	50	13.55
39/Female	50	14.43

Tab. 4.6. Umbilical Cord length in furcate cord insertion

Placental weight

The weight of placentas with a furcate cord insertion in our patient population ranges from 250g to 1100g, with a median of 600g (SD=168; 95% CI 578.67;647.11). This information is missing in 37 cases.

4.7. Case series: IUFDs caused by furcate cord insertion

In seven of the 132 cases, an intrauterine fetal death is observed. In three cases the cause of death can be linked to the furcate cord insertion. These cases are described in detail below.

4.7.1. Case 1 – Subject ID 141

37-year-old gravida 2 para 1
No history of illness or surgeries, severe obesity, one medical abortion

The patient presented in our labor ward with a referral regarding a suspicious NST at 29 weeks of gestation. The NST performed showed a base line at 155bpm with late decelerations but an undulatory oscillation. The umbilical Doppler and the uterine Doppler were normal. The estimated weight was at the 43rd percentile and the fetal position was breech. The placenta showed multiple lacunes and cystic formations. At this point, the patient was admitted to our prenatal ward and received corticosteroids to accelerate lung maturation. Further NSTs that were performed showed a physiological pattern. Ultrasound scans performed in the next days showed apart from the cystic lesions and lacunes in the placenta also a convolute of the umbilical cord with a slightly dilated umbilical vein close to the marginal insertion. After eight days of observation and physiological NSTs, the patient was discharged into our outpatient service. After two weeks, she was seen again at our prenatal diagnostics outpatient ward. At this point in time, the convolute showed a significantly reduced venous flow with the suspicion of a thrombus in the umbilical vein. In addition, the middle cerebral artery had an increased value of the maximum velocity indicating fetal anemia. The patient was counseled intensively about the fetal risks due to the above-mentioned findings. A cesarean section was recommended but declined by the patient. She was admitted to the ward and NSTs were performed three times a day and ultrasound every two days. The case was discussed with the patient and the informed consent was to wait until 36+0 in case of physiological NSTs to perform a planned cesarean section. In the gestational week 35+5, suspicious NSTs were observed once again. The cesarean section was recommended once again but declined by the patient. Three days later, the ultrasound confirmed an IUFD.
Labor was induced and an avital girl was born in gestational week 36+1. The placenta was complete and the blood lost was at 350ml.

The birthweight was 2070g (7th percentile), length 47cm and head circumference 31cm.

The patient declined an autopsy of the stillborn but an examination of the placenta was performed. The following report was filed:

Normal size and weight of a placenta in the gestational week of 36. Furcate cord insertion over a length of 18cm. The two umbilical arteries go together separated from the umbilical vein. A varicosis of the umbilical vessels is observed and additionally, the umbilical vein shows an ectasia with an old thrombus. The vein also separates before insertion. Focal chorioamnionitis.

The reason for intrauterine fetal death was the furcate cord insertion in combination with an ectasia and thrombosis of the umbilical vein and a placental villous immaturity.

Fig. 4.7. Subject ID 141 - Furcate cord insertion with an ectasia of the umbilical vein with partial thrombosis

4.7.2. Case 2 – Subject ID 19

39-year-old gravida 3 para 2, one abortion, one spontaneous vaginal delivery

Nicotine abuse: 20 cigarettes per day

An anomaly scan and amniocentesis did not show any malformation and a normal female karyotype. The patient was admitted with a fetal breech position to attempt an external cephalic version in the gestational week 38. The attempt was unsuccessful and the patient was discharged. She presented later in gestational week 39 at the outpatient clinic with a lack of fetal movements that had ceased three days after the attempted external cephalic version. An ultrasound revealed an intrauterine fetal death.

Labor was induced with prostaglandin gel and after a rupture of membranes with ensanguined amniotic fluid, an avital girl was born in breech position. A nuchal cord was seen.

Birthweight: 2970g (12th percentile), length 51cm, head circumference 35cm

Due to a retention of placenta, a manual extraction had to be performed. The blood loss was 400ml.

Summary of the pathological report of the placenta with its macroscopic and microscopic findings:

Placenta with normal weight of 480g in the gestational week 39.

No hematoma at the basal plate. The furcate cord insertion has a length of four centimeters with no protection of the Wharton's jelly. There are three umbilical vessels. Described is a rupture of one four-centimeter-long vessel within the furcate cord insertion and a rupture of a second one-centimeter-long vessel. On the placental surface, there is a vasa aberrantia marginalis: two centimeters long and the origin of this vessel also seems to be disrupted. Additionally, a rupture of an allantois artery two centimeters from the insertion of the umbilical cord is seen. The umbilical cord is 60cm long and 14mm in diameter.

The placenta shows signs of a reduced diffusion capacity and evidence of meconium. The insertion is a furcate cord insertion with a fresh rupture of two umbilical vessels and a recent rupture of a basal plate artery with a thrombus in the area of the rupture.

Autopsy of the stillborn:

Eutrophic female stillborn with anatomic development of the gestational week 39.

Extreme paleness of the skin, the inner organs and ensanguined amniotic fluid as signs of an acute intrauterine bleeding followed by intrauterine death.

Signs of meconium in all parts of the lung as a sign of meconium aspiration syndrome. The parenchymatous abdominal organs show signs of intrauterine hypoxia.

The probable explanation for the hypoxia might be the nuchal cord as described in the clinical presentation of the case.

The cause of death is the acute intrauterine loss of blood following the above-mentioned rupture of the vessels. Because of the normal NSTs after the unsuccessful external cephalic version and the recent changes in the umbilical vessels in the area of rupture, the cause of the intrauterine fetal death is some other unclear event affecting the vulnerable furcate cord insertion and not the attempt of the external cephalic version a few days before.

4.7.3. Case 3 – Subject ID 146

36-year-old patient, gravida 5 para 4, four spontaneous vaginal deliveries
History: Morbid obesity (BMI of 46,7) Hepatosplenomegaly with hemangioma of the liver, Epilepsy with recurring absence seizures, Operation: cholecystectomy.

In 30+4 weeks of gestation, the patient presented at the hospital with circulatory dysregulation and absence seizures. In the prenatal ultrasound, following parameters were evaluated: cephalic presentation, placenta on the posterior wall, amniotic fluid unremarkable. Due to the obesity of the patient, a more detailed scan was not possible. The estimated fetal weight was at 1600g. The patient was admitted to the hospital for three days. After an ultrasound of the upper abdomen, an internal medicine consultation and the prophylactic application of magnesium, the patient left the hospital against medical advice.

Two weeks later she was admitted again for the same complaints. The fetal weight now was estimated between 1600 and 1700g. This time also a Doppler sonography of the umbilical artery was performed and showed normal flow parameters. The patient became increasingly agitated so that she was transferred to a psychiatric ward in a different hospital for further treatment. At gestational week of 39+2 the patient was seen again. The admission to the ward and the induction of labor was discussed with the patient.

Up until then, ultrasound and NSTs have shown a physiological pattern. On the ultrasound performed on the day of admission intrauterine fetal death was diagnosed.

Labor was induced and boy with a birthweight of 2990g, length of 49cm and with a head circumference of 33cm was stillborn.

Pathology report:

Intrauterine fetal death: Placenta extrachorialis. The insertion is strongly eccentric and a furcate cord insertion is observed. In addition, there is a single umbilical artery.

Within the furcate cord insertion, there is a dilatation and rupture of one of the umbilical vessels also representing the cause of the intrauterine fetal death.

In four cases, the intrauterine fetal death was caused by other factors as listed in detail in the section below:

Subject ID 3

26-year-old patient with an IUFD at the gestational week 39, IUGR.

Pathological report: Placental insufficiency, a true knot of the umbilical cord and a nuchal cord were described as the contributing factors of intrauterine fetal death. Furcate cord insertion with a marginal insertion.

Subject ID 101

34-year-old patient with an IUFD in the gestational week 22.

Pathology report: Placental insufficiency with an endangiopathia obliterans or fetal thrombotic vasculopathy with a fresh thrombus in the portal vein of the stillborn were contributing factors to the intrauterine fetal death. The mother has a factor V Leiden mutation.

Length of the furcate cord insertion is four centimeters with a strong eccentric insertion.

Subject ID 104

33-year-old patient with an IUFD in the gestational week 40.

Pathology report: Placental insufficiency, acute intervillous thrombus, furcate cord insertion with four centimeters in length and an extreme eccentric insertion. As the cause of death, the placental insufficiency is documented.

Subject ID 151

24-year-old patient with an intrauterine fetal death caused by a nuchal cord.

Pathology report: Furcate cord insertion over two centimeters with a marginal cord insertion. A collapse of the fetal arteries with partial capillary hyperemia is seen as the consequence of the nuchal cord.

4.8. Results of the literature review

In total, there are 18 cases described. Four of these cases are only mentioned and no further details are available.

In six cases, an intrauterine fetal death is described. In three cases, the furcate cord insertion can be linked to the cause of death with a rupture of the umbilical vessels.

In one case, an asphyxia is described but the cause is not mentioned.

In another case, the intrauterine infection is described as the cause of death but it is also hypothesized that the furcate cord insertion might have played a role, as it was not possible to determine the fetal heart beat was not possible to determine anymore rather abruptly, hypothesizing a compression of the vulnerable furcate cord insertion during birth.

The median length of the furcate cord insertion in the cases reported in the literature is at four centimeters (SD=1.98; 95% CI 3.36;6.41).

The median birthweight of the cases in the literature is 3220g (SD=834.98; 95% CI 2568. 07;3850.366)

The site of insertion reported in the literature was in 60% a central or eccentric insertion whereas 40% have a marginal furcate cord insertion.

The median gestational week at birth in the literature is 40 (SD=3.14; 95% CI 36.47;41.30).

(45-47, 71-75, 77)

5. Discussion

The furcate cord insertion of the umbilical cord is an extremely rare anomaly occurring according to the 18 cases discussed in the literature in around 0.1% of all pregnancies (1).

The prevalence of this anomaly according to our data lies at 0.17%, with a risk for intrauterine death being 1.0%, confirming the rarity of this pathology.

The umbilical cord usually is not routinely investigated in a very detailed way in prenatal diagnostics. Frequently, the examination is confined to detecting the number of umbilical vessels. Sometimes, the type of insertion of the umbilical cord is evaluated, especially in cases of a marginal or velamentous cord insertion, as this is associated with a higher rate of complications (58). In two cases in the literature, the furcate cord insertion as such was suspected in prenatal diagnostics and confirmed in the pathological report (72, 73). An important differential diagnosis in the potential prenatal diagnostics of the furcate cord insertion are umbilical cord cysts. Some of the cysts might have vessels in their walls and therefore might be difficult to differentiate from a furcate cord insertion in ultrasound (34). As the pathogenesis of pseudocysts of the umbilical cord is a degenerative process of the Wharton's jelly, these cysts might even play a role in the etiology of the furcate cord insertion. This has not been discussed in the literature yet. In our case series, the furcate cord insertion had not been suspected prenatally as such. Nevertheless, in one case a thin umbilical cord was seen prenatally, possibly representing the furcate cord insertion with a good perinatal outcome. In another case, the patient was referred to our department with a suspicious NST and an ectasia of the umbilical vein with thrombosis that had formed as a complication of the furcate cord insertion. This led to an IUFD in the gestational week 36.

The umbilical cord has been investigated in several studies in recent years. The focus was the amount of Wharton's jelly, the flow in the umbilical vein, the size of the umbilical cord area and the diameter of the umbilical vessels for the different gestational weeks (24). An increased risk for hypertensive disease (9), intrauterine growth restriction (25), lower fetal birth weight (26) and fetal distress during labor (27) has been linked to a reduced amount of Wharton's jelly, a reduced diameter of the umbilical cord or a reduced flow in the umbilical vein.

In the literature, only 18 cases of a furcate cord insertion have been described and they were associated with varices and thrombosis of the umbilical cord, fetal hemorrhage and stillbirth.

To discuss these points, the perinatal data from pregnancies in this case series was compared with data from all births from 1993 until 2014 in the department of obstetrics at the Charité or, if not available, with data from the literature.

In this study, we did not observe an association of the furcate cord insertion with intrauterine growth restriction with the median birth weight being at the 38th percentile. 70.41% of the cases with a furcate cord insertion have a birthweight between 2500g and 3999g compared to 39% in all pregnancies at the Charité.

Intrapartum cesarean delivery was performed in 14.6% of all pregnancies compared to 12.8% in pregnancies with a furcate cord insertion. Vaginal operative delivery occurred in 8.5% of all pregnancies compared to 9.6% in pregnancies with a furcate cord insertion. Therefore, the furcate cord insertion does not increase the risk for intrapartum cesarean section or operative vaginal deliveries.

21.4% of all newborns compared to 16.3% of the newborns with a furcate cord insertion had to be admitted to the NICU.

The 5min Apgar score was nine or ten in 87.7% of all newborns compared to 84.2% in cases with a furcate cord insertion. In 14.8% of all newborns compared to 14.3% of newborns with a furcate cord insertion, the pH level of the umbilical artery was below the critical value of 7.20 representing the cut-off for metabolic acidosis. In summary, there is a slightly lower percentage of births with a 5min Apgar of nine or ten in pregnancies with a furcate cord insertion.

A retention of the placenta occurred in 5.1% of the cases. According to different observational studies in different settings in 1.5% to 3.3% of all pregnancies a retained placenta complicates birth and is therefore associated with the furcate cord insertion (78). Similar numbers are observed with the velamentous cord insertion according to a population-based study that observed a retention of placenta in 5.5% of the cases (57).

Regarding pregnancy-related diseases, we saw a slightly higher prevalence of HELLP syndrome (1.0%) compared to the prevalence in the literature ranging from 0.17-0.85% (79).

Preeclampsia was observed in 1.0% of the cases and therefore is not associated with the furcate cord insertion. According to Ronsmans et al. the prevalence in all pregnancies lies between 2 and 5% (80).

Gestational diabetes is observed in 13.2% of all pregnancies according to a population-based study (81). In 4.08% of pregnancies with a furcate cord insertion, gestational diabetes was diagnosed and therefore is not associated with the furcate cord insertion.

We observed an association with a single umbilical artery, occurring in 3.1% of the cases. In all pregnancies the single umbilical artery is found in around 0.61% (82).

According to the literature thrombosis of fetal vessels is associated with furcate cord insertion. In our case series, it occurred in 12.12% of the cases compared to 1 to 6.4 % in all pregnancies and therefore is associated with the furcate cord insertion in our case series as well (83).

The length of the umbilical cords with furcate insertion in our patient population ranges from 3cm to 95cm with the median at 45cm (SD=16.58; 95% CI 41.62;48.69).

We evaluated the median lengths of the gestational weeks 39 to 42 and could observe, after comparing our results with data from Georgiadis L. et al., that the average umbilical cord in furcate cord insertion appears to be shorter than in the average population (84).

Gestational week/Gender	Data furcate cord insertion Median in cm/Coefficient of variance		Georgiadis L. et al Median in cm/ Coefficient of variance (84)	
42/male	52	0.14	61.2	0.21
42/female	44	0.27	59.7	0.21
40/male	51	0.36	60.1	0.21
40/female	50.5	0.26	57.7	0.21

Tab. 5.1. Comparison of umbilical cord length

Regarding the insertion of the furcate cord insertion, we observed an association with the marginal cord insertion, which was observed in 25% of our cases. Ebbing et al. described in a population-based study the prevalence to be around 6.3% (58). With this high number of a marginal cord insertion in furcate cord insertion, it can be hypothesized that trophotropism might also play a role in the pathogenesis of the furcate cord insertion (1).

In two out of the three cases of intrauterine fetal death caused by the furcate cord insertion, the insertion was a marginal insertion. Additionally, in one of these cases, an ectasia with thrombosis of the umbilical vein was observed. In the third case, the insertion was eccentric. The length of the furcate cord insertion in these cases was above average, with an average length of 6.6cm (SD=6.38). After analyzing our data, we found that abnormal findings regarding the umbilical cord such as an ectasia or thrombosis of the umbilical vessels and an above-average long furcate cord insertion increase the risk for an adverse outcome in furcate cord insertion.

In the next section, the data from our series is compared to the data that is available from the 18 cases in the literature.

The median birthweight from the cases in the literature is 3220g (SD=834.98; 95% CI 2568. 07;3850.37) compared to 3390g (SD=659.82; 95% CI 3242.81;3511.64) in our cases.

The median length of the furcate cord insertion in the cases in the literature is four centimeters (SD=1.98; 95% CI 3.36;6.41) compared to the median furcate length in our cases which is three centimeters (SD=2.09; 95% CI 2.50;3.44).

The site of insertion in the literature was in 60% a central or eccentric insertion whereas 40% have a marginal furcate cord insertion. In our cases, 75% had a central or eccentric insertion and the marginal insertion was observed in 25,0% of the cases.

A single umbilical artery is associated with a pathological umbilical cord insertion as described by Leung et al and Suzuki et al. In all pregnancies the incidence of a SUA lies around 1%. In our collective of patients, it was observed in 3.1% of the cases and therefore is associated with the furcate cord insertion as well (37, 40).

The median gestational week at birth in the literature lies at 40 (SD=3.14; 95% CI 36.47;41.30) compared to 40 weeks of gestation (SD=2.99; 95% CI 39.12; 40.33) in our case series as well.

In the literature IUFD is reported in 6 out of the 18 cases. In three of those cases, the death can be directly linked to the furcate cord insertion with a rupture of umbilical vessels as the cause of fetal demise. In our 132 cases, we have 7 cases of an intrauterine fetal death linking the cause of death to the furcate cord insertion in three cases as well. In two of those cases also a rupture of the umbilical vessels occurred. A thesis investigating the cases of intrauterine fetal deaths at the Virchow Clinic, a level one perinatal center with a high rate of risk pregnancies, found the general risk for intrauterine fetal death to be at 0.52% (85). Therefore, with a risk of 1.0% in the case of a furcate cord insertion, an increased risk for this insertion anomaly is seen.

In some cases, even though the furcate cord insertion could not be identified as the cause of death, it still might have played a role in the fetal demise. Due to the loss of the Wharton's jelly and the separation of the vessels, twisting can occur more easily than in normal umbilical cords. This possibly can represent the cause for intermittent pathological NSTs and could be a contributing factor to the IUFD.

In the next section, the optimal time of delivery in the case of suspected prenatal furcate cord insertion is discussed. Fujita et al. counseled the patient to induce labor at 37 weeks of gestation to reduce the risk of sudden intrauterine death. Apart from this, no further recommendations regarding the optimal time for birth to avoid risk for the fetus are found in the literature.

From the data of this case series, the week of gestation in cases of intrauterine fetal death ranges from 22 to 40 weeks of gestation with the median at 39 (SD=7.01).

In the cases in which the furcate cord insertion supposedly played a significant role in the fetal demise, the gestational week of intrauterine fetal death ranges from 36 to 40 weeks of gestation with the median at 39 (SD=2.08).

In this group, only one case of fetal death occurred before 37 weeks of gestation, being a case with a venous ectasia and thrombosis of the umbilical vein as a result of a furcate cord insertion. After recurring pathological NSTs cesarean section was recommended but declined by the patient and an IUFD was observed.

Therefore, in cases of a suspected isolated furcate cord insertion without other complications such as an aneurysm, ectasia or thrombosis of the umbilical vessels, it is recommended to plan delivery at 37 completed weeks of gestation to avoid prematurity but to also avoid the risk of intrauterine fetal death as a complication of the furcate cord insertion. In case of additional sonographic abnormalities, the patient should be advised to have an even earlier delivery.

From Fujita et al., we know that the visualization of the furcate cord insertion with the separation of the umbilical vessels inserting around the center of the placenta is possible (72). This might justify examining the umbilical cord and its insertion more accurately as this could reveal further anomalies, increasing the risk for the fetus and changing obstetrical management as mentioned above.

To summarize, the furcate cord insertion indeed is a very rare anomaly of the umbilical cord leading to intrauterine fetal death in around 1% of the cases. Apart from this risk, the fetal and maternal prognosis is good. However, in our data we could observe a slight correlation with a lower number of 5min Apgar Scores nine and ten, manual removal of the placenta and the HELLP syndrome. Prenatal diagnostics of the furcate cord insertion has only been reported twice due to the rarity and the ignorance of this insertion anomaly. Even though bad outcome is rare, the risk for it might be reduced by taking a closer look at the insertion of the umbilical cord sonographically. If a separation of the umbilical vessels and very thin umbilical vessels with a central, eccentric or marginal insertion are observed, a furcate cord insertion should be suspected. There should be follow up visits with the patient to look for thrombosis, ectasia or aneurysm of the umbilical vessels, as this can increase the risk for the fetus. Finally, after completing 37 weeks of gestation or earlier in the case of further sonographic abnormalities of the umbilical cord, delivery should be planned to reduce the risk for the fetus.

6. Appendix

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6.2. List of figures

6.3. List of tables

6.4. List of abbreviations

ANP = atrial natriuretic peptide

IUFD = Intrauterine Fetal Death

IUGR = Intrauterine growth restriction

n.a. = not available

NICU = Neonatal intensive care unit

NPY = neuropeptide Y

NST = Non Stress Test

PGI_2 = Prostaglandine I_2

PGE_2 = Prostaglandine E_2

SUA = single umbilical artery

5-HT = 5-hydroxytryptamine

6.5. Eidesstattliche Versicherung

„Ich, Dr. med.univ. Philipp Kosian, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Furcate cord insertion of the umbilical cord: Pathological and clinical characteristics in 132 cases and a review of the literature selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)" des ICMJE -*www.icmje.org*) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o) und werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst."

06.09.2018   Unterschrift

6.6. Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

6.7. Acknowledgment