Placenta pathology associated with maturation abnormalities and late intra uterine foetal death.

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The placenta is the fastest growing organ of the human body. The placenta grows from a single cell to approximately $5x10^{10}$ cells in 38 weeks. A good blood supply from maternal blood via the spiral arteries to the placenta is not only very important for the foetus but also very important for normal development of the placenta. The maternal blood is supplied to the placenta by spiral arteries. Approximately 100-150 spiral arteries are formed and 50 to 200 veins are present to return the blood to the maternal circulation (see Pijnenborg on page 185-212 in 1 and 2-6).

The normal placenta parenchyma is divided into 10-40 lobes or lobules separated by grooves or septa. These interlobular septa usually do not reach the chorionic plate or foetal surface. In the centre of each lobule one or several spiral arteries can be found. From the chorionic plate 60-70 foetal stem vessels can be seen. Each stem vessel supplies a villous tree. The architecture of the villous tree changes dramatically during gestation (see for an excellent overview of the changes during gestation 7). During the first twelve weeks of development the placenta consists of mesenchymal villi. After this period subsequently stem or anchoring villi, immature intermediate, mature intermediate and terminal villi are formed. The terminal villi can be recognised by the presence of syncytio-vascular membranes. The development of syncytio-vascular membranes in the third trimester is very important to provide the foetus with adequate amounts of oxygen. Oxygen reaches the foetal blood by diffusion and the concentration of foetal oxygen is highly dependent upon the distance between maternal and foetal blood. An increase in the diffusion distance by 2 decreases the oxygen content by four. The terminal villi have small capillaries that lie immediately below the syncytio-trophoblast surface, the so-called syncytio-vascular membranes where the actual foeto-maternal exchange takes place. The syncytio-vascular membranes can be recognised by the anuclear surface of the syncytiotrophoblast directly opposite to the vessel wall. Immature intermediate villi can be

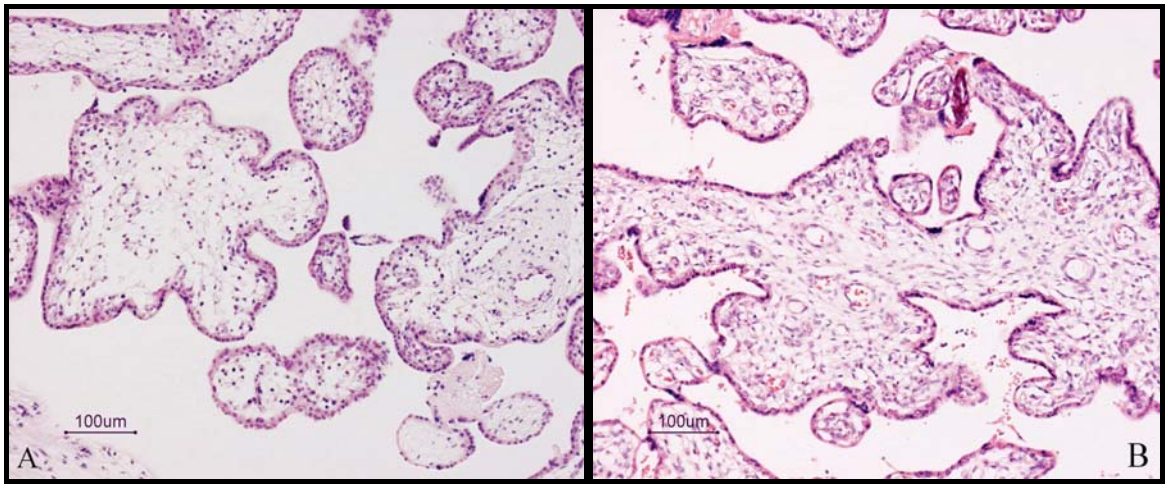


Fig. A normal placenta at 13 weeks and fig. B at 23 weeks. In the second trimester the placenta parenchyma consists of immature intermediate villi with some formation of mature intermediate villi. The villi show the largest variation in diameter and form. Note the increase of the fibrous central core in the stem villi with increasing gestational age and decrease of mesenchymal stroma.

recognised by their fine reticular connective tissue with Hofbauer cells (the macrophage of the placenta). In the first weeks of development the whole placenta consists of mesenchymal villi and after approximately 12 weeks immature intermediate villi are formed. Immature intermediate villi are normally no longer present after 24 weeks of pregnancy. In a mature placenta the main stem of the villous tree (stem or anchoring villus) is connected with the chorionic plate and consists of dense fibrous tissue with large arteries and veins with a clearly recognisable muscular layer. The trophoblast lining of the stem villi is slowly replaced by fibrin during development, at term hardly any trophoblast is present. The anchoring villi

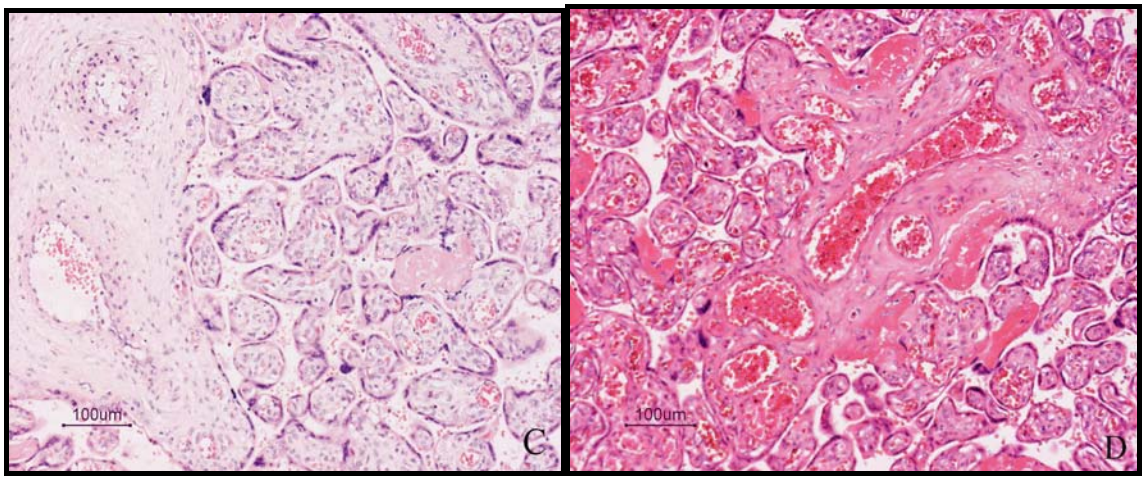
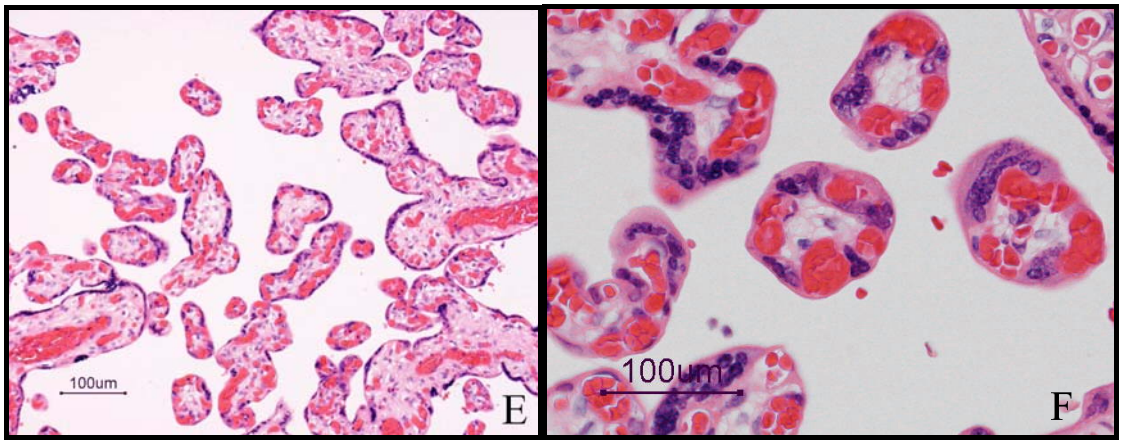


Fig. C shows a normal placenta at 27 weeks and fig. D a normal placenta at 35 weeks of gestational age. There is a decrease in villous diameter and the anchoring villi are partially covered with fibrin.

connect the stem villi with the basal plate. Mature intermediate villi are the connection between the stem villi and the terminal villi. These mature intermediate villi have vessels without a histologically recognisable muscular layer and have a continuous lining with trophoblast. Under normal conditions terminal villi can be recognised from 30-32 weeks onwards and around term 40% of the placental villi consists of these terminal villi (7).



and fig. E and F normal placenta at 40 weeks of gestational age. Terminal villi are formed in the third trimester. At 40 weeks of gestational age 40% of the villous volume are terminal villi. Terminal villi can be recognised by the syncytio-capillary membranes. Anchoring villi are covered with fibrin.

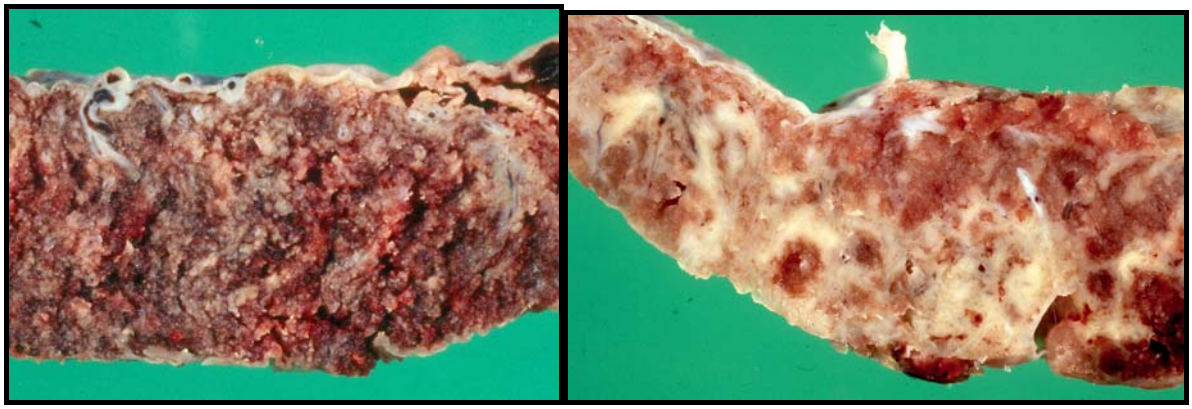
Abnormal maturation can be seen in several different conditions. Accelerated maturation i.e. premature formation of terminal villi can be seen as a reaction or adaptation of the placenta to a decreased materno-placental perfusion. Histologically it can be recognised by a decrease of villous diameter and by accelerated formation of syncytio-vascular membranes. Failure of the second phase of trophoblast invasion of the spiral arteries is generally believed to give rise to several pregnancy induced hypertensive disorders of pregnancy e.g. pre-eclampsia. In general a small placenta will be found and the foetus will be (severely) growth restricted. If a spiral artery becomes occluded an infarct of the placental parenchyma is observed. In a normal placenta up to 30% of the placental volume can be infarcted before the foetus dies but in a small placenta sometimes 5 % is enough to cause intra-uterine foetal death. A table of normal placental weight with percentiles was published in Ped.Pathol.Lab.Med. 16; 901-7, 1996. Accelerated maturation can be seen also in twin or triplet placentas and it can be seen in the recipient part of a monochorionic twin placenta in cases with mild to severe twin-transfusion syndrome, i.e. it can also occur in association with hyper viscosity of foetal blood. Delayed maturation can be seen in several different clinical situations. It is well known in association with maternal diabetes but it can be seen also in macrosomic placentas in mothers without diabetes (8). It can be observed in association with congenital and/or chromosomal anomalies, with chronic villitis of unknown etiology (VUE), in the donor part of a monochorionic placenta with twin-transfusion syndrome, in placentas from foetuses with anaemia, low colloid osmotic pressure or decompensatio cordis. Furthermore, it is observed in placentas with defective placental maturation a defect of unknown cause that results in a severely decreased formation to complete absence of terminal villi. In all these circumstances were the placenta can not provide the foetus with enough oxygen an increase of nucleated red blood cells can be seen (NRBCs). An increase in NRBCs in the foetal circulation is the consequence of either anaemia or hypoxia usually of at least 6-12 hours duration. It is the reaction to an acute elevation of erythropoietin in response to hypoxia followed by increased erythropoiesis with premature release of NRBCs in the blood. Increased erythropoiesis usually lacks behind a few days after the insult. The presence of NRBCs in more than two capillaries in a random 10x field is a mild elevation and NRBCs in a majority of capillaries is a marked elevation (1).

In a recent article from Horn et al (9) they studied the cause of death in 310 consecutive autopsies of intra uterine foetal death in the university hospital Leipzig. The placenta or umbilical cord was responsible for IUFD in 62%. Almost 40% of these 62% was due to utero-placental pathology, 23% was due to abnormal maturation of the parenchyma and 17% was caused by a congenital anomaly. So, several typical placental abnormalities not related to disturbed utero-placental blood flow can cause late intra-uterine foetal death and most of these abnormalities are related to an increased distance or absent decrease between the maternal and foetal blood compartment. Especially late in pregnancy (after 34-36 weeks) when the placenta hardly grows an increase in oxygen transport is achieved by a decrease in diffusion distance i.e. by the formation of terminal villi with syncytio-vascular membranes. In particular adequate oxygen supply to the foetus is dependent on diffusion and the formation of these syncytio-vascular membranes. Some of these entities are discussed below.

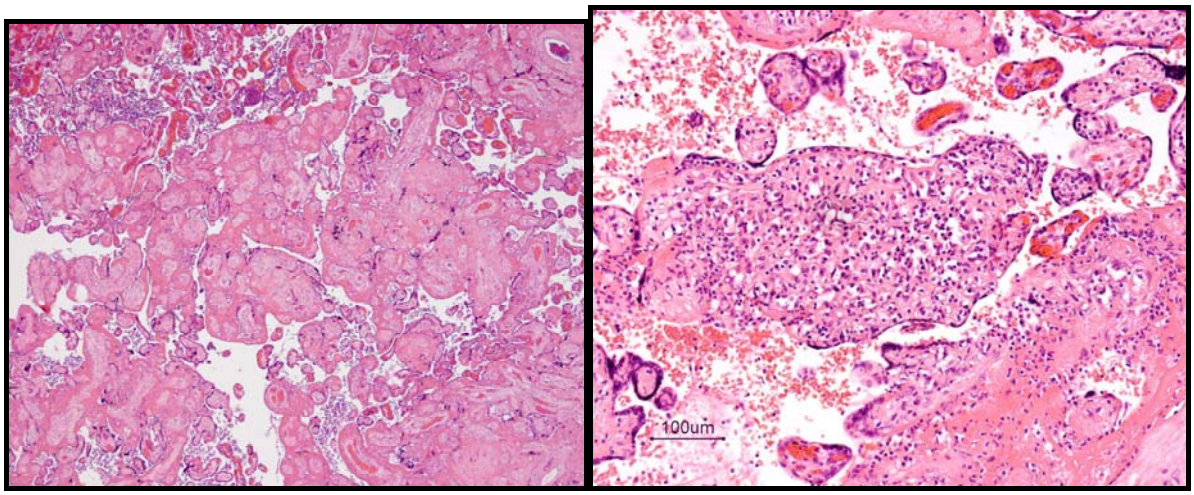
Massive fibrin depositions

Massive fibrin depositions in the placenta are known under several different names i.e. maternal floor infarct, massive perivillous fibrin depositions or gitter infarct. The fibrin depositions are surrounding the terminal villi and thereby decreasing the surface area necessary for normal exchange of nutrients and oxygen. The cause of these fibrin depositions is not known. It is not a post-mortem artefact. It has been suggested that immunological

abnormalities may be responsible for this condition. In some of these cases it is related with chronic villitis. There is a recurrence risk in subsequent gestations. The condition is difficult to detect during intra-uterine life, it is associated with growth restriction, usually with normal Doppler flow characteristics. In some cases a high level of alfa-fetoprotein can be found. In addition with growth restriction there is also an increased risk of cerebral damage resulting in mental retardation (1, 10).



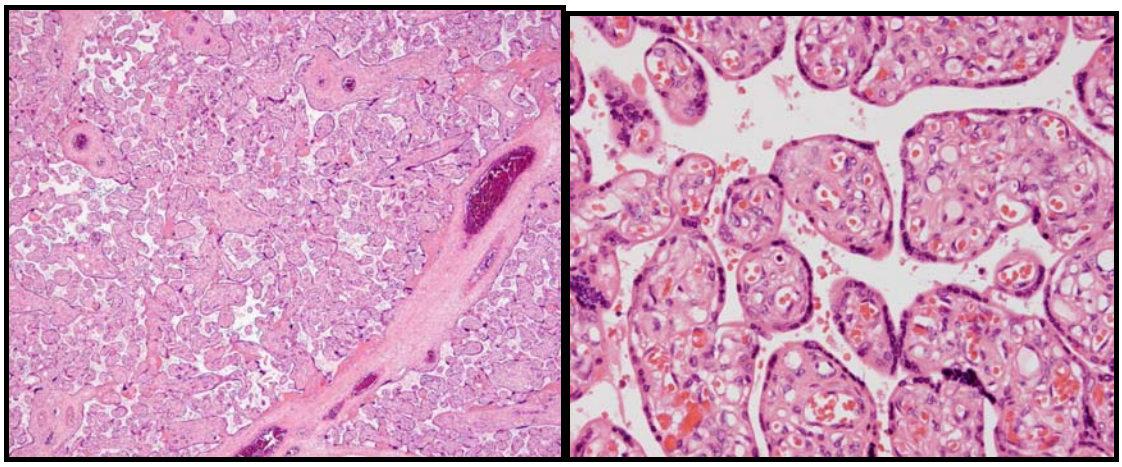
Two different macroscopical pictures of massive perivillous fibrin depositions.



Microscopical appearance of massive perivillous fibrin depositions without (left) and with severe villitis of unknown origin (right).

Defective placental maturation

Another abnormality known under several different names associated with late intra-uterine foetal death is delayed maturation of the terminal villi, defective placental maturation or probably also terminal villi deficiency (2,11). This abnormality is the result of abnormal or absent formation of terminal villi and absence of the formation of syncytio-vascular membranes and decreased formation of capillaries. This abnormality occurs after 34-35 weeks of pregnancy and cannot be diagnosed before this pregnancy duration. The formation of terminal villi with syncytio-vascular membranes and the increase in capillaries is essential for the increased demands of the foetus during the last 6-8 weeks of pregnancy. Especially oxygen delivery to the foetus is dependent on diffusion and the diffusion distance is decreased by formation of these syncytio-vascular membranes in the last weeks of pregnancy. During this period the placenta hardly grows and the formation of terminal villi is essential. This



Low and high power microscopical picture of two placentas of 38 and 39 weeks of gestational age with defective placental maturation, note the monotonous pattern of villi and the absence of terminal villi with syncytio-vascular membranes (compare with figure E and F.

abnormality of the placenta does not give rise to growth restriction but in the last few weeks of intra-uterine life it can give rise to foetal hypoxia. In the foetal circulation from foetuses with this placental abnormality a severe increase of nucleated red blood cells can be found as a sign of foetal hypoxia. There is an increased risk of recurrence in subsequent pregnancies. Compared with normal placentas there is a 70 times higher risk of intra-uterine foetal death in placentas with this maturation defect and the risk of recurrence stillbirth is tenfold. This maturation defect is not associated with maternal diabetes. In a population survey it was demonstrated that the incidence of this delayed placental maturation was 5% (11).

Maternal diabetes

It is well known that maternal diabetes is associated with increased perinatal morbidity and mortality (increased incidence of congenital anomalies, macrosomia and intra-uterine foetal death). The placenta shows several histological abnormalities of the placenta like immaturity and hydropic changes of the chorionic villi, increased fibrinoid necrosis and chorangiosis. Despite good glycemic control these abnormalities can still be found (12). The immaturity of the villi and decreased formation of terminal villi also results in a less decreased diffusion distance with similar detrimental effects as described for the other two above mentioned disorders. These placenta abnormalities however, are not specific and recently it was demonstrated that similar histological features could be found in placentas from large-for-gestational age infants from non-diabetic mothers. In the same study it was demonstrated that intra-uterine foetal death and asphyxia were associated with a relative low placental/foetal weight ratio again indicating that a decreased surface area for diffusion or increased diffusion distance can lead to late intra-uterine foetal death (8).

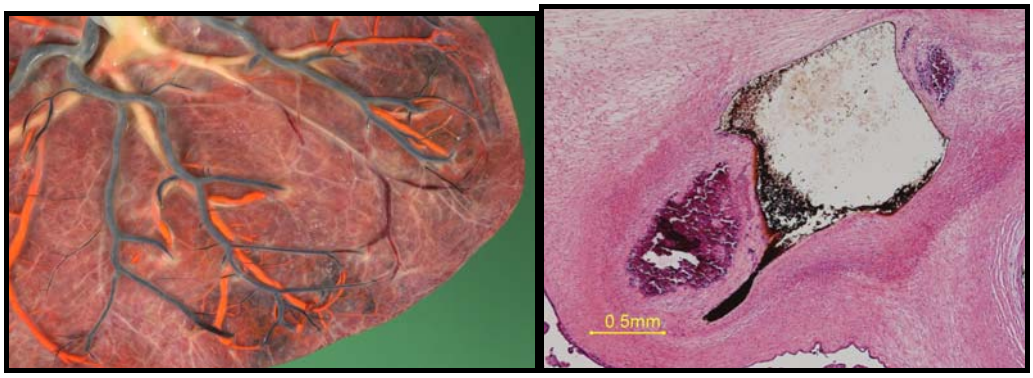
Chronic villitis

Severe chronic villitis recognizable as a severe infiltrate of lymfocytes and macrophages in the chorionic villi can be associated with perinatal death. Sometimes specific abnormalities can be found e.g. viral inclusion bodies. The villi are also recognizable by degeneration of the trofoblastic lining with fibrin depositions and loss of vessels in the villous stroma. These histological abnormalities can be found in association with cytomegalovirus, toxoplasmosis, rubella and syphilis. When no cause can be found this histological abnormality is known as villitis of unknown etiology. Chronic villitis has a high recurrence risk in subsequent pregnancies up to 27 % (2,14,15). In cases with severe villitis there is also a decreased surface

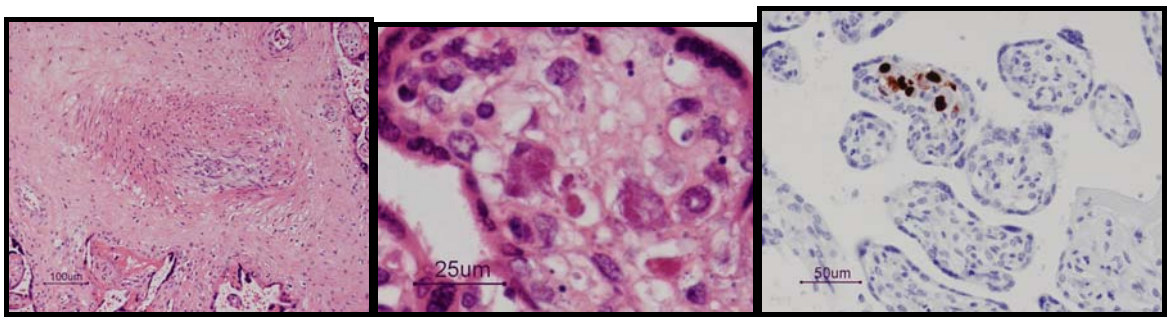
area for diffusion that can lead to late intra-uterine foetal death. See for a microscopic example of a villitis of unknown aetiology the last picture in the chapter of massive perivillous fibrin deposition.

Foetal thrombotic lesions

Thrombosis of foetal vessels can be recognised both macroscopically as well as microscopically. The macroscopically visible lesions consist of whitish sharply demarcated lesions with a triangular appearance usually with a sharp point projecting to the foetal surface. Microscopically it consists of large groups of avascular fibrotic villi as the result of foetal vessel thrombosis. They are the result of lack of foetal perfusion. Infarcts are the result of decreased or absent maternal perfusion. Small groups of avascular villi (scored as a group of



Macroscopical and microscopical picture of partial trombosis of chorionic plate veins (injected with an orange coloured dye). The white colour of the vessels is due to calcification of the vessel wall due to long before delivery occurring trombosis.



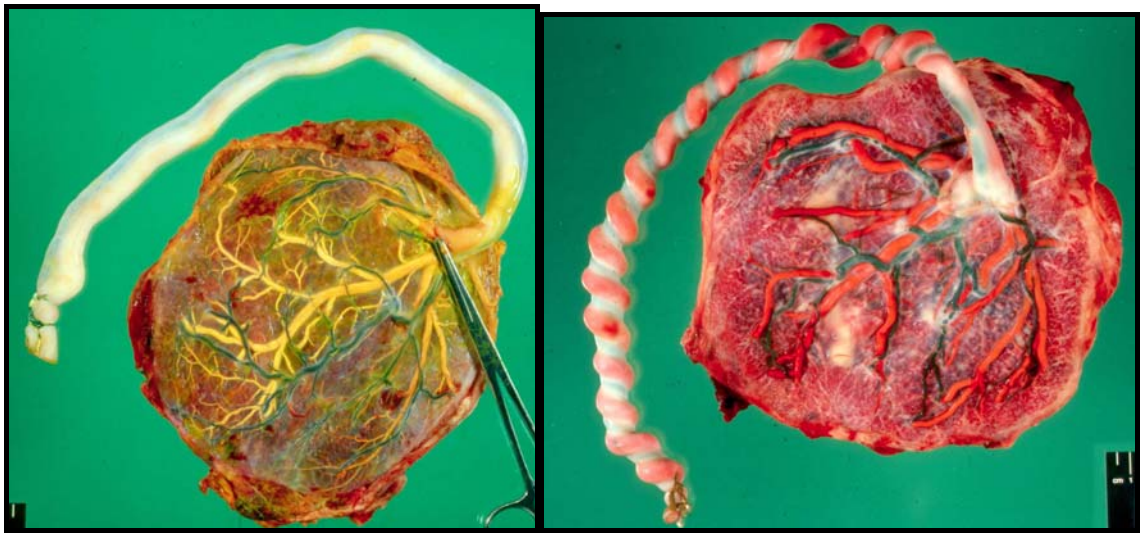
Example of recent trombosis associated with a CMV villitis and vasculitis.

at least 5 avascular fibrotic villi without inflammation or mineralization) as the result of minor foetal vessel thrombosis are not uncommon. In a normal population the incidence reaches 5-10 %. In placentas with an overcoiled cord it is approximately 20 % and in a group with pre-eclampsia with or without trombophilia and in diabetics it is approximately 20%. In placenta from LGA infants without maternal diabetes it was 44% (8,16). An increased incidence is also described in foetuses with several coagulant disorders, antiplatelet antibodies and hypercoagulability disorders. It has been associated with IUGR, IUFD, hydrops and asphyxia. Meconium could also give rise to thrombosis by focal degenerative vessel wall lesions (1).

Umbilical cord

One recently observed association with intra uterine foetal death is an umbilical cord with abnormal coiling. From the literature it is known that abnormal cord coiling is associated

with severe perinatal morbidity and mortality (17-25). Overcoiling (i.e. a coiling index of 0.3 or more; 3 or more coils per 10cm) and undercoiling (i.e. a coiling index of 0.1 or less; 1 or less than 1 coil per 10 cm) is associated with foetal demise, foetal intolerance to labor intra-



Placentas with an umbilical cord with undercoiling (left) and overcoiling (right).

uterine growth restriction and chorioamnionitis. Abnormal cord coiling was also associated with chorionic plate vascular thrombosis. In a study of the author from 565 umbilical cords the coiling index was determined and correlated with clinical outcome. In the majority of cases with intra-uterine death were no explanation was found for the intra-uterine death an undercoiled or overcoiled cord was found. It is suggested from this study and others (20) that abnormal cord coiling has a remarkable high association with unexplained death and it is tempting to speculate that abnormal cord coiling may have serious effects on foetal well-being and is probably the cause of foetal death in some cases. Umbilical cord coiling is not a standard measurement in pathology departments and it could well be that the so far unexplained intra-uterine foetal deaths, in some series up to 36-50 %, are caused by abnormal cord coiling.

It can be concluded that there are a lot of abnormalities and developmental disturbances in both umbilical cord and placenta, as mentioned above, which are responsible for late intra uterine foetal death. Several of these abnormalities are not well known or only recently described and it can be expected that the previously mentioned rate of unexplained intra uterine foetal death, up to 36-50 % in some series will decline to values below 5-10 % (26-28).

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