The Placenta

4

T. Yee Khong

The placenta and extraplacental membranes are an apposition of fetal and maternal tissues for the purposes of physiological exchange. The placenta has a finite life span and is the body's largest biopsy and yet its examination is often neglected, even in cases of fetal and neonatal deaths, of sick and premature neonates, and some maternal complications of pregnancy. Placental examination has also assumed an important role in litigation, commonly when there is perinatal death, fetal distress, or alleged cerebral hypoxia [1]. Recent monographs on placental pathology, including the Dublin Definitions [2], have helped with a better understanding of its examination and pathology [3–5].

Indications for triaging placentas and examination balancing likelihood of clinically relevant histopathological findings from placental examination with workload and resources were summarized [6], incorporating guidelines from the College of American Pathologists [7] and Royal College of Pathologists.(**Table 4.1**) [8] Interests of the local clinicians and pathology departments may also influence which placentas are sent for pathological examination. Poor compliance with guidelines is prevalent, however [9].

Placentas are often submitted for pathological examination with incomplete or absent clinical information [9]. A systematic topographical approach to its examination ensures that lesions are not missed but macroscopic and microscopic placental findings are contextual and clinical correlation is important before significance is ascribed. Similarly, the clinical context may provide clues to look for lesions that cluster with some clinical conditions.

Placentation and placental pathology in multiple pregnancy are detailed in Chap. 14.

Table 4.1 Triage system for dealing with placenta submitted to the pathology department [6]

Full examination including histology
Stillbirth (antepartum or intrapartum)
Late miscarriage
Severe fetal distress requiring admission to NICU (pH<7.21, scalp lactate >4.8 mmol/l or Apgar <7 at 5 min)
Prematurity (less than 30 week gestation)
Fetal hydrops
Morbidly adherent placenta
Fetal growth restriction (birth weight below first centile)
Full examination—histology taken but only examined if further clinical indication/on request of clinician
Fetal growth restriction (birth weight below third centile)
Maternal pyrexia[a]
Placental abruption[a]
Fetal abnormality[a]
Rhesus (and other) isoimmunisation requiring in utero transfusion[a]
Maternal coagulopathy[a]
Maternal substance abuse
Macroscopic examination—no histology (placenta retained for 2 weeks after examination)
Twins or other multiple pregnancy (uncomplicated)[a]
Abnormal placental shape (if clinically relevant)
Two vessel cord, etc.[a]
Storage for 2 weeks (no examination) - A report indicating that the placenta has been received and is being stored without examination may be sent to the referring clinician depending on local agreement/policy
Prolonged rupture of the membranes (more than 36 h)
Prematurity (30–36 weeks)[a,b]
Gestational diabetes[a]
Rhesus-negative mother (no fetal anemia)[a]
Maternal group B streptococcus
Uncomplicated preeclampsia/maternal hypertension[a]

[a]These conditions are considered indications for full examination by CAP guideline [7]
[b]Prematurity <34 weeks in CAP guideline [7]
NICU neonatal intensive care unit

T. Y. Khong (✉)
Women's and Children's Hospital, Anatomical Pathology, SA Pathology, Adelaide, Australia
e-mail: yee.khong@adelaide.edu.au

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4.1 Development of the Placenta

4.1.1 Early Development

Fertilization of the ovum usually occurs in the ampullary region of the fallopian tube. Cleavage begins at once and by 3 days after fertilization a cluster of twelve cells, called a morula, is formed, which enters the uterine cavity with the endometrium being in the luteal phase. Fluid then accumulates within the morula and trophoblast differentiation results in the formation of the blastocyst, which begins to attach to the uterine mucosa about 6 days following fertilization.

During the second week the outer layer of the blastocyst proliferates to form the trophoblastic or chorionic shell while the inner layer differentiates into a bilaminar embryonic disc, which then separates from the trophoblastic layer by the formation of a cavity that ultimately becomes the amniotic space. The primitive trophoblast differentiates into an inner layer composed of mononuclear cells known as the cytotrophoblast and an outer layer consisting of multinucleated cells known as the syncytiotrophoblast. Intercommunicating fluid-filled spaces appear in the rapidly enlarging trophoblastic mass from the 8th day. These coalesce to form a lacunar system that opens into maternal sinusoids, presumably derived from endometrial capillaries. With the involvement of more capillaries and, later, venous sinusoids the lacunae fill with maternal blood and endometrial glandular secretions to form a primitive intervillous space.

Invasion of the endometrium, which began on the 7th day after fertilization, is completed by the 12th day. A plug of blood clot and cellular debris covers the initial site of implantation but by the 12th day the endometrial epithelium is reconstituted resulting in an interstitial implantation.

The endometrial stromal cells around the conceptus enlarge and accumulate glycogen and lipid. The vascular and glandular changes in the endometrium together with the stromal cellular changes are known as the decidual reaction and soon spread to involve the entire endometrium. Until the 4th month of gestation three regions of the decidua are identified according to their relation to the implantation site. The decidua basalis is the part underlying the conceptus; the decidua capsularis is the superficial portion of the decidua overlying the conceptus. and the remainder of the uterine cavity is lined by the decidua parietalis or decidua vera (**Fig. 4.1**).

The last two days of the 2nd week are characterized by the appearance of chorionic villi. Columns of syncytiotrophoblast incompletely separate the lacunae from each other. Although the system is labyrinthine rather than villous and none of the trabeculae have free ends, nevertheless they are called primary villous stems. They possess a central core of cells derived from proliferation of cytotrophoblast at the chorionic base. With continuing development and expansion

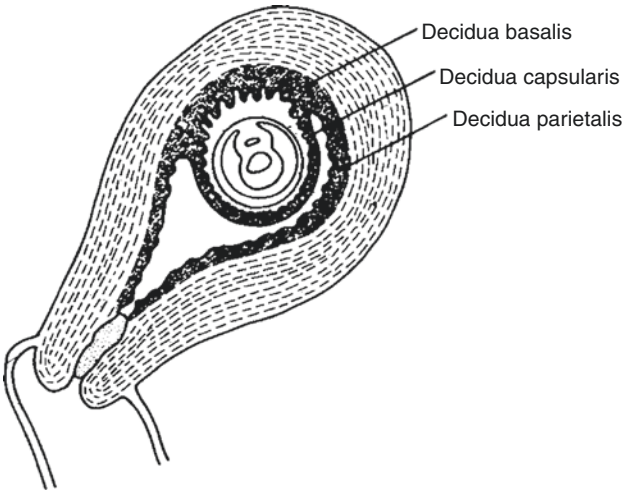

Fig. 4.1 Development of the decidua in early pregnancy

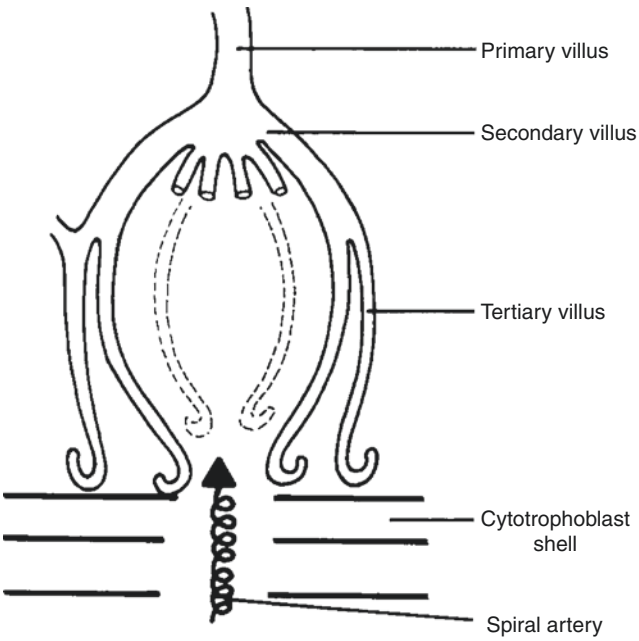

Fig. 4.2 Structure of a functional placental circulatory unit

of the implantation site, the primary villous stems increase in length and their cytotrophoblastic cells extend distally toward the attachment of the syncytium to the endometrium (**Fig. 4.2**).

During the 3rd week after fertilization, the bilaminar disc is converted into a trilaminar embryo composed of the three definitive germ cell layers. It also includes the development of the primitive streak, notochord, and somites. The primary villi develop mesenchymal cores, converting them into secondary villi, which then branch and cover the entire surface of the chorionic shell. Differentiation of the mesenchymal cells into vascular capillaries converts the villi into tertiary villi. These villous vessels soon become connected with the

embryonic heart via vessels that differentiate in the mesenchyme of the chorion and connecting stalk. By the end of the third week, completion of the development of arteriocapillary–venous network within the villi and contraction of the embryonic heart result in a true embryonic and villous circulation. Prior to establishment of the uteroplacental circulation, nutrition to the developing conceptus is histiotrophic, being derived from secretions from the endometrial glands.

Concurrent with the development of the secondary and tertiary villi, cytotrophoblastic cells derived from the tips of the villi break through the syncytiotrophoblastic layer and expand laterally to meet and fuse with adjacent columns to form a cytotrophoblastic shell that completely surrounds the conceptus. Thus, the primitive syncytium is split into an inner layer, the definitive syncytium, and an outer layer separating the cytotrophoblastic shell from the decidua. The outer layer eventually degenerates, being replaced by fibrinoid material known as Nitabuch's layer.

4.1.2 Development of the Definitive Form

During the 4th to 8th week, the embryo develops limbs and all internal organs are formed. By the end of the 16th week the external genitalia are well defined and ossification has commenced. During this period the placenta attains its definitive form and thereafter undergoes no further major modifications.

Rapid circumferential extension of the implantation site follows establishment of the cytotrophoblastic shell. The intervillous space expands and the primary stem villi now branch. Like their predecessor, these branches initially consist of syncytiotrophoblast but are rapidly invaded by cytotrophoblast, mesenchymal core, and fetal vessels.

Initially the entire chorion is villous, but differential growth results in the formation of the definitive placenta. The villi on the surface of the chorion adjacent to the decidua basalis continue to proliferate to form the chorion frondosum, which becomes the definitive placental parenchyma. The villi of the decidua capsularis regress, leaving a smooth relatively avascular area known as the chorion laeve, accompanied by the loss of associated intervillous space in this area. As the conceptus enlarges, the chorion laeve bulges into the uterine cavity to fuse with the decidua parietalis at about the 4th month of gestation, thus obliterating the uterine cavity.

During this period there is some regression of the cytotrophoblastic elements in the cytotrophoblastic shell and chorionic plate, but remnants of cells are found in the former location to form the cytotrophoblastic cell islands in the layer of Nitabuch. Cytotrophoblast derived from these remnants in the cytotrophoblastic shell and from tips of anchoring villi continue to migrate into the decidua basalis and myometrium to play a key role in the development of the uteroplacental circulation (vide infra).

The chorion frondosum continues to grow rapidly. Placental septa first appear in the 3rd month of gestation. The septa are formed partly as a result of differential growth of villi relating to a given stem villus with compression of decidua in the regions where villous growth is more vigorous, and partly by the pulling up of the basal plate into the intervillous space by relative diminished growth of some anchoring villi.

By the end of the 4th month of pregnancy the placenta has attained its definitive form. Growth continues by further arborisation of the stem villi and production of new villi. The proportion and size of the fetal components of the placenta increase as gestation proceeds. There is continuous growth until term, although the rate of increase gradually decreases from approximately 34 to 36 weeks gestation. Morphometric studies indicate that the villous surface area continues to increase till term while the quantity of DNA as an indicator of nuclear (not cell) number in the placenta continues to rise linearly until term.

4.1.3 Mature Placenta

Macroscopically the placenta shows wide variation in shape, size, and weight. The fetal surface is normally shiny and bluish. The most superficial layer is the amnion through which large vessels running to the umbilical cord insertion are seen. Arteries and veins may be distinguished as arteries lie superficially to the veins. A small white plaque, the yolk sac remnant, is commonly seen beneath the amnion surface. Insertion of the umbilical cord is variable. The chorionic plate lies beneath the amnion. Subchorionic fibrin deposition is variable and may obscure the subchorial lake. Blood vessels course perpendicularly through the chorionic plate toward the decidua. Beneath the chorionic plate lie chorionic villi and the intervillous space. The floor of the placenta is formed by the basal plate to which remnants of the maternal decidua may be adherent. The basal plate or maternal surface is loosely divided into 15–20 cotyledons, which are demarcated by septa. Extraplacental membranes extend from the lateral margin of the placenta and form, in utero, a closed cavity containing the fetus and approximately 500 ml of amniotic fluid. Calcium deposition is commonly seen near term and is usually at or near the maternal surface.

4.1.4 Villous Structure: Vasculature and Histology

Each primary stem villus gives off several secondary stem villi, each of which forms a lobule by division into ter-

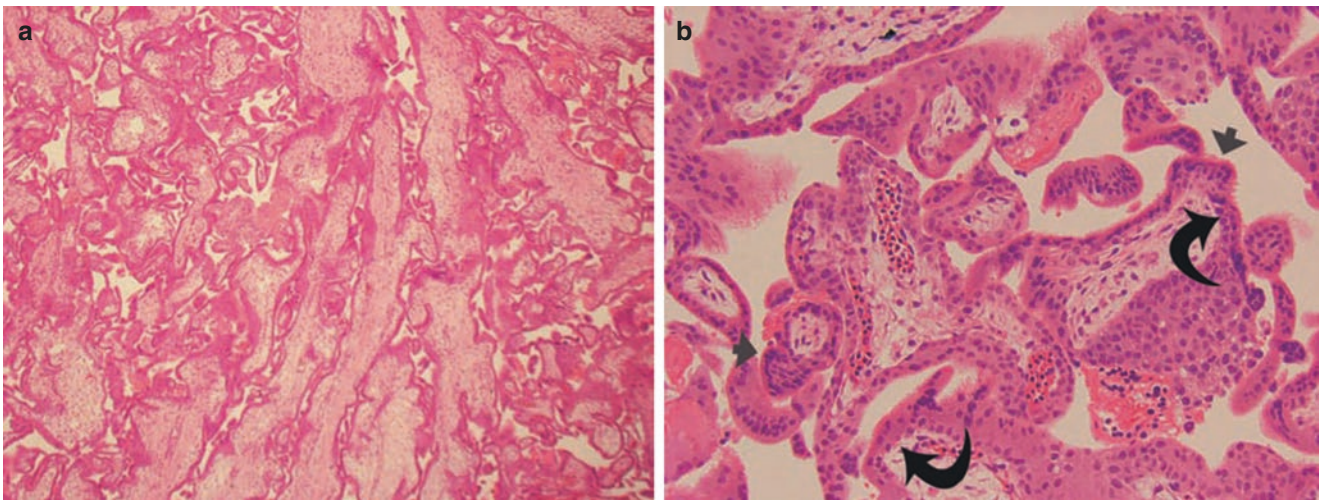

Fig. 4.3 (**a**) Placental villi at 8 weeks gestation. (**b**) High-power view showing trophoblastic sprouts (arrowhead), prominent cytotrophoblast layer (curved arrows), and nucleated fetal red blood cells within the vessels

tiary stem villi that are arranged in a circular manner running toward the basal plate and leaving a central, relatively villus-free area in the center of the lobule. The tertiary stem villi turn back from the basal plate and break up into terminal villi (**Fig. 4.3**).

The intermediate villus has been proposed as an additional type to the stem and terminal villi. The stem villi, responsible for the mechanical stability of the villous tree, is defined on the basis of containing blood vessels with media. Branches arising from these stem villi are either smaller stem villi or intermediate villi. Intermediate villi are defined on the basis of a reticular stroma with vessels lacking media and are located between the stem and terminal villi. Two types of intermediate villi are distinguished: the mature intermediate villus, seen in the mature placenta, which is slender and bears a large number of terminal villi, and the immature intermediate villus, which is thicker and with fewer terminal villi arising from its surface. The immature intermediate villus corresponds to the immature villus that were thought to be not yet fully developed terminal villus. In the schema of this classification, as pregnancy progresses, the number of immature intermediate villi is reduced with only a few persisting to term, tending to be in the centers of functional placental circulatory units acting as growth centers, and the growth of the placenta slows down accordingly.

The terminal villi are final branchings of the villous tree and are the sites for maternofetal and fetomaternal exchanges.

In early pregnancy the villi are relatively few and large (approximately 170 μm in diameter). There is a regular double layer of trophoblast, the outer syncytiotrophoblast and inner cytotrophoblast (Langerhans' layer) enclosing a loose stroma. At this stage fetal capillaries are small and centrally placed. The villous core also contains stellate mesenchymal and Hofbauer cells, the latter acting as fetal macrophages. As pregnancy and placental growth proceed, new terminal villi form by the development of trophoblastic sprouts, which are then invaded by stroma and fetal capillaries. Those sprouts that do not form villi tend to become pedunculated and break off to be deported and lodge in the maternal pulmonary vasculature.

As pregnancy proceeds, terminal villi become more numerous and smaller (average diameter of 70 μm and 40 μm in second and third trimesters, respectively). The cytotrophoblast becomes less numerous and has largely disappeared by term, although its regenerative potential remains. The syncytiotrophoblastic layer becomes gradually thinner and the fetal capillaries occupy an increasing cross-sectional area of the villus and move more peripherally to eccentric positions beneath the syncytiotrophoblast (**Fig. 4.4**). In some areas the fetal capillaries appear to fuse with the overlying attenuated syncytiotrophoblast to form vasculosyncytial membranes that are believed to be the optimal area for gaseous exchange (**Fig. 4.5**). While the vascularity of the villus increases, the villous stroma becomes increasingly condensed and Hofbauer cells, though present at term, may be difficult to visualize because of compression by vessels and stromal tissue.

Syncytial knots formed by the sequestration of nuclei of the syncytiotrophoblast increase in number in the last two months of gestation. They may bulge into the intervillous space where they meet similar knots from adjacent villi to form an intervillous bridge. Toward the end of pregnancy, fibrinoid increasingly is deposited on the surface of the villi.

4.1.4.1 Electron Microscopy

The villous cytotrophoblast is relatively simple at the ultrastructural level, with few cytoplasmic organelles. It has a large nucleus with prominent nucleolus, and the cytoplasm contains large mitochondria, a few well-developed Golgi

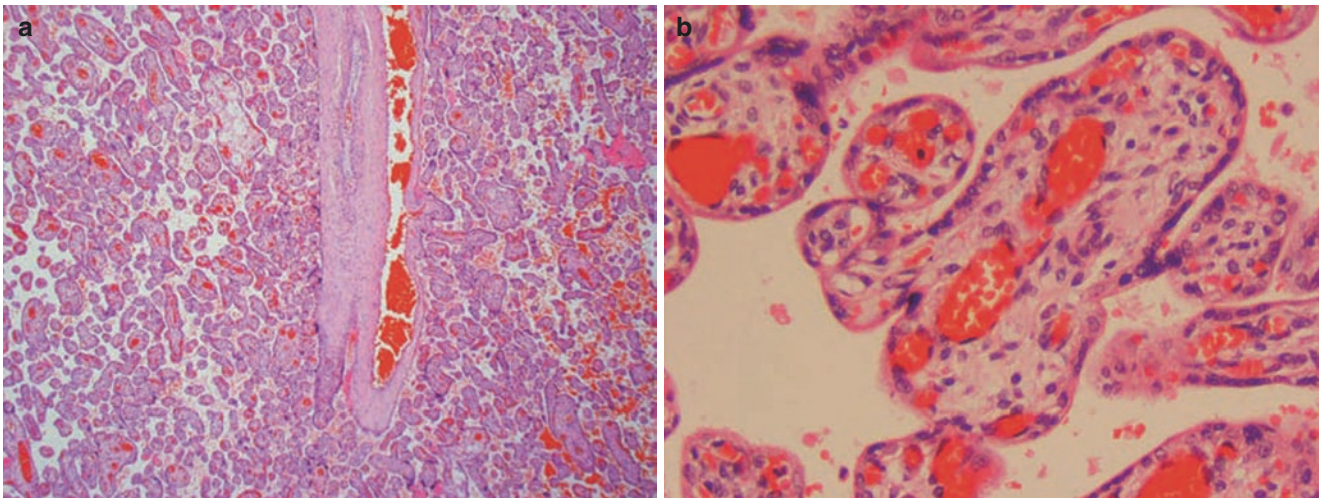

Fig. 4.4 (**a**) Placental villi at 27 weeks gestation. (**b**) High-power view showing reduced cytotrophoblastic layer, readily evident Hofbauer cells, and eccentrically placed vessels

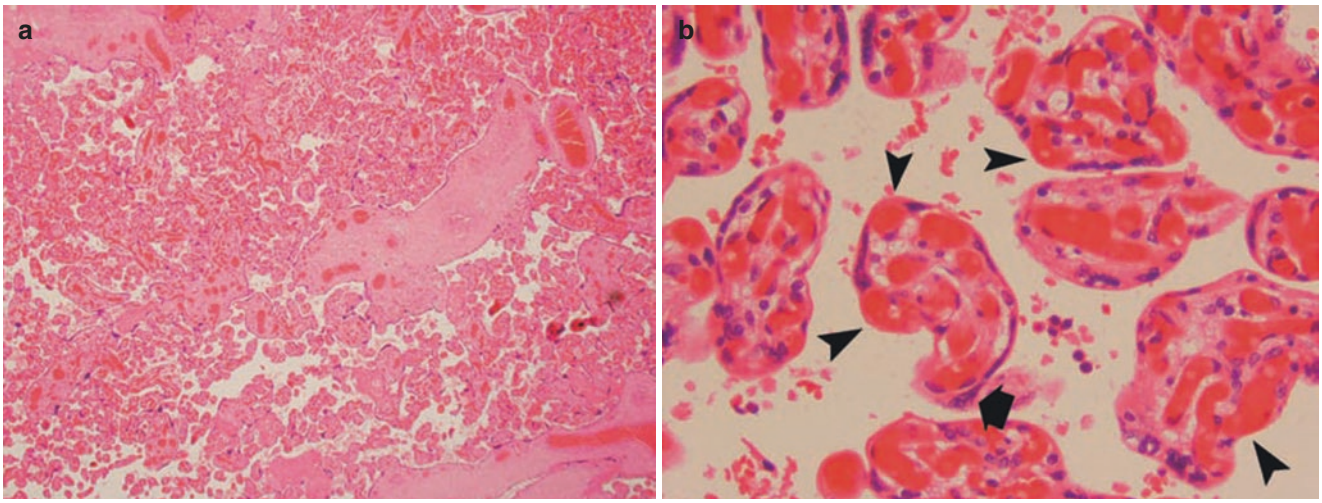

Fig. 4.5 (**a**) Placental villi at 38 weeks gestation. (**b**). High-power view showing numerous vasculosyncytial membranes (arrowheads). Occasional syncytial knot is evident (arrow)

bodies, and abundant free ribosomes. This ultrastructure is appropriate for its role in growth and differentiation. Syncytiotrophoblast is electron-dense with many organelles related to its role in steroid and protein synthesis and transport. It contains abundant dilated rough endoplasmic reticulum, pinocytotic vacuoles, free ribosomes, and numerous glycogen granules. Well-developed Golgi apparatus and mitochondria are present. The surface has a microvillous border associated with pinocytotic vesicles and vacuoles. Large numbers of densely packed microvilli are seen in the first trimester, becoming less dense, blunter, and variable in size and focally absent as pregnancy proceeds. They are reduced in number over vasculosyncytial membranes.

4.1.4.2 Morphometry

Measurements on the fixed delivered placenta may not relate directly to the organ in vivo but they provide useful information for comparative analysis during ontogeny and in normal and abnormal pregnancies. Many investigations have used the immersion fixed placenta for simplicity but perfusion-fixed, and ideally dual-perfusion fixed, placenta replicate the in vivo placenta more closely.

In general, the villous surface area seems to be significantly lower in placentas from women with severe pre-eclampsia or with small-for-gestational age infants uncomplicated by hypertensive diseases. A larger surface area was found in those with diabetes mellitus.

4.1.5 Development of the Membranes

By the 8th day following fertilization, a slitlike cavity destined to be the amniotic cavity is formed superior to the bilaminar embryonic disc, while inferior, a cavity that initially is the blastocyst cavity and later the primitive yolk sac cavity is formed. With formation of the extraembryonic coelom, the primitive yolk sac decreases in size and a secondary yolk sac develops. These sacs are surrounded by the developing extraembryonic coelom, extraembryonic mesoderm, and trophoblast. The embryo, amnion, and yolk sac suspended by the connecting stalk are thus contained within the chorionic sac. As the amniotic sac enlarges it obliterates the chorionic cavity and adheres to the chorion, covers the umbilical cord, and displaces the receding yolk sac to the base of the umbilical cord, this process being completed by 12 weeks' gestation.

The amnion is multilayered with a cuboidal epithelium lying on a well-defined basement membrane, deep to which are the compact, fibroblast, and spongy layers. The compact layer is relatively resistant to leucocyte infiltration and confers the strength of the amnion while the fibroblast layer permits distensibility. The spongy layer consists of collagen fibers, mucus, fibroblasts, and macrophages. The chorion is also multilayered comprising cellular and reticular layers, pseudomembrane, and trophoblast.

The amnion and chorion grow till approximately 28 weeks' gestation after when mitotic activity is rare. Subsequent enlargement of the chorioamniotic sac takes place by stretching.

4.1.6 Development of the Umbilical Cord

At the beginning of fetal development there are two stalks: the yolk sac stalk containing the vitelline duct and vitelline vessels, and the connecting stalk containing the allantois and umbilical vessels. These two stalks fuse to form the umbilical cord. The umbilical cord is covered by amnion that is continuous with the outer layer of the embryo. The blood vessels in the allantois become the umbilical vein and arteries and are supported by Wharton's jelly. Anastomoses between the arteries often occur close to the placenta and occasionally the arteries fuse.

4.1.7 Development of the Uteroplacental Circulation

Concurrent with the formation and development of the early placenta, trophoblast proliferating from the cytotrophoblastic shell and, later, from the tips of anchoring villi, infiltrate into the maternal decidua basalis and subjacent myometrium.

Interstitial trophoblast tends to be concentrated around spiral arteries at both the decidual and myometrial levels and its migration continues for the first 6 months of pregnancy, although invasion of the myometrium is probably most prolific during the first 18 weeks of gestation [10]. There is a relative absence of mononuclear cytotrophoblast in the myometrium at term, such cells having either disappeared or transformed into characteristic syncytial placental bed giant cells by symplasmic fusion.

Endovascular trophoblast migration into the spiral arteries appears to occur in two waves, the first wave from about 6 weeks' to about 12 weeks' gestation and the second wave from about 16 to 22–24 weeks' gestation, affecting predominantly decidual segments and myometrial segments of the spiral arteries respectively. The endovascular trophoblast penetrates the vessel wall through the endothelial lining, disrupting the intima, internal elastic lamina, and much of the muscular media, the process being accompanied by the deposition of fibrinoid material. These extensive structural alterations in the walls of the invaded arteries result in their conversion to uteroplacental arteries and as these changes are obviously adaptations to pregnancy, the term "physiological changes" was used to describe them. While the veins draining the intervillous space must be opened up, presumably by trophoblast, intravascular trophoblast migration has not been seen in decidual veins.

When maternal blood flow into the intervillous space is established is not actually clear. The spiral arteries are putatively opened up at 28–30 days post-conception, but whether the blood flow is anything more than a seepage at this stage is debated. It seems that a through circulation is not established until about 12 weeks' gestation. In the final stages of transformation of the spiral arteries into fully developed uteroplacental arteries the trophoblastic cells become entirely incorporated into the wall of the vessel and there is no longer direct contact with intraluminal trophoblast, the endothelial lining being reconstituted. During the third trimester the affected vessels undergo progressive distension, resulting in a series of dilated, funnel-shaped, tortuous vessels opening into the intervillous space (**Fig. 4.6**). It is assumed that the fully developed uteroplacental arteries lose their ability to respond to vasomotor influences because of the loss of their musculoelastic tissue and probably their autonomic nerve supply. There is certainly a significant drop in peripheral resistance at the opening of the uteroplacental arteries into the intervillous space allowing greater conductance and, hence, an increased blood flow at a low pulse pressure into and through the intervillous space. In this way the tenfold increase in blood supply required by the fetoplacental unit in the third trimester can be accommodated.

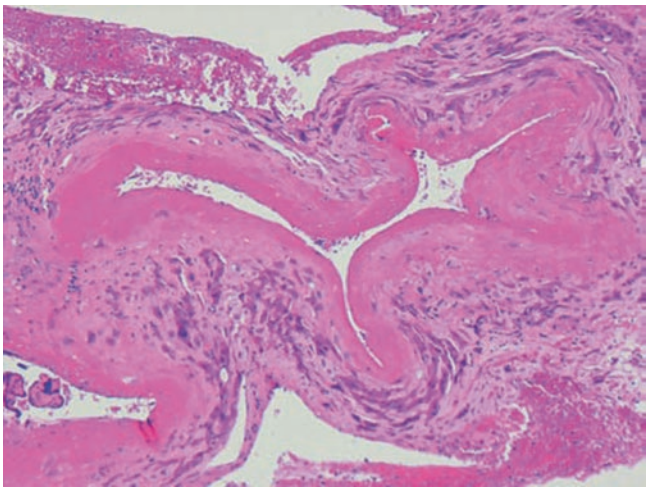

Fig. 4.6 Uteroplacental artery at term with distended lumen and fibrinoid matrix within the wall, surrounded by interstitial trophoblast

4.2 Abnormalities in Development and Placentation

There is a wide variation in placental shape that has no effect on the outcome of pregnancy, although recent studies suggest that they may have an effect on later adult life. Accessory lobes occur in 3–8% of pregnancies and are the result of non-involution of chorion laeve in the membranes. They are usually of no clinical significance except when retained in utero after delivery or associated with vessels running a velamentous course and situated near the cervical os when there is danger of vessel rupture during labor and fetal exsanguination. Bilobate placentas are uncommon and are not associated with any effect on perinatal morbidity. Fenestrate placenta with central absence of villous growth is very rare.

Extrachorial placentation where the chorionic plate from which the villi arise is smaller than the basal plate (i.e., where the transition from villous to non-villous chorion takes place within the circumference of the fetal surface of the placenta) is present in 24% of pregnancies. Where the membranes form a flat ring comprising only amnion and chorion with fibrin, the placenta is classified as circummarginate and this is without clinical significance. Where the transition is raised and contains decidual tissue, ghost villi, functioning villi and blood clot, the placenta is classified as circumvallate (**Fig. 2.29** in Chap. 2). The totally, but not the partially, circumvallate placenta is associated with low birthweight and a high rate of threatened abortion and premature onset of labor. It is not uncommon to find partially circumvallate or circummarginate placentas, or a mixture of both. Circumvallate placentas are found more commonly in multigravida.

Placenta previa occurs when implantation is in the lower uterine segment, lying in advance of the presenting fetal part. This may be total, where the placenta covers the internal os completely; partial where part of the internal os is covered; or marginal, where the placental edge just reaches the internal os. It occurs in approximately 1 in 250 births, the majority in parous women. It is associated with severe antepartum hemorrhage and delivery by cesarean section is required. Placenta previa is a clinical diagnosis and cannot usually be diagnosed by examination of the placenta, although the finding of the site of rupture of the membranes at the placental edge is supportive evidence.

Placenta accreta spectrum refers to abnormal placentation that results in partial or complete retention of the placenta at delivery [11]. The reported incidence in USA was 1:272 in 2016. Predisposing factors are advanced maternal age, multiparity and previous uterine surgery including curettage but the main risk factor in developed countries is prior cesarean section delivery. It is associated with antepartum hemorrhage, uterine inversion and rupture and postpartum hemorrhage. A missing piece of tissue from the maternal surface macroscopically may indicate a degree of accreta. Histologically, extended areas of absent decidua between villous tissues and myometrial fibers are seen (**Fig. 4.7**). The finding of basal plate myometrial fibers, however, does not necessarily correlate with symptoms of placenta accreta [12]. Between 1990 and 2000, a study of 310 pregnancies complicated by placenta accreta found an increased incidence of preterm delivery and small-for-gestational age infants [13].

In placenta membranacea there is persistence of villous growth over the whole surface of the placental membranes. It is very rare (1 in 3300 to 1 in 21,500 deliveries) and is associated with low birthweight, recurrent bleeding in the first and second trimesters, often leading to miscarriage or premature labor, retained placenta, and postpartum hemorrhage.

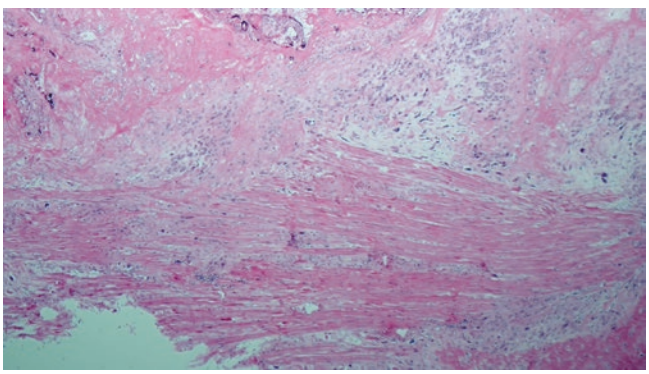

Fig. 4.7 Placenta accreta showing myometrial fibers in the basal plate in an en face section of the placenta, demonstrating its value in addition to assessing the maternal vasculature

4.3 Umbilical Cord Pathology

4.3.1 Cord Dimensions

The length of the umbilical cord varies widely throughout gestation, being between 54 cm and 61 cm at term (Table 2.14). Measurement of umbilical cord post-delivery should take into account lengths attached to the infant, removed for blood gas analysis and shortening following loss of turgor and fixation. Cord length is dependent on the stretch provided by fetal intrauterine motor activity. Accordingly, short cords may be a marker of abnormal fetal brain development, secondary to maternal ingestion of β-blockers or intrauterine constraint, such as twin pregnancy, uterine abnormalities, or reduced amniotic fluid volume. Conversely, long cords are associated with conditions such as multiparity, higher maternal age, and maternal diabetes, which are related to increased uterine size thereby permitting greater fetal movement, and delivery of infants subsequently diagnosed as being hyperkinetic.

The minimum length considered sufficient to permit unrestricted vertex delivery is 32 cm; a short cord is defined as ≤35 cm at term and is found in between 0.4% and 0.9% of cords. Fetal hypoxia may result from stretching with obstruction of vessels, placental separation, or cord rupture. Fetuses with a short cord had a 40% increased risk of having a major malformation and also an increased risk of perinatal death, while mothers were more likely to have a retained placenta or placental abruption [14].

A long cord is defined as ≥70 cm at term and is seen in 3.7% of cords. While long cords predispose to prolapse, cord knots, and fetal entanglement [15], they were associated with a reduced risk for malformations and placental abruption [14]. Histologically, long cords were associated with nucleated red blood cells, chorangiosis, fetal vascular thrombi, intramural fibrin deposition, and single umbilical artery. The umbilical cord is often edematous when there is fetal or placental hydrops, in maternal diabetes and Beckwith-Wiedemann syndrome.

4.3.2 Single Umbilical Artery

Single umbilical artery may result from primary aplasia of one vessel or secondary atrophy. The incidence varies from 0.2% to 1.1% of births, but in perinatal autopsy series the incidence has varied from 2.7% to 12%. The incidence is higher in girls than in boys [16]. Ultrasound diagnosis, whilst specific, is not highly sensitive. Naked-eye examination can be misleading and histology should be the definitive method of ascertainment. The cord must be sampled at least 5 cm distant from its placental insertion as the two arteries may fuse into one trunk giving rise to an erroneous diagnosis of a single umbilical artery; this is more common in females than in males [17]. Single umbilical artery is associated with maternal diabetes and maternal smoking and with low birthweight and preterm births. About 15% of fetuses with single umbilical artery have associated structural or chromosomal anomalies [18], the incidence being higher in autopsy than liveborn series. Frequently associated malformations are sirenomelia sequence, VACTERL complex (**V**ertebral defects, **A**nal atresia, **C**ardiac defects, **T**racheo-**e**sophageal fistula and **E**sophageal atresia, **R**adial and **R**enal anomalies), and anorectal atresia and esophageal atresia. Single umbilical artery is seen more frequently in trisomy 13, trisomy 18 and Zellweger syndromes, and infrequently in trisomy 21 [19]. About 65% of cases of single umbilical artery are isolated; there is an increased likelihood of small-for-gestational age infants. It is debated whether occult renal anomalies, the most common anomaly reported with isolated single umbilical artery, are minor and self-limiting.

4.3.3 Umbilical Cord Insertion

The umbilical cord may be inserted into the placental disc centrally, eccentrically (paracentrally), marginally (battledore), or velamentously (via the membranes). Marginal cord insertions are defined as being less than 1cm of the placental edge [20] although most studies used a 2 cm cut-off, which may correlate better with antenatal ultrasound assessment and risk management [21]. The term peripheral insertion has been used for cords that insert within 3cm of the nearest edge. Clinical significance of the first three types of insertion is uncertain because of the different definitions used [22].

In velamentous insertion, the cord inserts into the membranes and, hence, the vessels run unprotected for some distance in the membranes before insertion into the placenta (**Fig. 4.8**). Velamentously inserted cord vessels may rupture during labor, especially if vessels run across the internal os (vasa previa); perinatal mortality is highly dependent on prenatal diagnosis [23]. Velamentous cord insertions were associated with increased risk of term and preterm prelabor rupture of membranes, perinatal death at term, low Apgar score at 5 min, transfer to neonatal intensive care unit, and malformation are also increased [24, 25]. The umbilical cord can be ensheathed within Wharton's jelly until it reaches the fetal surface; this interposition, or interposito velamentosa, is uncommon.

The umbilical cord can be tethered at its insertion by an amnionic web (chorda) or free fold of amnion, which can potentially restrict blood flow when the cord becomes angulated with movement or at delivery (**Fig. 4.9**). In furcate insertions, the umbilical vessels lose the protective covering of Wharton's jelly prior to the insertion.

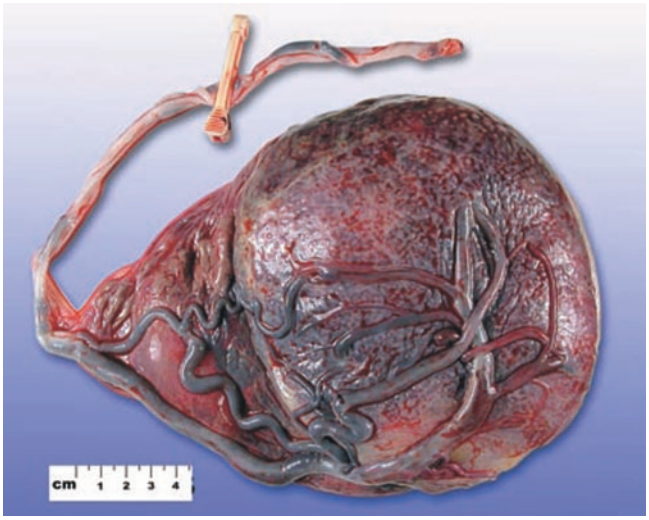

Fig. 4.8 Velamentous cord insertion

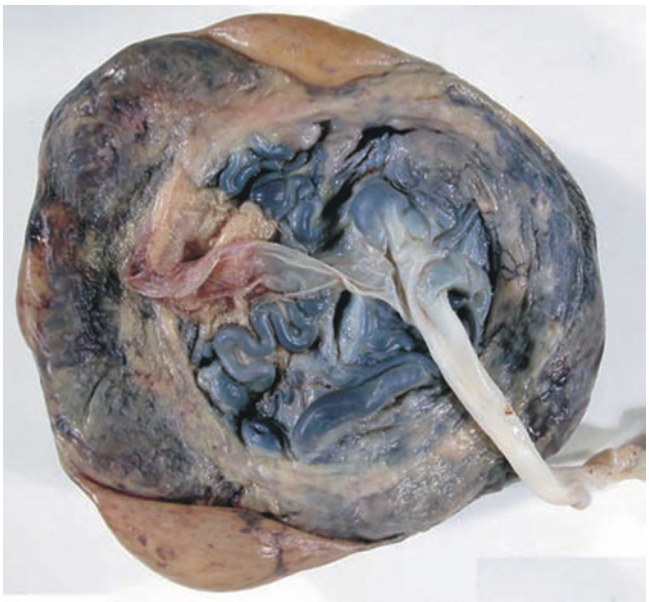

Fig. 4.9 Amnionic web tethering umbilical cord

4.3.4 Cord Knots and Entanglements

"False knots" of the cord are localized accumulations of Wharton's jelly or vascular dilatation producing asymmetrical cord expansion. They are insignificant.

The incidence of true knots at birth is ~1% [26]. A review of 145 studies between 1960 and 2020 found the likelihood of stillbirth was significantly higher in pregnancies with a true knot in the umbilical cord at birth than in those without. Statistically significant associations were found between true cord knots at birth and preterm birth, 5 min Apgar score <7, NICU admission, birth weight <2500 g and SGA infant [26]. Knots that have been present for some time produce grooving and kinking of the cord, with localized loss of Wharton's jelly, constriction and sometimes thrombosis of the vessels. Previously loose knots may tighten just before or during labor and cause asphyxia. The significance of such knots may be overlooked, but intrapartum death, fetal distress, or neonatal asphyxia could be ascribed to such knots if there is edema and congestion or thrombosis of vessels in the vicinity of a knot.

The incidence of any nuchal cord at birth, determined from data from 57 studies of 830,624 pregnancies, was 22% [26]. A tight nuchal cord, defined as the inability to manually reduce the loop over the fetal head, was seen in 6.6% of more than 200,000 births compared to 21.6% of "loose" nuchal cords where the loop could be reduced manually over the head [27]. Entanglement around a limb or torso is seen in 2% [28]. In the large meta-analysis, no statistically significant association was detected between presence of any nuchal cord and stillbirth but a suggestion of such an association with multiple loops compared with no or single loop. They also found a single loop of nuchal cord at birth was only associated with a 1 minute Apgar score <7 whereas multiple loops of cord were associated with increased likelihood of cesarean section and Apgar scores of <7 at bith 1 and 5 min. Tight loops of nuchal cord but not loose loops were associated with low Apgar scores [26]. Edema and congestion on one side of the alleged obstruction should be sought while hemorrhage into Wharton's jelly and thrombosis of vessels and grooving of fetal parts increase the significance of cord entanglement.

4.3.5 Cord Coiling, Torsion, and Constriction

The umbilical cord is usually coiled as a result of active or passive rotation of the fetus, differential umbilical vascular growth rates, or from hemodynamic torque. Generally, cords have a predominant counterclockwise twist, but some cords have a combination of clockwise and counterclockwise twists. Coiling appears to be established by 8 weeks gestation and loss of coiling has not been observed. The coiling index (coils/cm) is about 0.20, but is higher at the placental (0.49) and fetal ends (0.72) [29, 30]. The difficulties of measuring the coiling index were reviewed [31]. Although hypocoiling and hypercoiling have been reported with adverse perinatal outcome [32], this was not confirmed in an unselected population [33]. Recurrence of hypercoiling in successive pregnancies has been reported, so far in male miscarriages suggesting a possible X-linked association [34, 35].

Marked cord torsion can be distinguished from the normal spiraling of the cord and may be observed at delivery of an uncompromised infant or following termination of pregnancy for fetal anomaly. Following fetal death, fluid is lost from Wharton's jelly leading to loss of turgor. Autolytic

change in the cord may be accelerated in the 30–40 mm close to the umbilical cord insertion to the fetus. The generalized loss of turgor will serve to make any torsion more apparent, and unopposed asymmetrical uterine action may produce further fetal torsion. Twists in the cord are often most apparent in the narrow segment of cord at the umbilical insertion to the fetus when torsion leading to cord constriction may be blamed for fetal demise. It is more likely that the twists collect in the constricted part of the cord as a purely mechanical phenomenon. Cord torsion per se is rarely the cause of fetal demise.

Constriction of the umbilical cord or a cord stricture usually occurs close to the fetal insertion and is much less commonly recorded elsewhere. In the constricted segment, vessels are collapsed or contracted and the stroma appears dense. It has been suggested that such constrictions are the result of congenital absence or degeneration of Wharton's jelly. As noted in the previous paragraph, ascribing cause of fetal demise to cord constriction should be made carefully. Where there are strictures remote from the fetal insertion or multiple ones, fetal demise can reasonably be due to the cord constriction [36]. Cord constriction at the fetal end is exceptionally described with live birth when the constricted segment was very short. It is more likely that it is the result of more rapid autolysis occurring close to the fetus. Three rare cases where there was complete absence of Wharton's jelly around the umbilical cord arteries but present around the umbilical vein were described; these three cases were associated with perinatal death [37].

Localized pressure can lead to constrictions elsewhere in the cord. They are seen much more frequently in the presence of localized physical constriction, such as amniotic bands or significant cord knot, than as isolated lesions.

4.3.6 Localized Cord Swelling

Remnants of the allantoic and omphalomesenteric (vitelline) ducts may be found, typically located toward the fetal insertion of the cord, and ranging between 4 mm and 60 mm in size. The allantoic duct serves as a diversion for the fetal bladder and its remnant is situated between the two umbilical arteries and generally lined by flattened and rarely by transitional epithelium. The omphalomesenteric duct connects the fetal yolk sac with the small intestine at the site of Meckel's diverticulum. Remnants of the omphalomesenteric duct are located more peripherally in the cord than allantoic duct remnants and show an intestinal, often mucinous, lining. Prevalence of vitelline duct remnants decrease with gestational age while allantoic duct remnants remain constant irrespective of gestational age [38]. Inflammation of both remnant types have been described [39].

Cysts of the umbilical cord may arise from these remnants. The linings of these cysts mirror those of the duct remnants. These cysts are usually small and found by chance, but an occasional cyst may reach 40–50 mm in diameter when there is a risk of vascular tamponade. Amniotic inclusion cysts are uncommon. Pseudocysts, formed by cavitation because of mucoid degeneration of Wharton's jelly, lack an epithelial lining and contain clear mucoid material and can be located anywhere along the cord. Cysts detected antenatally on ultrasound appear to be frequently associated with fetal anomalies but the association with chromosomal anomalies, such as trisomy 13 and 18, may be biased, including the cord cyst being found incidentally following detailed assessment of the associated fetal structural anomalies [40].

Tumors of the cord are exceedingly rare. Teratomas of the cord are extremely rare.

4.3.7 Abnormalities of Umbilical Cord Vessels

Inflammation of the umbilical cord vessels, vasculitis, and of the stroma, funisitis, are described later.

Hematomas of the cord may be iatrogenic secondary to umbilical cord blood sampling, amniocentesis, or intrauterine blood transfusion. Accordingly, it is important to seek such clinical information before describing them as spontaneous cord hematomas. Spontaneous hematomas in the cord arise from focal hemorrhage from an umbilical vessel, usually a vein. The majority appear to accumulate before the onset of labor. Their etiology is unclear. Although the perinatal mortality rate in infants whose cord contains a hematoma is about 40–50%, it is unclear whether the hematoma is responsible for the death and if so, how, or whether the hematoma and death are related through a common cause.

The prevalence of thrombosis of umbilical cord vessels is 1 in 1290 among prospectively examined placentas. There is a slight male predominance and venous thrombosis occurs more frequently than thrombosis of one or both umbilical arteries. In his landmark review, Heifetz did not find an association between cord thrombosis and perinatal mortality and morbidity, and thought that thrombosis, when present, was related to additional umbilical cord abnormalities, obstetrical complications, or systemic fetal conditions that were likely cause of both the thrombosis and poor fetal outcome [41]. A review at a single hospital found thrombosis of umbilical cord vessels in 10% of 317 consecutive stillbirths; related findings included hypercoiled cords, nuchal cords, funisitis, true knots, maternal thrombophilia and preeclampsia [42].

Linear ulceration of the umbilical cord in association with congenital intestinal atresia has been described (**Fig. 4.10**) [43]. Severe hemorrhage from the cord ulceration into the amniotic cavity results in severe neonatal asphyxia

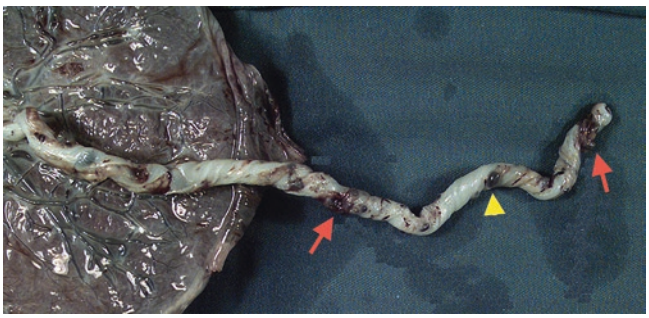

Fig. 4.10 Linear ulceration of the umbilical cord (arrows); other hemorrhagic areas align with the umbilical vessel (arrow showing one example)

or intrauterine death. Additional abnormalities, including Hirschsprung's disease and an interstitial deletion of chromosome 13q [44] and trisomy 21 [45] have been described. The overwhelming majority of cases of umbilical cord ulceration in association with intestinal atresia have been reported from Japan [45], but whether this due to underreporting elsewhere or a truly geographically confined lesion is unclear.

A closely related lesion is necrosis of the umbilical cord induced by prolonged meconium passage [46]. Necrosis of the arterial wall is associated with meconium-laden macrophages in the Wharton's jelly (**Fig. 4.11**).

Marked segmental thinning of umbilical cord vessels was found in 1.5% of placentas. The media is reduced to only one or two layers of smooth muscle fibers. It is a focal lesion that shows a relatively abrupt transition from the normal to the abnormal segment. The lesion faces the cord surface in half the cases and affected the vein in 76% of cases and the arteries in the remaining 24%. All cases showed abnormalities of the vessels in the chorionic plate and primary stem villi. An association with congenital malformations was found and there was a high incidence of fetal distress. The origin of the lesion is unclear but may represent dysplasia of the media [47].

Calcification of umbilical cord vessels is thought to be rare and two different lesions have been described [48]. In one there is complete calcification of arterial lumen resulting in total obliteration while in the other, so-called sclerosing funisitis, there is sclerosis of the wall associated often with inflammation in the umbilical cord and its vessels, membranes, and decidua suggesting intrauterine infection (see section on necrotizing funisitis).

Hemangiomas, which may arise from either the umbilical vein or the artery, may give rise to cord hemorrhage and is may be associated with elevated maternal alpha-fetoprotein levels. A high perinatal mortality rate due to premature delivery, fetal hydrops, cardiac failure, and intrauterine death is reported [49]. Pseudocysts have been found in 8 of 20 cases of umbilical cord hemangioma [50]. Aneurysms of the umbilical vein or artery are rare: dissection or increase in size of the aneurysm may lead to compression of adjacent vessels.

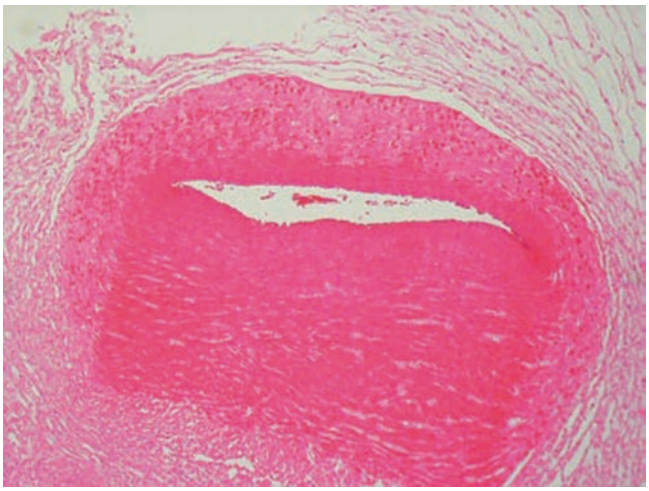

Fig. 4.11 Meconium-induced myocytolysis of cord vessel

4.4 Amniochorial Membranes Pathology

4.4.1 Amnion Nodosum and Squamous Metaplasia

Squamous metaplasia appears as slightly elevated granular deposits on the amniotic surface and are not easily displaced. Histologically, foci of stratified epithelial cells with layers varying from 6 to 20 are seen (**Fig. 4.12**). There is usually a sharp transition at the edge of the lesion from columnar to squamous epithelium. The lesion has no clinical significance.

Amnion nodosum is evident as numerous raised, shiny, greyish nodules measuring up to 5 mm lying on the amniotic surface of the placenta (**Fig. 4.13**). The nodules are easily dislodged, a distinguishing feature from squamous metaplasia of the amnion. Histologically, amnion nodosum consists of granular material containing fetal cells and debris with occasional hair fragments and may be covered by amniotic epithelium (**Fig. 4.14**). The nodules derive from close contact between fetus and amnion and consist predominantly of vernix caseosa. The presence of amnion nodosum accompanies oligohydramnios from any cause so that an associated abnormality such as urinary tract obstruction, renal agenesis, or a history of prolonged rupture of membranes should be sought. Squames may accumulate in the subchorionic space, presumably from cells shed into amniotic fluid, in prolonged amniotic fluid leakage not occurring over the cervical os [51].

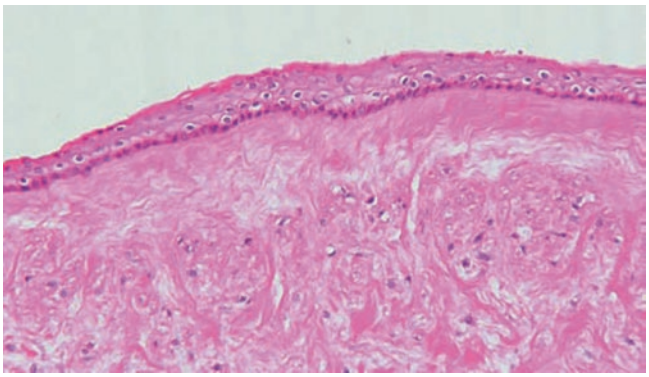

Fig. 4.12 Squamous metaplasia of the amniotic epithelium

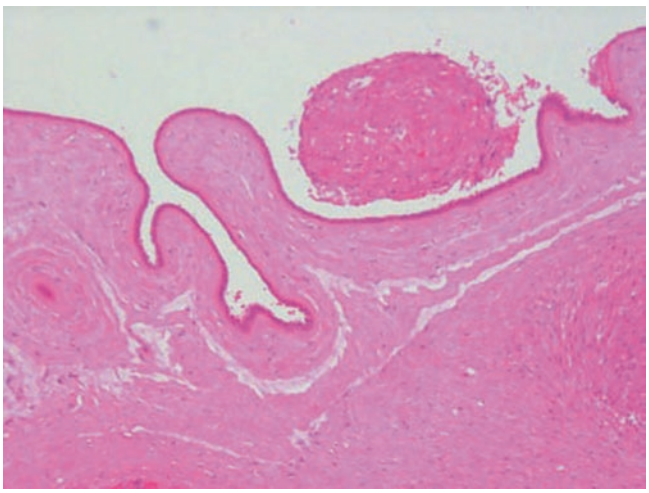

Fig. 4.13 Amnion nodosum. Granular material containing squames is seen on the surface of the amnion

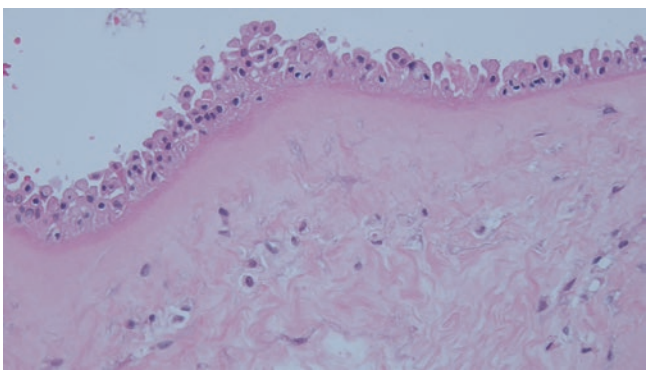

Fig. 4.14 Meconium-induced changes in the amnion with epithelial columnar metaplasia and meconium-laden macrophages within the amnion

4.4.2 Amniotic Bands

A range of fetal abnormalities can be found with amniotic bands or adhesions. Synonyms are amniotic band syndrome; amnion rupture sequence; amniotic deformity, adhesion and mutilation (ADAM) complex. The abnormalities range from constriction rings, amputations, syndactyly, fusion defects of the cranium and face and clefts. Two explanations have been advanced for the constellation of signs that cannot be readily explained by disordered development, teratogenic, or environmental influence. One is that the disruption of the amnion gives rise to bands causing a mechanical effect on the fetus. The other is that there may be a vascular compromise or a genetic or germ cell disruption. Immersing the placenta in water may allow the amniotic bands to be more easily seen. Histologically, the amnion will be seen to be absent from the placental surface.

4.4.3 Meconium Staining

Meconium in the amniotic fluid at birth is a common event which has been estimated to occur in up to 5% prior to 37 weeks' gestation, 25% of births at term and 23–52% among post-term gestation. The vast majority of cases of meconium stained amniotic fluid is a normal physiological phenomenon but some cases may be a result of intrauterine fetal hypoxia and distress [52]. There is no evidence to support an association between meconium stained amniotic fluid and increased neurological impairment and serious morbidity is principally associated with meconium aspiration syndrome.

Meconium staining can be identified by its uptake by macrophages in the membranes. However, not all pigment, in the membranes or chorionic plate, is meconium and must be distinguished from hemosiderin. An in vitro study showed meconium-containing macrophages within the amnion within 1 h of meconium exposure and within the chorion within 3 h [53]. Reliance of this timing of meconium exposure has been used in medico-legal circles, but it is questionable whether the in vitro conditions can be extrapolated to the in vivo clinical situation. Prolonged meconium exposure results in epithelial vacuolisation, stratification and, later, necrosis (**Fig. 4.14**).

4.4.4 Inflammation and Decidual Vasculopathy

Inflammation in the amniochorial membranes and maternal vascular lesions are described later in the chapter.

4.4.5 Myometrial Fibers

Smooth muscle may occasionally be seen subjacent to the chorion laeve, sometimes immediately and sometimes intervened by a thin fibrinoid or decidual layer. Although extraplacental myometrial fibers can be an incidental microscopic

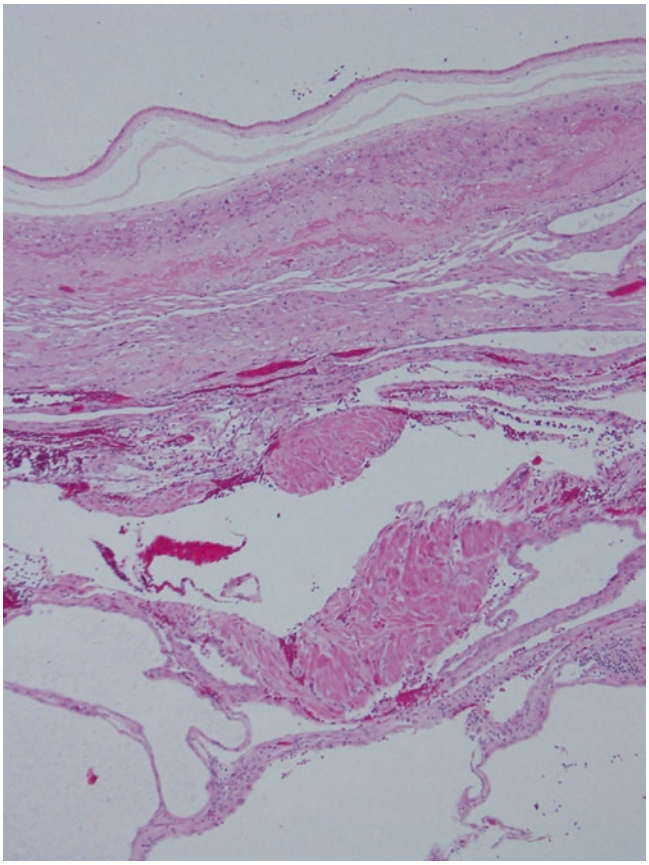

Fig. 4.15 Myometrial fibers attached to amniochorial membranes from a woman with postpartum hemorrhage

observation in a routine placenta, it may be the fetal membrane counterpart of basal plate myometrial fibers. The designation of chorion laeve accreta is suggested when there are clinical manifestations of the placenta accreta spectrum, such as retained fetal membranes (**Fig. 4.15**) [54].

4.5 Placental Parenchyma Pathology

Many of the pathological abnormalities that are seen on gross examination of the placenta are related to disturbances in the maternal, intervillous, or fetal circulations, but these abnormalities may be difficult to distinguish from each other and may require histological examination for identification. Some placental lesions are evident only microscopically.

4.5.1 Uteroplacental Circulation

4.5.1.1 Pathological Basis of Maternal Vascular Malperfusion

Defective invasion of the endovascular trophoblast in early pregnancy leads to less complete plugging of the implantation site spiral arteries and consequent maternal vascular overperfusion or unrestrained blood flow into the developing placental lacunae and intervillous space.

The same defect in invasion of the spiral arteries by endovascular cytotrophoblast leads to absence of physiological vascular changes in the myometrial segments of spiral (uteroplacental) arteries and in the decidual segments of many of these arteries (**Fig. 4.16**) [55] resulting in maternal vascular underperfusion in the second and third trimesters. The absence of physiological changes may be incomplete, affecting only part of the circumference of the spiral artery or branches of the same. Where the spiral arteries have not undergone physiological changes, the undisturbed vascular anatomy would render them responsive to vasomotor influences. En-face blocks of the basal plate often yield more decidual spiral arteries for assessing the maternal vasculature than conventional sagittal placental blocks [56].

Another vascular lesion is acute atherosis, which is characterized by fibrinoid necrosis of the smooth muscle arterial wall accompanied by lipid-laden macrophages and a perivascular round cell infiltrate (**Fig. 4.17**) [57, 58]. The lesion is seen in arteries in the uterus that have not undergone physiological vascular changes of pregnancy and, thus, may be seen also in the decidua parietalis underlying the amniochorial membranes as well as unconverted spiral arteries and basal arteries in the decidua basalis and in the myometrium. Embedding the amniochorial membranes by stacking them can enable better detection of acute atherosis [59]. The possibility of an immunological pathogenesis of the lesion is suggested by the morphological similarity of this lesion to that seen in allograft rejection and by clinical parameters. Immunoglobulin IgM and complement C3 have been found in acute atherotic lesions similar to the findings in atherosis-like lesions from rejected renal and cardiac transplants, leading to speculation that acute atherosis is primarily an immunologically determined vasculopathy [58].

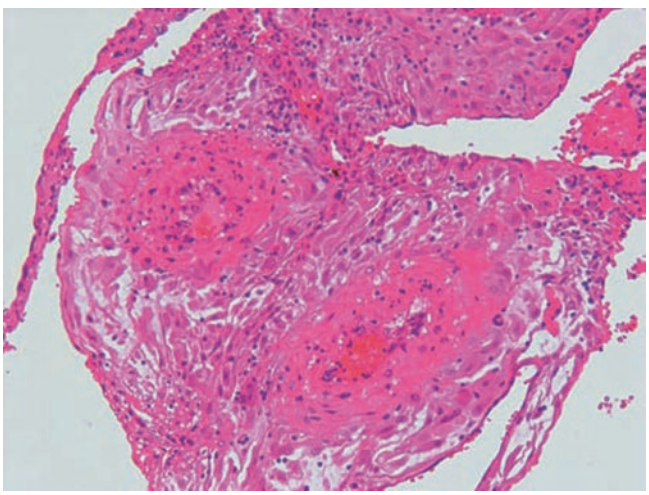

Fig. 4.16 Absence of physiologic changes in the spiral arteries

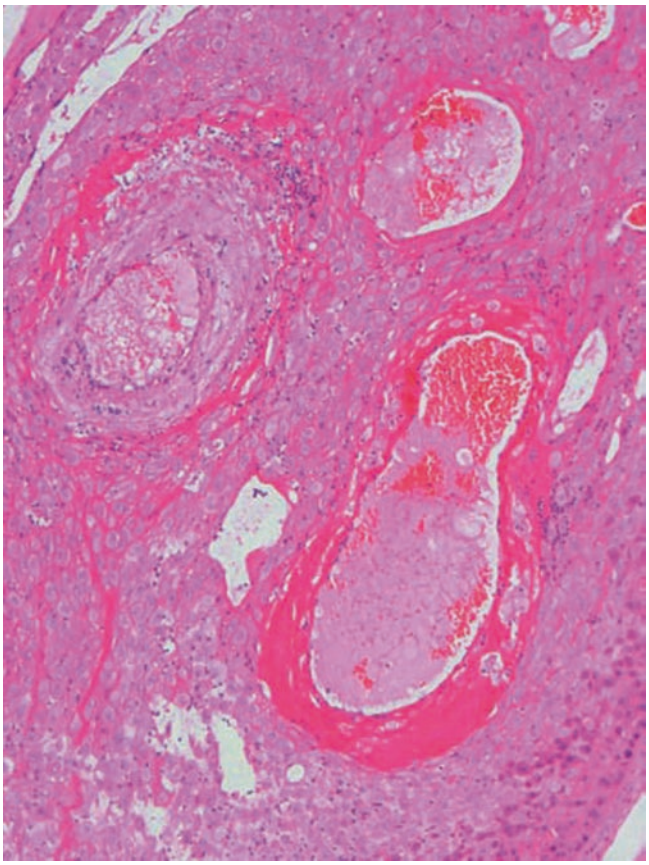

Fig. 4.17 Acute atherosis. Section through maternal arteries in the decidua parietalis show fibrinoid necrosis, lipid-laden macrophages, and a scanty perivascular inflammatory infiltrate

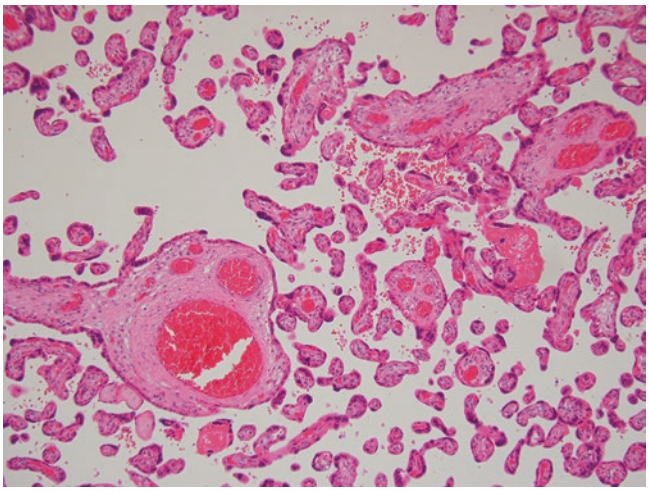

Fig. 4.18 Distal villous hypoplasia showing increased syncytial knot formation and paucity of terminal villi in a 26-week placenta from a fetus with severe intrauterine growth restriction

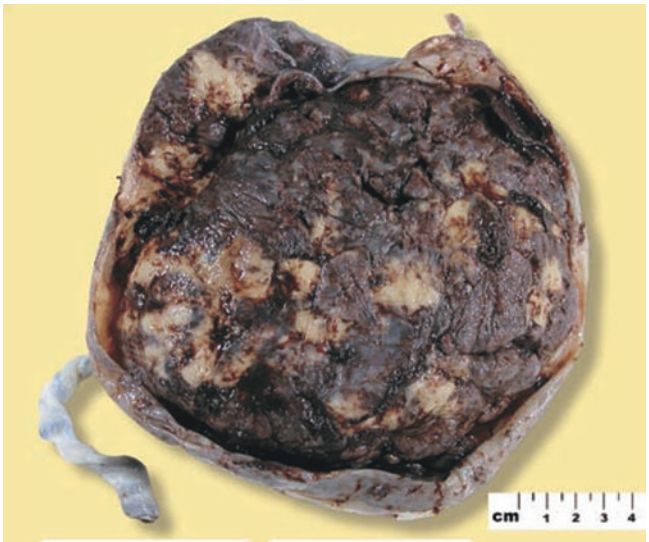

Fig. 4.19 Maternal surface of placenta showing multiple areas of infarction

4.5.1.2 Pathological Effects: Gross and Microscopic

Maternal vascular malperfusion leads to damage patterns or lesions [60]. Decreased uteroplacental blood flow can lead to reduced arborisation of the placental villous tree that can manifest macroscopically as a placenta that is smaller or less heavy for gestational age and microscopically as distal villous hypoplasia. In distal villous hypoplasia there is paucity of villi in relation to the surrounding stem villi, the villi being thin with increased syncytial knots (**Fig. 4.18**).

Infarction

Occlusion of the maternal spiral arteries from thrombosis or rupture of vessels weakened from acute atherosis results in infarction of the cotyledons supplied by those arteries. A fresh infarct seen in the cut surface of the placenta is dark red and moderately soft. As the infarct ages it appears brownish then yellow and finally white and firm (**Figs. 4.19** and **4.20**) The histological appearance of an infarct is characterized by villous crowding, narrowing of the intervillous space, congestion of the fetal vessels, and pyknosis of the syncytiotrophoblast nuclei. As the infarct ages, villi undergo necrosis and an old infarct consists of "ghost" villi (**Fig. 4.21**). Thrombosis of the uteroplacental arteries may sometimes be seen in basal plate (**Fig. 4.22**). It is generally accepted that infarcts occupying less than 10% of the parenchyma are insignificant, but infarction of a larger proportion of the placenta is associated with a high incidence of fetal growth restriction and intrauterine death.

Retroplacental Hemorrhage

Retroplacental hemorrhage is a pathological diagnosis and is to be distinguished from abruptio placenta, which is a clinical diagnosis, where there is a premature separation of the placenta from the maternal surface with decidual hem-

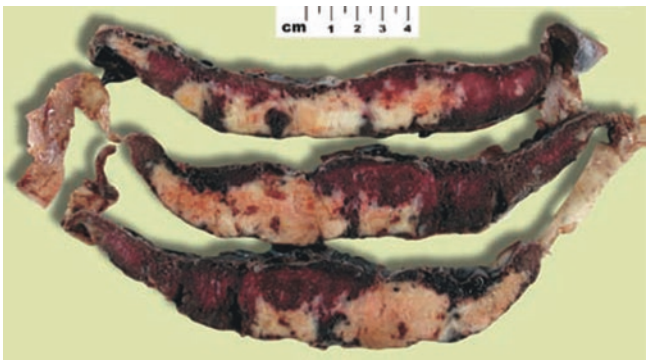

Fig. 4.20 Placental slices showing multiple infarcts, with two areas of more recent infarcts in the upper slice

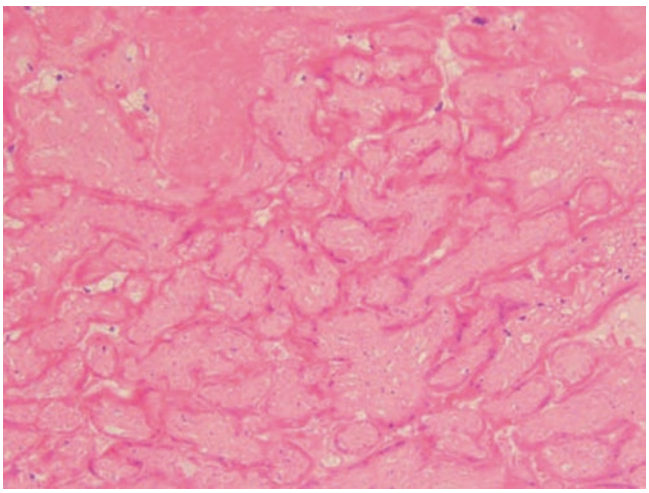

Fig. 4.21 Old placental infarct. The villi are crowded and ghost-like; the trophoblast has undergone necrosis

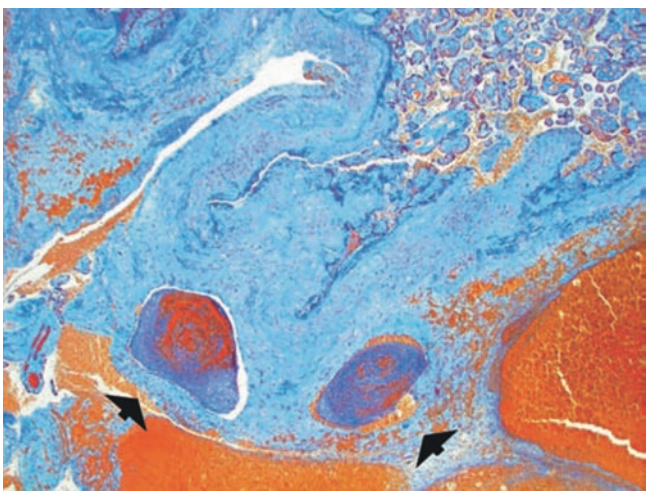

Fig. 4.22 Thromboses in the maternal uteroplacental arteries in the basal plate (arrowheads) (Martius scarlet blue stain)

orrhage. Correlation between the pathological and clinical diagnosis is poor [61].

Damage to the uteroplacental vessels can also result in retroplacental hemorrhage, the source of which may be arterial, venous, or both. Intramyometrial segments of spiral arteries lack physiological changes in 60% of placenta abruptio cases whether hypertensive or not; bleeding in the myometrium due to the presence of abnormal vessels, not clearly identified as arteries or veins, was suggested [62]. Peripheral or marginal hematomas tend to be venous in origin and form at the lateral margin of the placenta, and may spread onto the maternal surface but do not compress it. Arterial retroplacental hematomas are often accompanied by adjacent placental infarction and decidual necrosis. The hematomas vary in size from less than 10 mm—only apparent when the placenta is sliced—to large lesions that may involve much of the maternal surface. On the cut surface of the placenta the hematoma may be seen bulging into placental tissue, compressing it and causing infarction (**Fig. 4.23**). The clot, when newly formed,

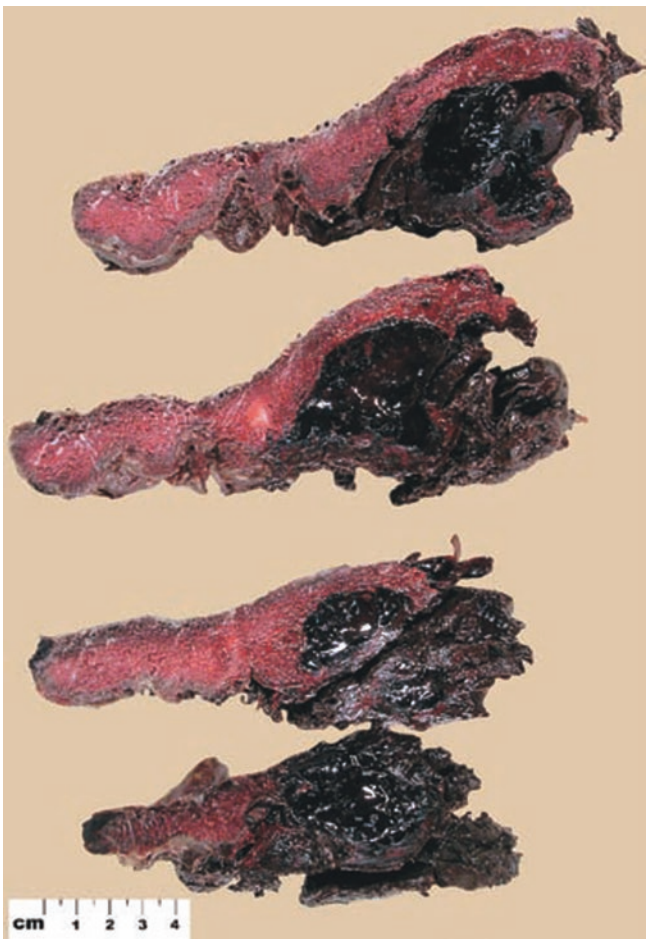

Fig. 4.23 Retroplacental hematoma with excavation of the clots to laeve indented placental parenchyma

is soft and red in color and may become separated from the placenta during delivery. Careful inspection of the maternal surface will reveal a depression at the site of hematoma formation, and adherent strands of fibrin give the surface a dull rough surface. This enables distinction from insignificant blood clot, which may be delivered with the placenta, but which does not indent the maternal surface. An additional histological clue is the dissection of blood along the basal plate in retroplacental hemorrhage. The histological appearance of hematomas is age related: fresh clots consist entirely of red blood cells while, with age, there is increasing fibrin deposition, degeneration of red blood cells, and infiltration of the basal plate by polymorphonuclear leucocytes and hemosiderin-laden macrophages. There may be intense congestion and dilatation of the fetal vessels, and chorionic intravillous hemorrhage can be seen in half of cases of retroplacental hemorrhage (**Fig. 4.24**) [61, 63].

The effects of a retroplacental hematoma are dependent on the size and on the integrity of the underlying maternal blood supply. In an uncompromised pregnancy, a large lesion involving the central area and up to 40% of the maternal surface will cause fetal embarrassment while smaller retroplacental hematomas may prove equally embarrassing in pregnancies where the maternal blood supply is diminished already. An association has been noted between premature delivery, premature rupture of the membranes, and peripheral placental hemorrhage [64]. If placental separation takes place over a long period of time, in stages, the fetus may survive but suffers from disruption of its maternal blood supply. This prolonged sequence of events results often in retroplacental hematoma. The acute placental separation, on the other hand, occurring immediately prior to delivery or causing sufficient fetal distress as to warrant emergency delivery, may not be recognized reliably by the pathologist as no gross evidence may be present; there may be no adherent blood clot or indentation of the placental parenchyma.

Laminar Necrosis

Basal plate laminar necrosis or diffuse decidual leukocytoclastic necrosis (DDLN) is a diffuse band of coagulative necrosis at the choriodecidual interface, admixed with karyorrhectic debris [65, 66]. Little is known in the literature about the clinicopathologic correlations of DDLN. Decreased uteroplacental perfusion is suggested as a cause [65, 66], but it has not been confirmed [67].

4.5.1.3 Adaptive Changes

Intraluminal endovascular trophoblast, which is not seen normally in the third trimester, is sometimes seen in decidual arteries (**Fig. 4.25**) [55, 68]. An excessive proliferation of extravillous trophoblast in the implantation site has been described also [69].

Chorangiosis

Chorangiosis is defined as the presence of ten villi each with ten vascular channels in ten or more non-infarcted and non-ischemic zones of at least three different placental areas when examined with a ×10 objective (**Fig. 4.26**) [70]. The etiology is not known but is thought to be an angiogenic response to uteroplacental hypoxia [71]. Focal chorangiosis shares similar fetal, maternal and placental associations as traditionally-defined chorangiosis [72]. Conversely, chorangiosis absent of diffuse lesions indicating hypoxic patterns of placental injury is associated with significantly fewer pregnancy risk factors, abnormal outcomes, and other placental abnormalities [73], supporting the lesion being an adaptive change.

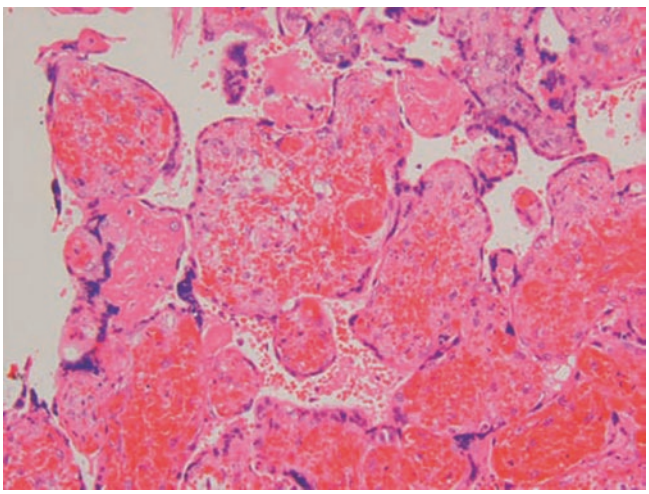

Fig. 4.24 Intravillous hemorrhage in congested villi in placental abruption

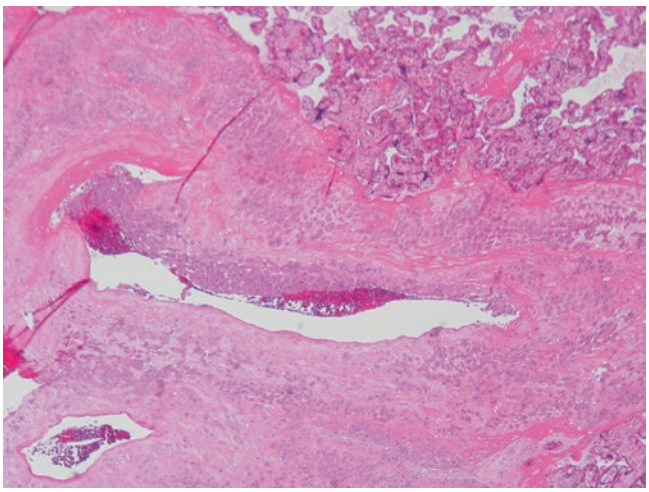

Fig. 4.25 Intraluminal endovascular trophoblast within uteroplacental artery in the basal plate of a placenta from a woman with antepartum hemorrhage and decreased fetal movements at 40 weeks gestation

Villous Maturation

Accelerated villous maturation is thought to be a compensatory mechanism for uteroplacental ischemia. There is increased formation of syncytial knots (Tenney–Parker changes), which are aggregates of syncytial nuclei that have been damaged by oxidative stress thus sequestering them away from vasculosyncytial membranes so as not to impede maternofetal exchange (**Fig. 4.27**) [74]. Assessing villous maturity is fraught with observer reproducibility errors [75] and should be performed on sections of central placenta free of lesions [74] with reference to normal numbers [76].

Increased Intervillous Fibrin and Villous Agglutination

Perivillous fibrin deposition is seen over damaged syncytiotrophoblast, which may also be due to maternal blood turbulence or stasis, to help limit further hypoxic injury [77]. Such deposition of fibrin can be seen around villi on histological examination of all placentas at term. Increased amounts of intervillous fibrin, which then act as a glue for the adjacent villi resulting in villous agglutination, can be seen as an adaptive response. These villi commonly show stromal fibrosis, cellular degeneration, and fibrinoid necrosis, in effect, a microscopic infarction (**Fig. 4.28**).

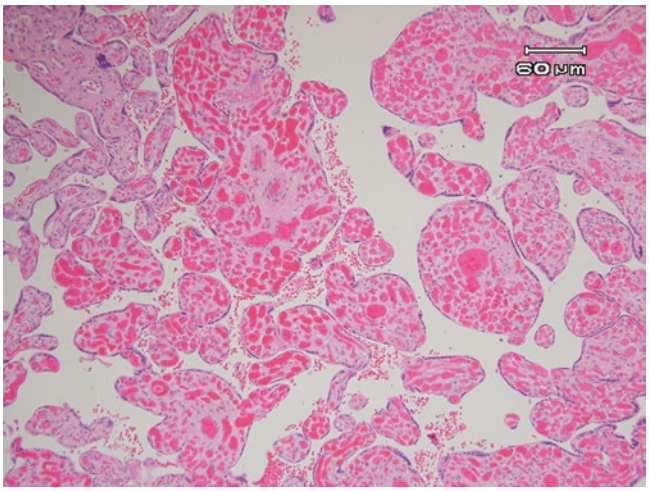

Fig. 4.26 Chorangiosis: there are multiple fetal vascular profiles in excess of ten in more than ten terminal villi in this field

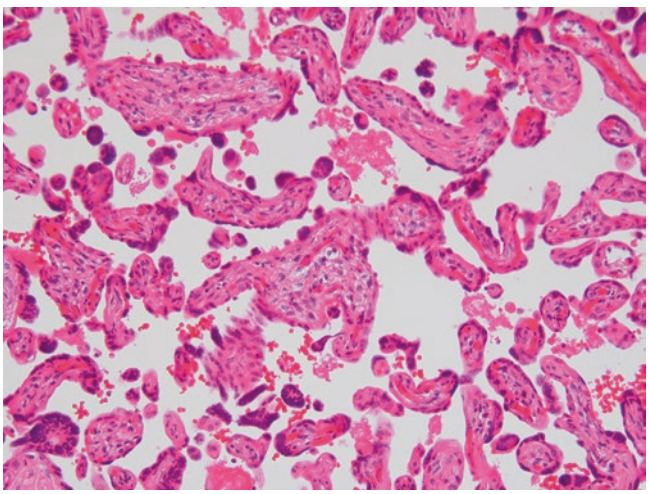

Fig. 4.27 Accelerated villous maturity with increased syncytial knot formation and thin villi

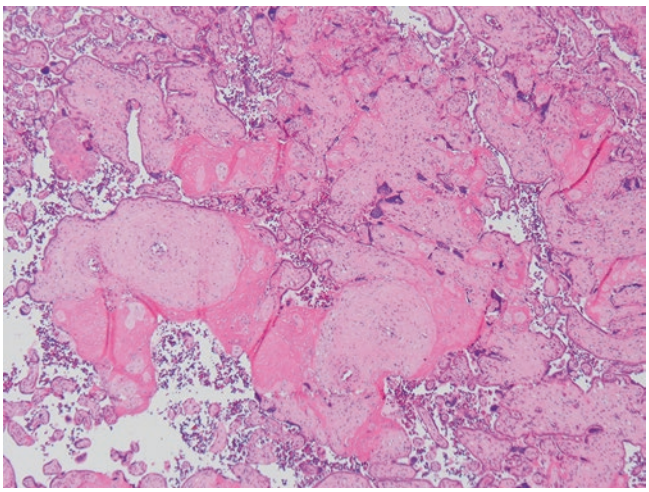

Fig. 4.28 Agglutinated villi with stromal fibrosis and cellular degeneration

Nucleated Red Blood Cells

The fetus responds to hypoxia by increasing erythropoietin production and the erythroblastosis can manifest in the placental fetal vessels as nucleated red blood cells [78].

4.5.2 Intervillous Circulation

4.5.2.1 Intervillous Thrombosis

An intervillous thrombus (preferably termed intervillous thrombohematoma) is a localized area of thrombosis within the intervillous space that displaces adjacent trophoblastic villi. A subchorionic intervillous thrombus has a similar histologic composition and borders the chorionic plate. A massive subchorionic thrombohematoma (so-called Breus' mole) is a similar, but much larger, lesion that underlies a large portion of the chorionic plate, suggested to be ≥1 cm thick and underlie ≥50% of the chorionic plate [79].

The intervillous thrombus is seen in 36% of placentas from uncomplicated term pregnancies [80]. Grossly, it is roughly polygonal to spherical and as the thrombus ages it changes in color from soft to firm and from dark-red to brown and eventually becomes a laminated white lesion (**Fig. 4.29**). Subchorial thrombosis is also a common and insignificant finding. Massive subchorionic thrombohema-

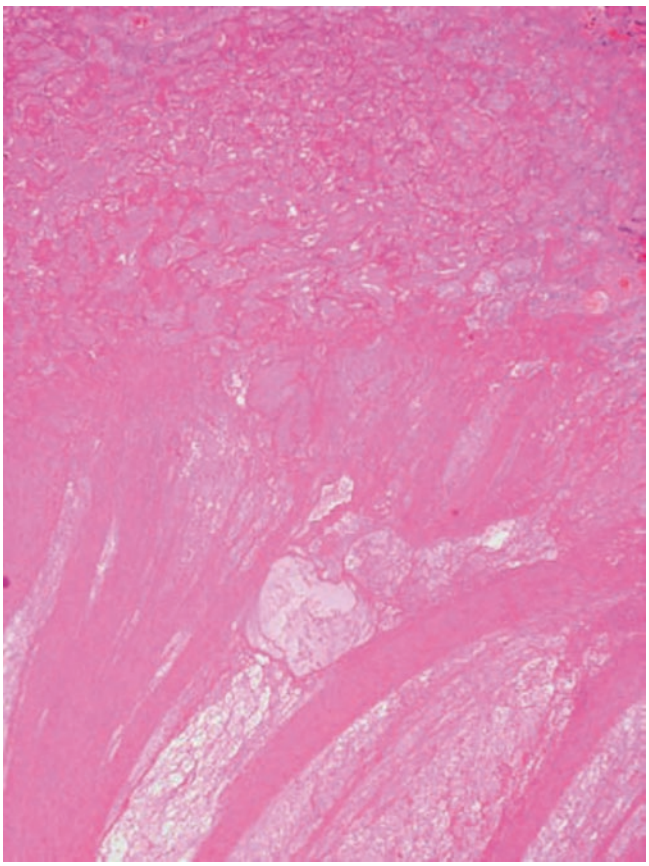

Fig. 4.29 Area of intervillous thrombosis (lower half) with contiguous infarction (upper half)

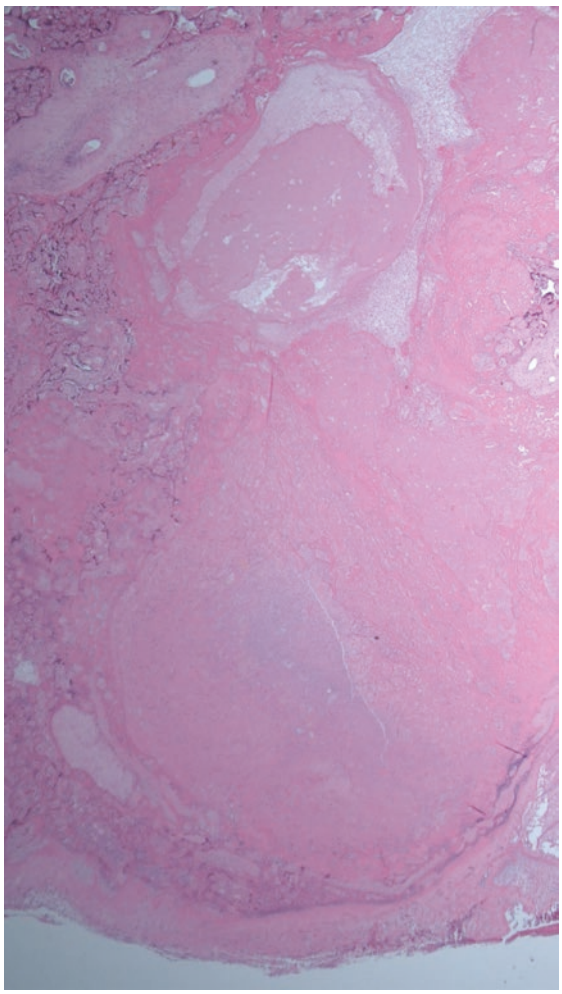

Fig. 4.30 A rounded intraplacental hematoma showing basal location and rounded configuration

toma may be seen in placentas of live-born infants, but may be a cause of mid-trimester fetal losses. Slicing shows a mass of red thrombus dissecting the chorionic plate from the underlying villi.

Fetal and maternal cells are seen in the thrombi and the increased frequency near to term when fetomaternal hemorrhage is most frequent suggests that thrombosis may occur at the site of fetomaternal hemorrhage. Intervillous thrombosis and infarcts often occur together and maternal thrombophilias has been suggested as a common pathogenetic pathway [81].

A lesion, termed a rounded intraplacental hematoma [82] or infarction hematoma, [83] that resembles an intervillous thrombus located in the basal part of the placenta except for its rounded instead of a polygonal contour, absence of laminations and compression of surrounding villi likely has a different etiology (**Fig. 4.30**). It is proposed to result from rupture of a diseased maternal spiral arteriole in the context of decidual vasculopathy or, alternatively, reperfusion of an area of placental infarction. Rounded intraplacental hematoma show an association with higher risk obstetric outcomes when compared to other lesions characteristic of maternal vascular malperfusion [82].

4.5.2.2 Perivillous Fibrin Deposition and Maternal Floor Infarction

In contrast to the minor intervillous fibrin deposition seen at term or as an adaptive response to uteroplacental hypoxia, the perivillous fibrin deposition can be extensive, sometimes affecting 30% or more of the placental parenchyma.

In massive perivillous fibrin deposition, there is gross involvement of >50% parenchyma and/or microscopic involvement of >50% by fibrinoid material on a single slide, in which the fibrinoid material involves the intervillous space spanning from the fetal to the maternal surfaces. It can be detected macroscopically as irregular white areas, best described as marbling of the sliced placental surfaces, and may be indistinguishable from infarcts (**Fig. 4.31**). Histologically, the lesion consists of villi that are widely separated by fibrin. The syncytiotrophoblast becomes degenerate but the cytotrophoblastic cells may proliferate (**Fig. 4.32**). The entrapped villi become secondarily infarcted.

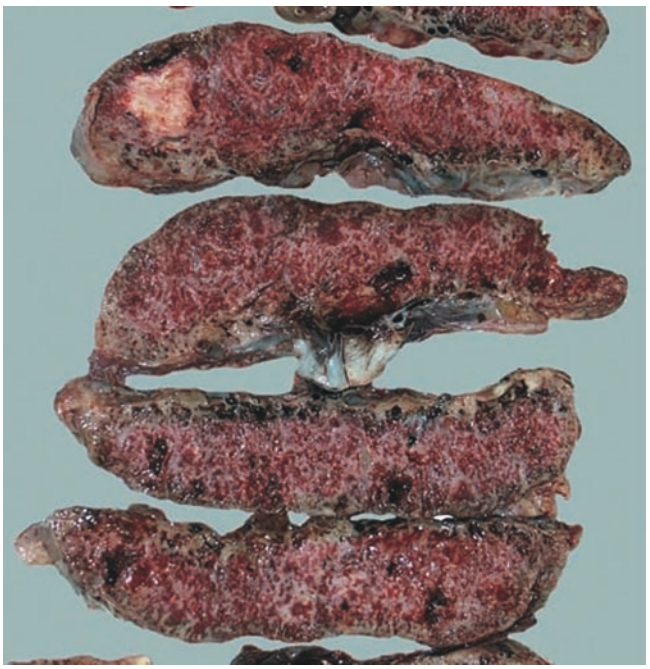

Fig. 4.31 Slices from a placenta with massive perivillous fibrin deposition showing characteristic mesh of affected villi adjacent to cystic areas of normal villi. One infarct is also seen in the upper slice

A related entity to massive perivillous fibrin deposition is maternal floor infarction. Maternal floor infarction is a misnomer as the lesion is not due to an ischemic process but due to an excessive fibrin deposition in the basal plate. Grossly, the furrows of the lobes are lost as the maternal surface becomes encased within fibrin, giving the placenta a ligneous feel. Histologically, maternal floor infarction is characterized by a thickened layer of perivillous fibrin deposition involving villi at the maternal surface, which subsequently become necrotic and avascular.

Massive perivillous fibrin deposition can affect up to 20–30% of the villous population without significant complications. Lesions affecting over half the villous tissue are rare and are associated with fetal distress and fetal growth restriction. The apparent anomaly whereby infarcts affecting 10% of the villous parenchyma are significant, whereas massive perivillous fibrin deposition affecting up to 30% cannot be explained by the underlying compromised maternal uteroplacental blood supply seen with infarction, whereas massive perivillous fibrin deposition usually occurs in the setting of a good maternal uteroplacental blood supply [80].

Maternal floor infarction and massive perivillous fibrin deposition are associated with fetal death and fetal growth restriction and may recur in subsequent pregnancies [84]. Mutations in the gene encoding long chain hydroxyl coenzyme A dehydrogenase (*HADHA*) may be associated or causative [85].

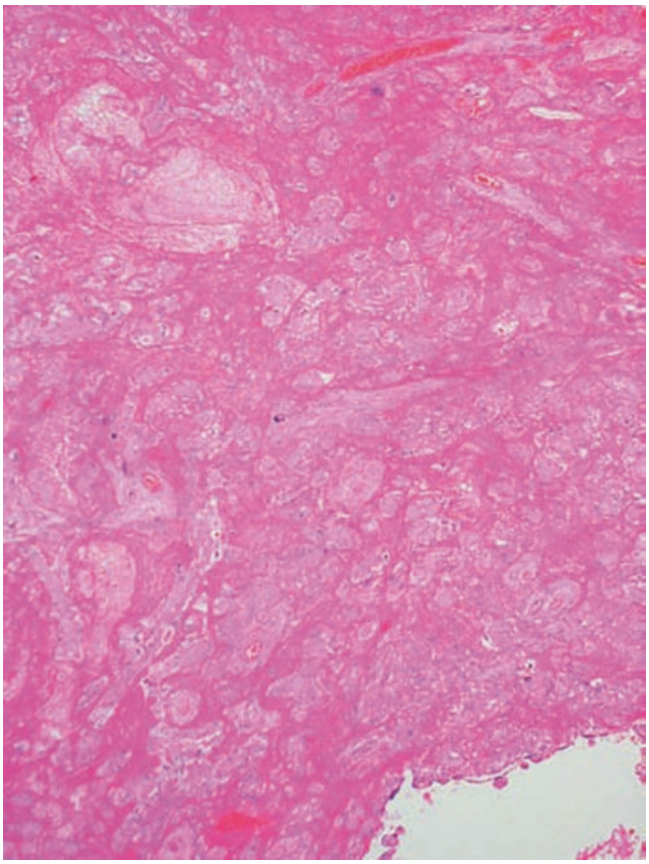

Fig. 4.32 Massive perivillous fibrin deposition showing villi encased within and separated form each other by intervillous fibrin. The lower right shows normal intervillous space, corresponding to the cystic areas of normal villi

4.5.3 Fetal Circulation

4.5.3.1 Pathological Basis of Fetal Vascular Malperfusion

Abnormal perfusion between the fetus and placenta can manifest as lesions that fall under the umbrella term of fetal vascular malperfusion. The underlying basis is Virchow's triad, namely (a) hemodynamic changes (stasis, turbulence), e.g. obstruction to feto-placental flow, such as umbilical cord knots, abnormal cord insertions, or fetal disease, eg cardiac dysfunction [86], (b) hypercoagulability, eg maternal diabetes, and (c) endothelial injury/dysfunction, e.g. inflammation from villitis or chorioamnionitis or direct vascular damage, e.g. *Col4A1*-related disease [87]. Effects may be exerted through multiple pathways, such as in diabetes where plasma levels of many clotting factors are elevated and oxidative stress leads to endothelial injury. There does not appear to be any correlation between histological fetal vascular malperfusion lesions and most of the currently known inherited thrombophilias [88, 89],

although discordance in placental pathology and twin genotypes argue for such an association [90].

4.5.3.2 Pathological Effects

Fetal vascular malperfusion manifests as thrombosis of muscularised placental vessels and other changes in the placental vessels. Fetal artery thrombosis is easy to identify as a pale triangular area with its base in the chorionic plate and produces a zone of avascular villi. A sharp division between avascular and uninvolved villi and no villous crowding is observed histologically (**Fig. 4.33**). A large thrombosed stem artery can be identified at the apex of the lesion (**Fig. 4.34**). Organization and recanalization of the thrombus may be seen, accompanied by intramural fibrin deposition that can be recent (**Fig. 4.35**) or remote (**Fig. 4.36**).

Cessation of flow results in ischemia and loss of integrity in the vessels distal to the thrombus. Extravasation of fetal red blood cells and nuclear debris are seen in the vessel walls and stroma. These features, of villous stromal-vascular karyorrhexis, were termed hemorrhagic endovasculitis (**Fig. 4.37**). Downstream vessels show stem vessel obliteration (also known as fibromuscular sclerosis) and the connective tissue is fibrous with a hyalinised appearance (**Fig. 4.35**).

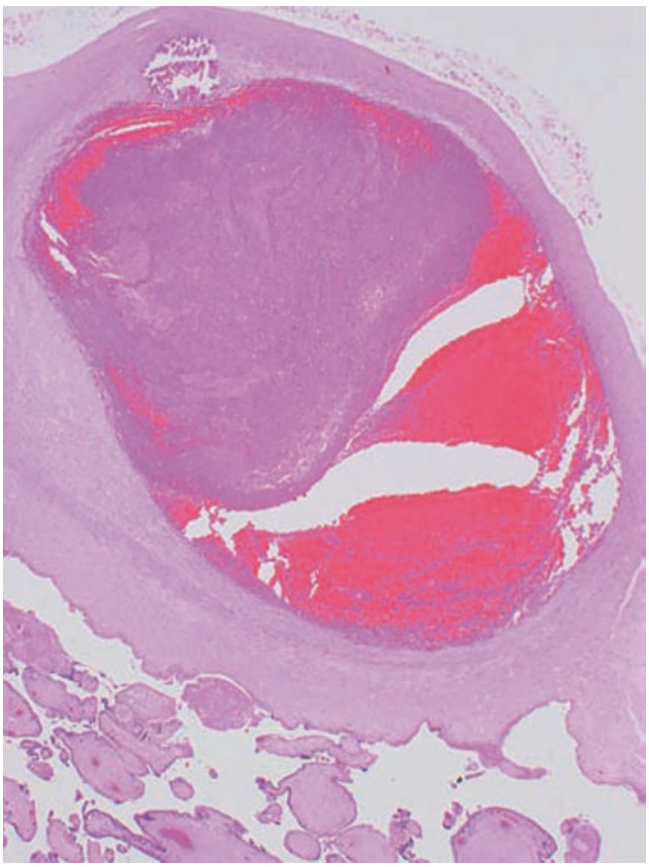

Fig. 4.33 Thrombosis of chorionic plate vessel with collapse of villous vessels in downstream villi

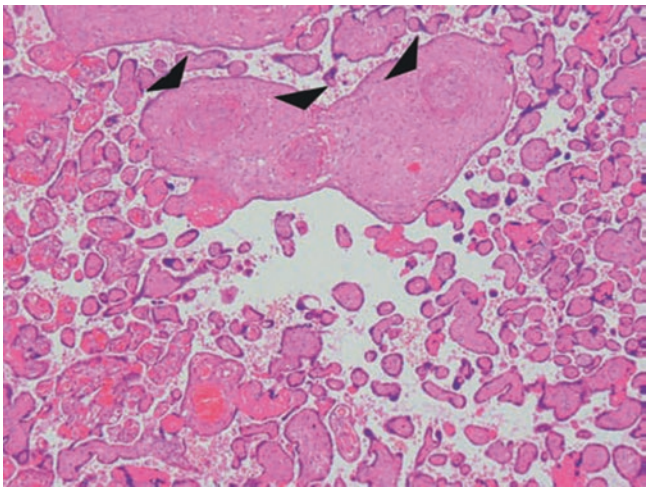

Fig. 4.34 Fetal vascular malperfusion: tracts of avascular villi on the right demarcated from the vascularized villi on the left, downstream from occluded stem vessels (arrowheads)

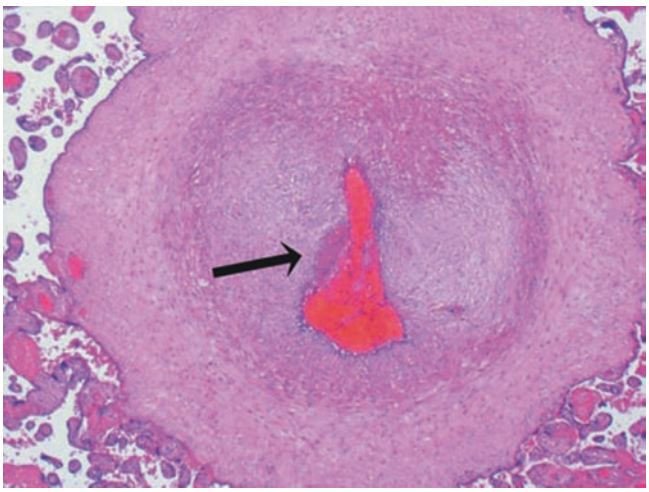

Fig. 4.35 Intramural fibrin deposition (arrow) in a stem vessel also demonstrating obliterative fibromuscuar sclerosis

There may be linear deposition of hemosiderin on the trophoblastic basement membrane of many avascular villi and also deposition in the stroma.

Fetal vascular malperfusion can be associated with an adverse perinatal outcome, including neurodevelopmental disorders and stillbirth [91].

4.5.3.3 Chorangiosis, Chorangioma

Chorangiosis has been described in the section on adaptive changes to uteroplacental vascular insufficiency.

Chorangiomas are hemangiomas occurring within villi and they occur in 1% of all placentas. Most are small, single, discrete and intraplacental; because of their characteristic red color they may be indistinguishable from fresh infarcts on gross examination. Small chorangiomas are clinically

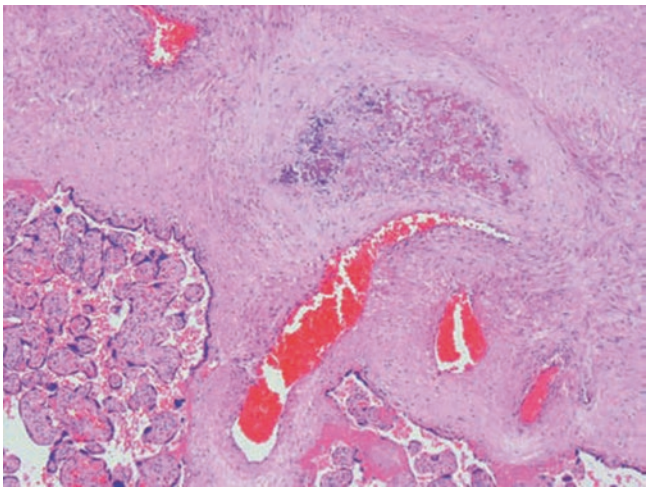

Fig. 4.36 Calcified plaque within media in an older intramural fibrin deposition

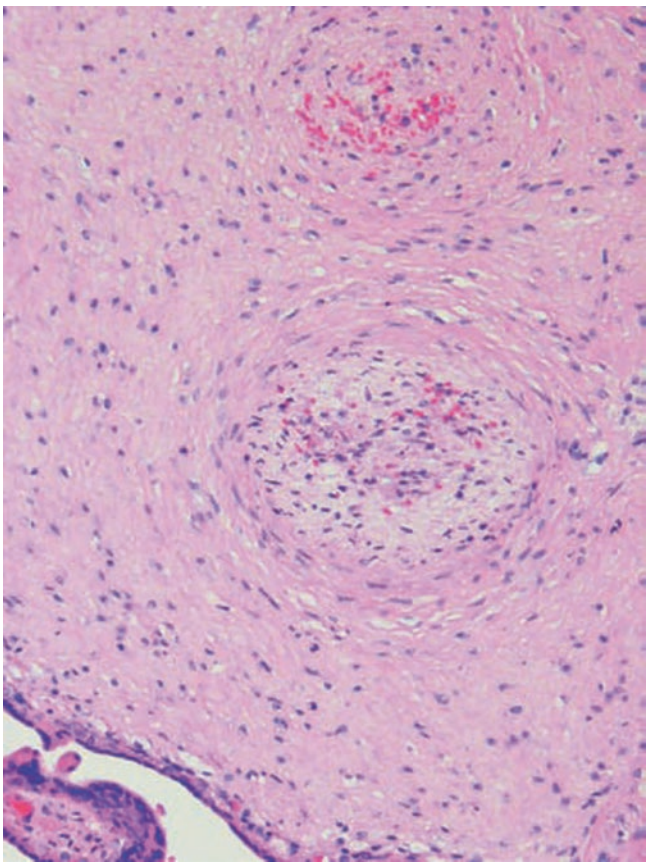

Fig. 4.37 Villous stromal-vascular karyorrhexis showing nuclear debris in vessel wall and recanalization

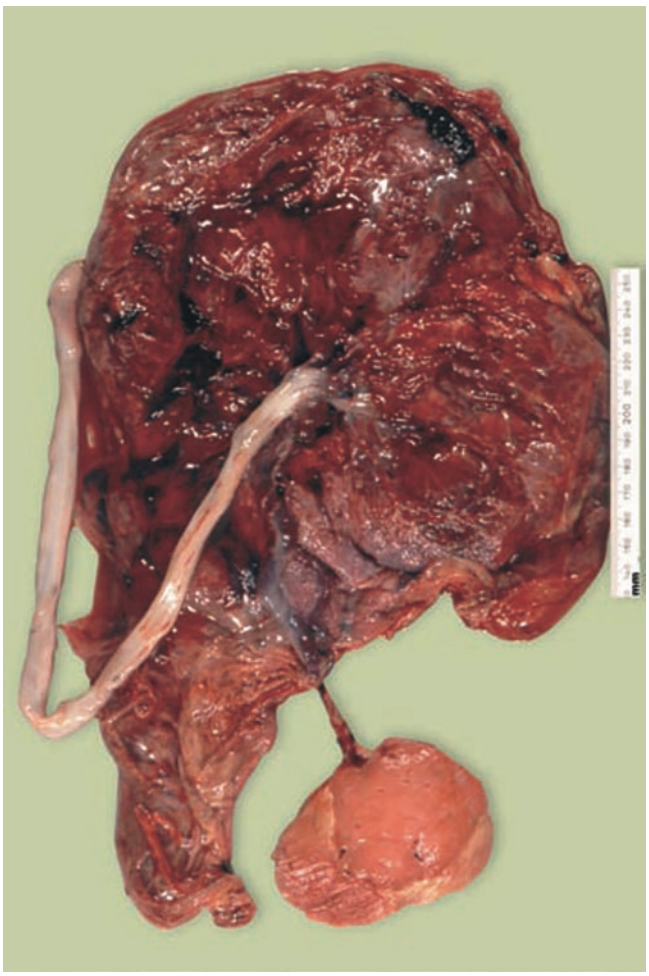

Fig. 4.38 Chorangioma attached to the fetal surface of the placenta by a vascular pedicle

insignificant. Larger chorangiomas (larger than 50 mm in diameter) may be intraplacental and elevate the fetal surface. They may lie on the maternal surface or within membranes, or may be attached to the placental disc by a vascular pedicle (**Fig. 4.38**). They may be visualized antenatally by ultrasound examination and may be an infrequent cause of elevated maternal serum alpha-fetoprotein [92]. Large or numerous chorangiomas may affect the fetus by inducing high-output cardiac failure due to arteriovenous anastomoses. Polyhydramniosis reported in a high proportion of large chorangiomas and fetal hydrops, anemia, thrombocytopenia and cardiomegaly, premature labor and antepartum hemorrhage have been described. Hemangiomas of the fetus are occasionally found in association with large chorangiomas.

Large chorangiomas are usually purplish-red, encapsulated, of variable shape, and frequently divided by fibrous septa. Histologically, they resemble a capillary hemangioma or with a predominant spindle-cell pattern, or both (**Fig. 4.39**). Degenerative changes such as necrosis, calcification, hyalinization or myxoid change are frequently present. The trophoblastic mantle may be hyperplastic (**Fig. 4.40**) but this appearance does not appear to confer any different clinical significance to the common variety chorangioma [93].

In chorangiomatosis, which affect stem villi, multiple nodules of hemangiomatous tissue are scattered throughout

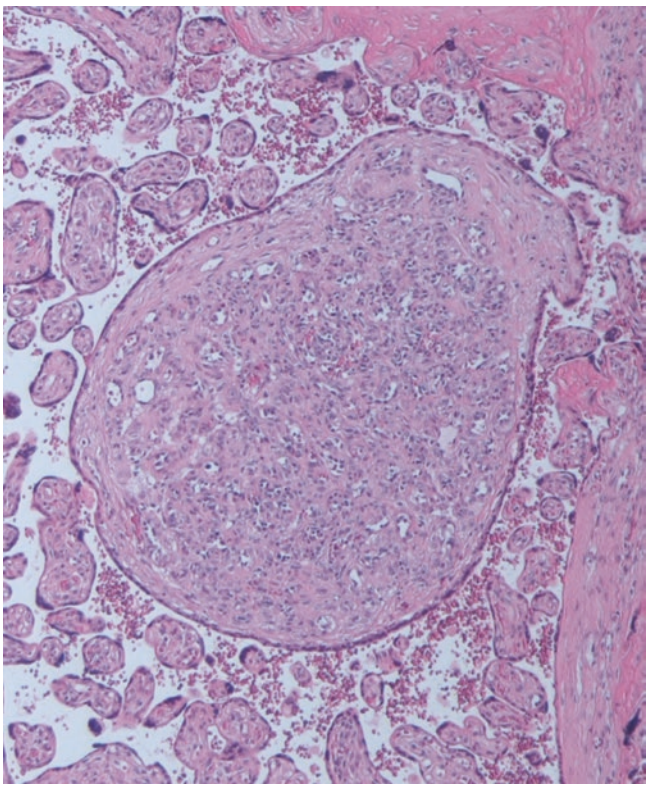

Fig. 4.39 Chorangioma showing proliferation of vascular channels with a normal syncytial trophoblast layer

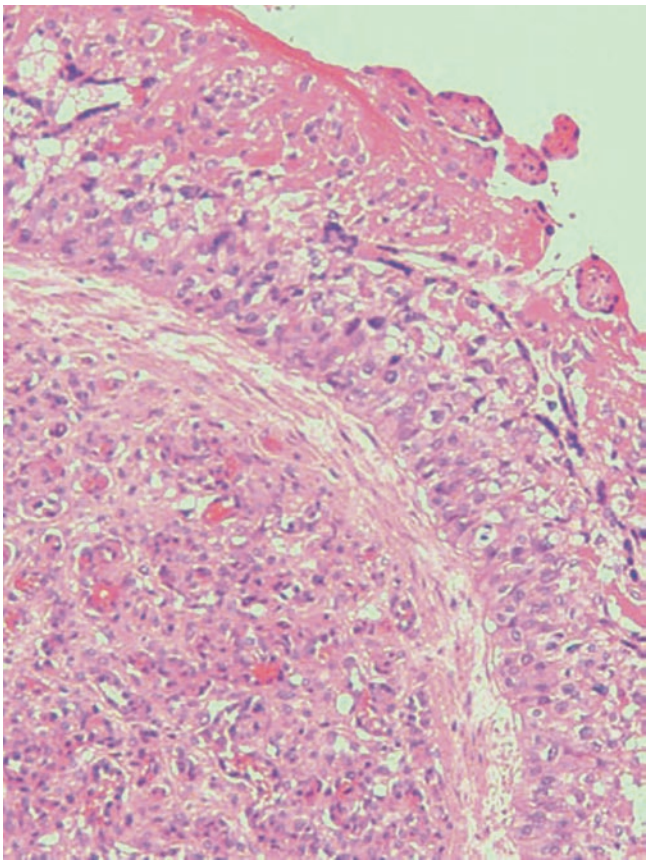

Fig. 4.40 Chorangioma with trophoblastic hyperplasia

the placenta, a condition that should be distinguished from chorangiosis, which affect terminal villi [94].

4.5.4 Villous Maturation Irregularities

Irregularities in the villous maturation pattern are recognized only histologically. An important consideration is that assessment of villous maturation is dependent on the concept of the functional circulatory lobule: the immature intermediate villi are located in the center of the lobule; in the immediate path of the blood flow from the uteroplacental arteries the terminal villi in the centrally located and better oxygenated intervillous areas are relatively less mature, whereas the terminal villi at the periphery in the venous intervillous areas, being relatively less well oxygenated in the downstream of the uteroplacental-intervillous blood flow, are relatively more mature [95]. Observer reliability in assessing villous maturity can also be problematic [75, 96].

4.5.4.1 Delayed Villous Maturity

Delayed villous maturation is characterized by an abnormal increase in immature or mature intermediate villi for the gestational age or decreased development of terminal villi after 36 weeks. Villi show reduced vasculosyncytial membrane formation with centrsally placed capillaries and, in severe forms, bulbous large villi (**Fig. 4.41**) [97].

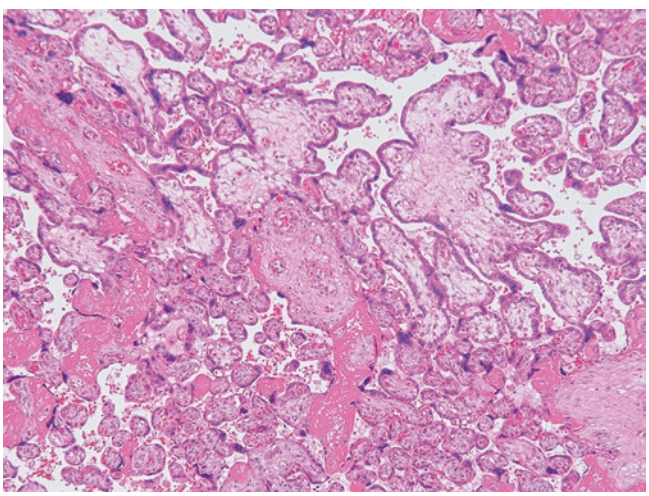

Fig. 4.41 Focus of villous immaturity in a placenta at 37 weeks gestation showing bulbous shape and persistence of cytotrophoblast

The incidence of delayed villous maturation is about 5–8% [98]. It is seen in placentas from diabetic women,

maternofetal rhesus incompatibility, and in syphilis, anencephaly and trisomies, and in stillbirth [97].

4.5.4.2 Accelerated Villous Maturation

This has been discussed in the section on adaptive changes to uteroplacental circulation.

Accelerated villous maturity is seen in a proportion of placentas from immature, prematurely delivered infants, and in pre-eclamptic pregnancies.

4.5.4.3 Placental Edema

Villous edema is seen in 11% of unselected term placentas, with significant associations with fetal and neonatal death [99]. The placenta is often edematous in those conditions that give rise to fetal hydrops, particularly when hydrops is the result of chronic fetal anemia. The degree of placental edema and fetal edema may or may not correlate: some abnormalities that produce fetal hydrops are rarely accompanied by placental edema and, conversely, the placenta may be hydropic while the fetus is normal, as in congenital nephrotic syndrome.

The hydropic placenta is pale, friable, and bulky, often weighing more than 1 kg. Fluid exudes from the cut or damaged surface. Because of its friability, manual removal of the placenta is often necessary and postpartum hemorrhage may occur. There is fluid accumulation in the villous stroma between capillaries and the trophoblastic layer giving a microcystic appearance in the stroma (**Fig. 4.42**). Hofbauer cells and cytotrophoblast appear prominent. Villous syncytiotrophoblast is usually normal and thickening of the basement membrane may be seen. Edema may be diffuse or focal. Grading or quantification remains to be determined.

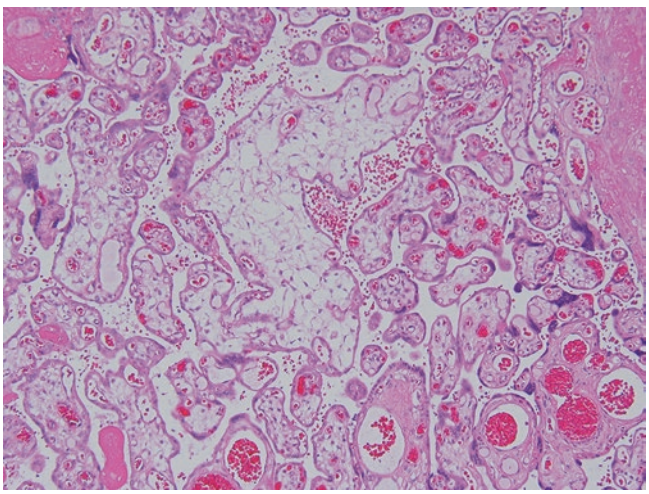

Fig. 4.42 Villous edema showing villous swelling and microcystic change with prominent Hofbauer cells

4.6 Inflammation

4.6.1 Acute Inflammation

4.6.1.1 Acute Chorioamnionitis

The term chorioamnionitis has been mired in confused usage to describe clinical suspicion of intrauterine infection. A suggestion has been made replace the previous term of clinical chorioamnionitis, as it was inconsistently defined and applied, with "intrauterine inflammation or infection or both (Triple I)" [100]. However, this too lacks sensitivity and specificity with regard to ruling in or out intraamniotic infection or for adverse clinical infectious outcome [101, 102].

Histologic chorioamniionitis is a morphologic description of the presence of inflammation in the extraplacental membranes or chorionic plate. In the earliest stage of a maternal neutrophilic inflammatory response, generally developed over a period of less than 12 h, neutrophils are seen marginating in the subchorial intervillous space beneath the chorionic plate (acute subchorionitis) and at the decidual-chorionic junction of the amniochorial membranes (acute chorionitis) (Stage 1) (**Figs. 4.43 and 4.44**). The infiltrate then spreads into the amnion, normally within 12–24 h (Stage 2), and thereafter the neutrophils undergo karyorrhexis while the amniotic epithelial cells become necrotic (Stage 3). The membranes lose their translucency indicating necrotizing chorioamnionitis. After days to weeks, the acute inflammatory infiltrate is replaced by a mixed neutrophilic-histiocytic infiltrate, a pattern termed subacute (chronic) chorioamnionitis (**Table 4.2**) [103].

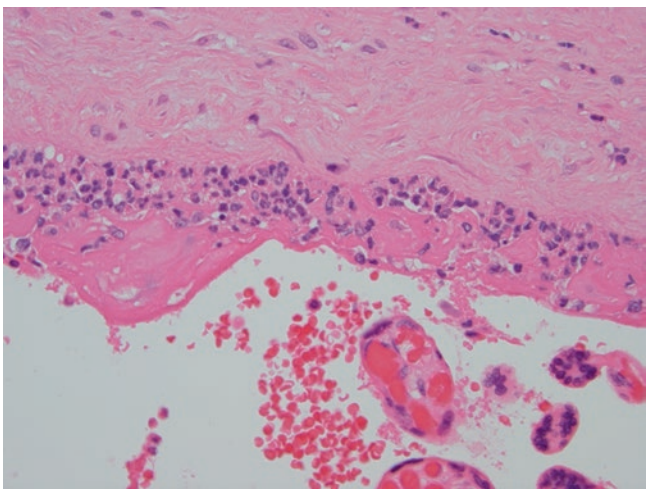

Fig. 4.43 Acute subchorionitis: margination of maternal neutrophils at the roof of the intervillous space, beneath the chorionic plate, some admixed within fibrin

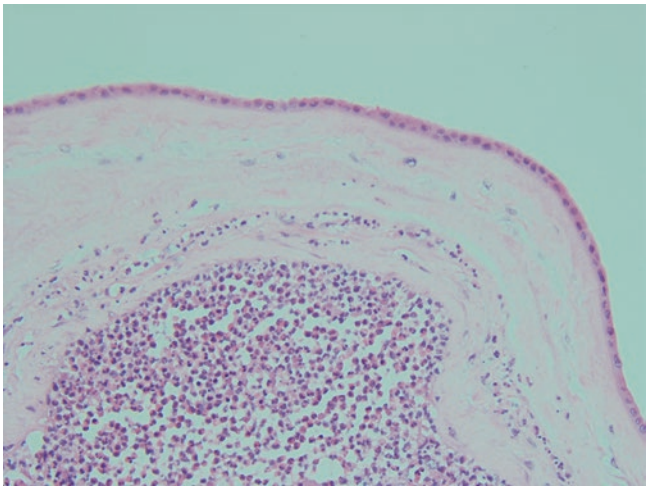

Fig. 4.44 Acute chorionitis: a dense accumulation of neutrophils is seen in the chorion laeve layer with some infiltrating into the chorion mesenchymal layer but falling short of reaching the amnion mesenchyme

Table 4.2 Acute chorioamnionitis [103]

Stage and timing	Histological pattern
Maternal inflammatory response: Stage 1 Early (6–12 h) Stage 2 Mid (12–36 h) Stage 3 Late (days) - (>36 h) Late (weeks)	Acute subchorionitis/membranous chorionitis Acute chorioamnionitis Necrotizing chorioamnionitis Subacute (chronic) chorioamnionitis
Fetal inflammatory response: Stage 1 (variable timing) Stage 2 (variable timing) Stage 3 (days) Late (weeks)	Umbilical phlebitis or chorionic vasculitis Umbilical arteritis Concentric periarteritis Necrotizing funisitis

The fetal inflammatory response begins in chorionic vessels or the umbilical vein usually in the fetal end prior to the placental end. Fetal inflammatory responses in the wall of umbilical arteries take longer to develop and the differential between the number of fetal umbilical vessels at the fetal and placental ends that display vasculitis has been used to estimate the timing of the infection [104]. At a later stage, neutrophils migrate into the stroma of the umbilical cord (Wharton's jelly) orienting preferentially toward the amniotic cavity. In time, they become aligned in an arc-like configuration around fetal vessels with inflammatory debris and even calcification, termed as necrotizing funisitis.

The prevalence of histologic acute chorioamnionitis decreases with gestational age from a high of 70% in infants born at less than 30 weeks to approximately 10% at term [105]. Not all histologic acute chorioamnionitis is infective: between 30 and 50% of term and preterm chorioamnionitis may be non-infectious and this has been confirmed using molecular techniques to overcome any culture technique bias [106]. Consequences of acute chorioamnionitis include preterm birth and premature labor. The fetal inflammatory response sets up a cytokine cascade that predisposes the infant to neurodevelopmental disorders, chronic lung disease, retinopathy of childhood and necrotizing enterocolitis [107]. Intrauterine fetal death is seldom the consequence of chorioamnionitis alone, unless there is evidence of overwhelming fetal sepsis. Furthermore, acute chorioamnionitis in a macerated stillbirth or one that has been retained in utero for a length of time may not be due to infection.

4.6.1.2 Acute Villitis

Isolated acute villitis, i.e. acute inflammation in villi not in continuity with the chorionic plate with chorioamnionitis or adjacent to infarcts or severe villitis, is uncommon. Most cases are due to fetal sepsis with Escherichia coli or Group B Streptococcus. Abscess formation may be seen in Listeria monocytogenes (**Fig. 4.45**) and in syphilis.

4.6.2 Chronic Inflammation

4.6.2.1 Villitis of Unknown Etiology

Chronic villitis is defined as a mixed lymphocytic-histiocytic infiltration of the terminal villous stroma with occasional involvement of stem villi and chorionic plate (**Fig. 4.46**). In villitis of unknown etiology (VUE), a prerequisite is no association with a known pathogen. VUE is reported to occur in 2–34% of pregnancies; the wide variation likely reflects diagnostic criteria and population differences.

In a small subgroup of VUE, the inflammation is confined to basal villi only with contiguous inflammation in the basal plate (basal chronic deciduitis) (**Fig. 4.47**). The inflammatory infiltrate in basal VUE is a mixture of B and T lym-

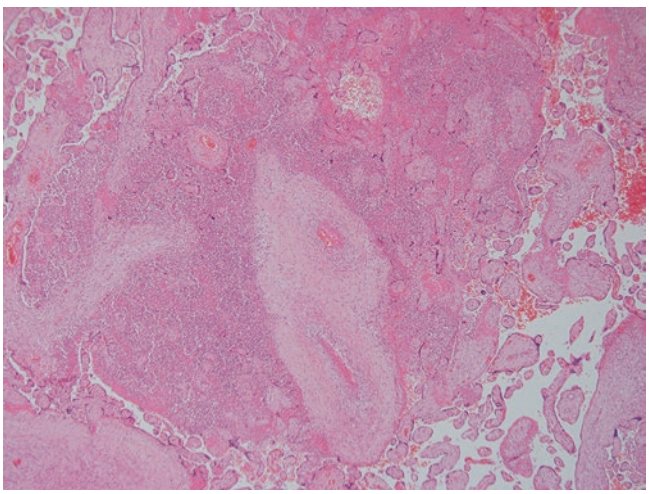

Fig. 4.45 A macroabscess, with acute intervillositis and villitis, typical of *Listeria monocytogenes* infection

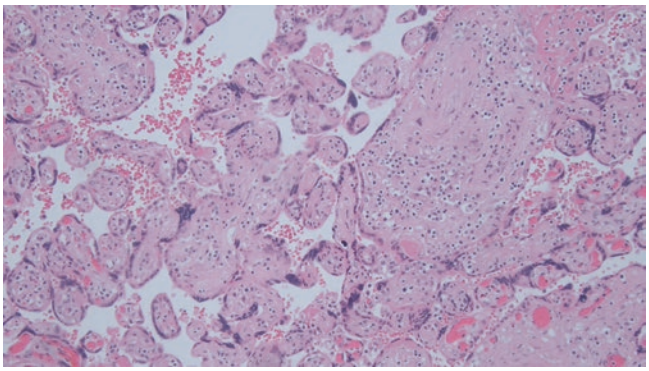

Fig. 4.46 High grade villitis of unknown etiology: there is marked chronic inflammation of the villous stroma with collapse of the fetal vessels in more than 10 contiguous villi

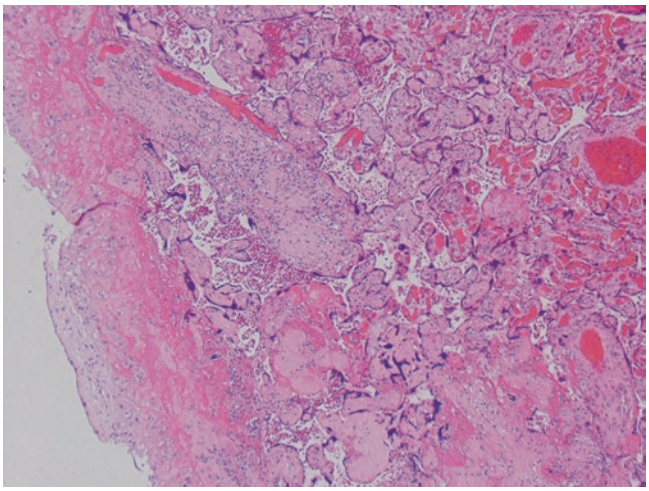

Fig. 4.47 Basal chronic villitis with contiguous chronic deciduitis

phocytes. Most VUE cases affect villi randomly elsewhere throughout the placenta. Various grading systems have been used to quantify the extent and severity of the inflammation. A two-tier grading scheme classifying cases as being low or high grade is used commonly. In low-grade VUE foci of inflamed villi contained 10 or fewer villi and were termed focal (2–3 foci) or multifocal (>3 foci). In high-grade VUE there were more than 10 inflamed villi per focus and were termed as patchy (<5% of all villi affected) or diffuse (>5% of all villi affected). The intravillous inflammation can extend to engulf fetal vessels causing chronic perivasculitis or vasculitis and leading to an obliterative vasculopathy and resultant avascular villi.

The inflammatory infiltrate in VUE comprises mainly T-lymphocytes (both CD8+ and CD3+) and macrophages with fewer B-lymphocytes. T-regulatory cells (Tregs CD4+CD25+FOXP3+) are also present. Most of the T-lymphocytes seen in VUE are maternal in origin. VUE appears to be an alloimmune phenomenon, but whether the pathogenetic initiator is maternal or fetal, and thus resembling an allograft or a graft versus host disease, respectively, remains unclear at this stage. It remains possible that VUE represents an immune response to yet unidentified organisms [108].

There is an association between VUE and maternal autoimmune disorders, obesity, and ovum donation pregnancies. Basal VUE is commonly seen with ovum donor pregnancies and also where these pregnancies are complicated by hypertension in pregnancy or fetal growth restriction (FGR) [109]. Normal pregnancy is the most common outcome with VUE. Adverse pregnancy outcome is correlated with severity of the lesion. Low-grade VUE appears to be of little clinical significance. High-grade VUE is associated with FGR with the severity of FGR generally corresponding to the extent of placental involvement. VUE has been described in stillbirths but the link is unclear. Recurrence is seen in 10-25% of cases, often with increasing severity, but cannot be predicted by the severity in the index case [110].

4.6.2.2 Chronic Villitis, Infectious

A small percentage of placentas with chronic villitis are associated with a documented pathogen. The main infections causing chronic villitis in developed countries are cytomegalovirus (CMV), syphilis, parvovirus, herpes virus (varicella-zoster, herpes simplex, and EBV) and toxoplasmosis. The villitis in these infections is believed to be the result of hematogenous dissemination from the mother to the placenta. Most occur during primary maternal infection in the absence of protective antibodies. Placental involvement in patients with chronic or recurrent disease is much less common.

Characteristic inclusions may be seen with CMV, parvovirus and herpes infections (**Fig. 4.48**). In CMV, the placenta

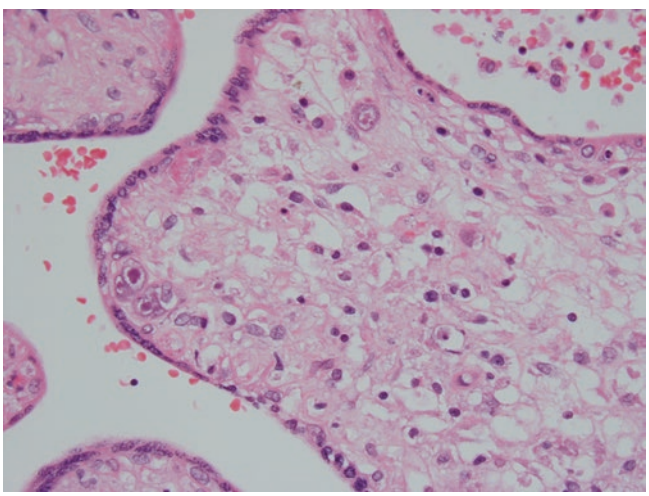

Fig. 4.48 Chronic villitis in cytomegalovirus infection with three characteristic inclusions seen

is often fibrotic and small with focal villous calcification; villous stromal plasma cells are virtually diagnostic for CMV while another clue is finding villous endothelialitis (hemosiderin deposition, vascular occlusion, and development of avascular villi). Vascular and intravascular calcification is rare in the normal placenta and their finding should prompt the possibility of CMV infection. In syphilis, the placenta is usually large and immature, but not hydropic, with a predominantly histiocytic diffuse villitis; three features taken together are highly suggestive: (1) villous immaturity with nucleated red blood cells, (2) prominent perivascular fibrosis and perivasculitis surrounding large stem villous arteries, and (3) focal lymphocytic or plasmacytic villitis. Necrotizing funisitis is seen in syphilis and in herpes simplex infections. In parvovirus, the placenta tends to be large and edematous. Herpes simplex infections can cause ascending infection leading to acute chorioamnionitis or spread hematogenously producing villitis, or there may be a combination of both mechanisms of infection.

4.6.2.3 Chronic Deciduitis

Chronic deciduitis has been defined as either a diffuse band of mononuclear cells extending across the basal plate or localized aggregates of basal plasma cells mixed with other mononuclear cells [111]. On occasion, chronic deciduitis of either type may also affect the extraplacental membranes. Rarely, eosinophils may predominate. Chronic deciduitis with plasma cells is seen more frequently in preterm labor than in control placentas suggesting a role for the inflammatory cells [112]. Severe chronic deciduitis is seen in donor-ovum pregnancies. Chronic deciduitis is also implicated in fetal growth restriction [113].

4.6.2.4 Chronic Chorioamnionitis

Chronic chorioamnionitis has been defined as the lymphocytic infiltration of the amniochorial membranes and chorionic plate akin to that of neutrophils in acute chorioamnionitis [114]. It is frequently seen with VUE and with chronic deciduitis, suggesting a common etiology. The frequency is about 19% in normal term placentas from women not in labor and about 8% from women in labor. It is seen commonly in preterm labor and preterm prelabor rupture of membranes, especially late preterm births [115].

4.6.2.5 Chronic Intervillositis

Chronic intervillositis (also known as chronic histiocytic intervillositis, massive perivillous histiocytosis, or massive chronic intervillositis*)* is defined the presence of an infiltrate occupying 5% or more of the intervillous space with approximately 80% of mononuclear cells positive for CD68 in the absence of an infection [116]. (**Fig. 4.49**). Some

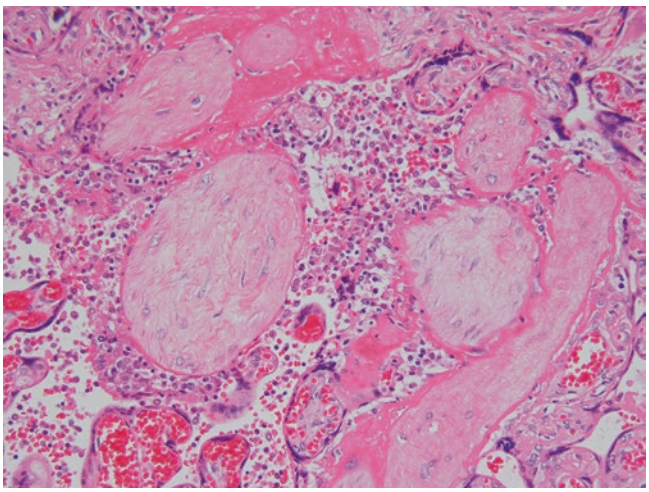

Fig. 4.49 Infiltration of the intervillous space by macrophages in massive chronic intervillositis

reports have included cases with coexisting chronic villitis, but the inflammatory infiltrate is different; similarly, cases with a polymorphic intervillous infiltrate (i.e., lymphocytes, eosinophils or neutrophils) should be excluded. The lesion is rare (about 1% in miscarriages and 0.06–0.8% in placentas) and has been associated with recurrent pregnancy losses primarily in, but not restricted to, the first trimester and with fetal growth restriction [117, 118]. CD39, a ectonucleotidase that protects tissues from inflammatory stress and cell injury, is downregulated in villous surface in massive chronic intervillositis [119], which explains the attendant perivillous fibrin deposits. Maternal serum levels of alkaline phosphastase are often elevated. Massive chronic intervillositis must be distinguished from that seen with malaria infection as the pathogenesis in the latter is clear and recurrence is unusual; malarial-infected placentas will demonstrate malarial pigment and parasitized maternal red blood cells.

4.6.2.6 Eosinophil T-Cell Chorionic Vasculitis

Eosinophil T-cell chorionic vasculitis is characterized by an inflammatory infiltrate composed of eosinophils and T-lymphocytes within vessels in the chorionic plate radiating away from the amniotic cavity and toward the intervillous space in the direction opposite to what is normally seen in fetal inflammatory response to amniotic fluid infection (**Fig. 4.50**) [120]. It is often focal, affecting a single artery or vein, and, accordingly, the true incidence is unknown although it has been infrequently reported [120]. Although initially reported as an isolated lesion, chronic villitis has been seen in between a third to half of cases. The clinical significance is unclear and the diverse range of clinical correlates reported thus far may be fortuitous [121].

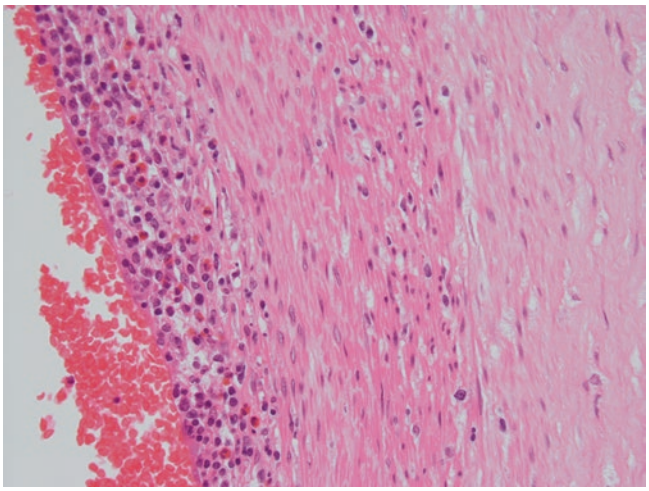

Fig. 4.50 T-cell eosinophilic vasculitis showing a mixture of eosinophils and T-cell lymphocytes typically in the chorionic vessel wall away from the amniotic cavity

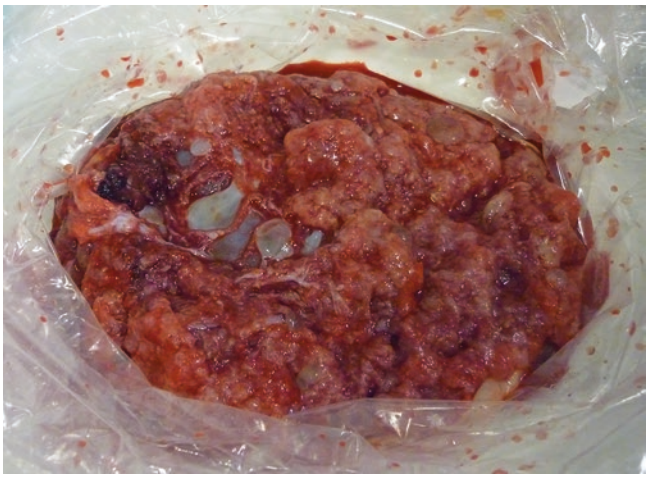

Fig. 4.51 Placental mesenchymal dysplasia: the villi, which are distended from edema and tortuous stromal vessels, could be easily mistaken for a partial hydatidiform mole

4.7 Other Miscellaneous Lesions

4.7.1 Placental Mesenchymal Dysplasia

Placental mesenchymal dysplasia is a recently recognized placental vascular malformation. The placenta is generally large and thickened for gestational age and there are numerous dilated and thick-walled vessels on the fetal chorionic surface that may extend into the intraplacental parenchyma. The vessels are variously described as being thick walled and varicose or aneurysmal. Stem villi may be hydropic and present as vesicles on ultrasound and thus mimic a molar pregnancy, but there is no trophoblastic hyperplasia histologically (**Fig. 4.51**). Pregnancies are often complicated by prematurity and fetal growth restriction [122] and associated with Beckwith-Wiedemann syndrome.

4.7.2 Other

- Visible calcification of the placenta, which may be extensive, is of no clinical significance, being found equally frequently in fresh stillbirths and in live-born infants.
- Septal cysts are oval or round cysts formed by a smooth thin glistening membrane and are often located in the subchorionic zone. They are of no clinical significance.
- A laminated, white plaque of fibrin devoid of any entrapped villi is sometimes seen on the undersurface of the chorionic plate. Subchorionic fibrin plaques are insignificant clinically. An unconfirmed finding is an association of absence of subchorionic fibrin with an increased incidence of postnatal mental handicap [123]; diminished fetal activity or movement as a result of neurological impairment in utero is suggested to lead to reduced trauma of the chorionic plate and subsequent reduced or absent fibrin plaque formation.
- Placental teratomas are rare tumors of disputed histogenesis. Some believe them to be a separate entity while others believe that they are extreme examples of fetus amorphus. They are histologically benign, with complete disorganization of its various structures and an absence of an umbilical cord. They are clinically insignificant.

4.8 Clinico-Pathologic Correlation

The various lesions described may be seen in isolation or clustered together in different clinical situations, although their correlation is imprecise and complex, but they may be seen also in uncomplicated pregnancies with normal maternal and infant outcomes. Most placental pathology fall into one of four main clusters: maternal or fetal vascular malperfusion, acute or chronic inflammation, or to other specific entities. Reporting these lesions and providing a clinical-pathologic correlation helps to explain the pregnancy outcome, identify immediate or future treatment pathways and estimate recurrence risks (**Table 4.3**).

4.8.1 Maternal Disorders

4.8.1.1 Maternal Hypertension

There are numerous terminology and diagnostic criteria for hypertension during pregnancy and several categories are recognized: gestational hypertension, preeclampsia and eclampsia, chronic hypertension, chronic hypertension with superimposed preeclampsia, and HELLP syndrome (hemo-

Table 4.3 Placental lesions with high recurrence risk

Massive perivillous fibrin deposition
Massive chronic intervillositis
Villitis of unknown aetiology (VUE)
Maternal vascular malperfusion
Multiple chorangioma syndrome
Placenta accreta spectrum[a]
Abnormal umbilical cord coiling[b]

[a]Cases sans hysterectomy
[b]Suggested

lysis, elevated liver enzyme levels and low platelet count). Preeclampsia affects 2–8% of pregnancies and is a leading cause of maternal and perinatal morbidity and mortality.

Maternal vascular malperfusion lesions are seen in all types of hypertensive disease of pregnancy [124]. Clinical, biochemical and pathology features suggest that preeclampsia can be of early or late onset with 34w being a reasonable cut-off gestational age [125]. More pathologic features of maternal vascular malperfusion and smaller sized placentas are seen in the former group while the latter demonstrate normal or larger-sized placentas [126], pointing to early-onset preeclampsia as being a placental disease and late-onset preeclampsia as a maternal disease with little or no placental pathology [127]. Maternal vascular malperfusion lesions dominate in early onset preeclampsia but there is no gestational age when those lesions would not be present [128, 129], suggesting that placental/maternal phenomenon appears to be a continuum. This is corroborated by epidemiological data showing risk factors do not dichotomously segregate neatly [130]. Chronic villitis and chronic deciduitis have also been reported but these did not seem to be associated with preeclampsia after logistic regression modeling [131].

4.8.1.2 Diabetes Mellitus

The many studies of placental pathology in diabetes mellitus have differing results owing to the failure to account for confounding variables such as the type and severity of disease, glycemic control, premature delivery, and other related abnormalities such as preeclampsia, obesity and fetal birthweight, and diagnostic criteria [132]. Diabetes in pregnancy is important because of increasing rates of the disease and its effect on maternal and fetal and neonatal health, such as preeclampsia, primary cesarean delivery, macrosomia and birth injury, and clinical neonatal hypoglycemia.

Many placentas are histologically normal and numerous studies show no difference in placentas from women with well-controlled diabetes and non-diabetic women. Placental abnormalities most consistently associated with maternal diabetes are an increased incidence of delayed villous maturation, increased measures of angiogenesis, and increased placental weight. The placenta may be edematous. Umbilical cord edema is frequent, and the incidence of single umbilical artery is increased.

4.8.1.3 Maternal Obesity

Maternal obesity is associated with multiple pregnancy complications including gestational diabetes mellitus, preeclampsia, and macrosomia, and is a major risk factor for intrauterine fetal death and stillbirth [133], and predisposes the fetus to being large for dates as well as growth restricted. Systemic chronic inflammation has been documented in obese women and obesity was positively associated with high-grade chronic villitis [134]. Features of maternal vascular malperfusion (infarcts, and decidual vasculopathy) have been reported to be commoner in placentas of obese than nonobese women [134–136]. Delayed [136] and accelerated villous maturation [134] have described. Increased prepregnancy body mass index was associated with heavier placentas.

4.8.1.4 Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy is associated with adverse perinatal mortality, such as preterm delivery and stillbirth clustering around 37–39 weeks gestation. No specific abnormality has been noted [137–139], but villous edema, cytotrophoblastic proliferation, increased syncytial sprout formation and syncytial knots have been described [139, 140].

4.8.1.5 Collagen Vascular Disease

Much of the literature pertaining to placental pathology in maternal collagen vascular diseases pertain to women with antipholipid antibodies, and may be confounded by hypertension and fetal growth restriction. Most placentas are histologically normal. Others may show massive perivillous fibrin deposition or maternal floor infarction and placental infarction [141], and a vasculopathy similar to acute atherosis.

4.8.1.6 Sickle Cell Disease and Other Hematological Disorders

Sickle crises are more common during pregnancy and miscarriage and perinatal loss may exceed 50%. The reduced oxygen tension in the intervillous space predisposes to infarction, and placental weight may be increased as a non-specific adaptation to severe maternal anemia. Microscopically, sludging and characteristic sickling of cells in the intervillous space may be seen, even in the sickle cell trait. Maternal vascular malperfusion is the predominant pathologic lesion [142].

Routine histochemical staining revealed iron deposits at the trophoblastic basement membrane in a term placenta from a woman with homozygous β thalassemia, although successful pregnancy in this condition is rare [143].

Placentas from pregnancies complicated by severe maternal anemia appear larger, the weight of the placenta being inversely related to the maternal hemoglobin level [144]. A subsequent study, admittedly with smaller sample size, found no significant association between placental:birth weight ratio and first antenatal hemoglobin concentration [145]. In women developing anemia in the third trimester, the placental weight was not different to non-anemic women, but the placental weight was increased relative to the fetal weight [146].

Maternal hyperhomocysteinemia is associated with fetal growth restriction, placental abruption, early onset pre-eclampsia, and early pregnancy loss. The placentas may show an increased incidence of retroplacental hemorrhage, associated with the abruption, and infarction. Findings in the placenta and placental bed were non-specific and not related to thrombosis per se although placental weights were reduced [147].

4.8.1.7 Cigarette Smoking

Maternal cigarette smoking is a significant risk factor for stillbirth in high income countries, [133] and the association between maternal cigarette smoking and low birthweight is well established. There is an increase in placenta previa and abruption amongst smoking mothers, the latter condition being ascribed to decidual ischemia and necrosis. Sampling, test methodology, and other confounders, amongst other factors, cloud reports on the effects of smoking on the placenta. For example, placental weights or the incidence of infarction have been found to be increased, smaller, or not different. Morphometric studies on the characteristics of the villous capillary tree are similarly diverse.

4.8.1.8 Maternal Malignant Disease

Cancer complicates approximately 0.1% of all pregnancies. Placental metastases from maternal neoplasms have been reviewed [148]. Most commonly reported tumors are malignant melanoma, and breast carcinoma. Melanoma and lung cancer may have a proportionally high risk of chorionic invasion and fetal metastases. Tumor deposits may be visible macroscopically and histological examination reveals clumps or sheets of tumor cells in the intervillous space. Villous involvement is uncommon.

4.8.2 Intrauterine Fetal Death

Following the death of the fetus in utero, the fetal circulation ceases. However, the placenta survives as maternal circulation within the intervillous space continues. Characteristic changes take place in the placenta post-mortem and it is important to recognize them so as not to implicate them in fetal demise.

Macroscopically, the placenta may appear normal if fetal death has been recent but will more likely be pale and feel firm if the fetus has been dead for a while. The histological changes may vary depending on the interval between fetal death and delivery of the placenta. No changes may be apparent if the fetus has been dead for less than 6 h. Intravascular karryohexis in the villous vessels is an early post-mortem change, being present when the time interval is between 6 h and 48 h. A striking histological feature is progressive fibromuscular sclerosis of fetal stem arteries, which eventually lead to their obliteration. The villi appear avascular because of capillary collapse and become increasingly fibrotic. If these features are present in 50% or less of the villi, fetal demise most likely occurred between 2 and 14 days before delivery. More marked changes indicate an in utero retention period of more than 14 days [149]. Another prominent feature is an increase in villous syncytial knot formation, thickening of the trophoblast basement membrane and cytotrophoblast hyperplasia. There may be patchy villous edema with an apparent increase in Hofbauer cells.

Placental lesions are seen in 11–65% of stillbirths [150] and may add more to identify a cause of death than an autopsy [151]. Placental findings in singleton stillbirths are also seen in live births but are highly associated with stillbirth. Findings reported as significantly different to live births were single umbilical artery, velamentous cord insertion, villous maturation anomalies, inflammation, chorionic plate vascular degenerative changes, maternal vascular malperfusion lesions, fetal vascular malperfusion lesions, massive perivillous fibrin deposition, and placental edema [152–154]. The prevalence of these findings were gestational age related - for example, with inflammation and retroplacental hemorrhage seen more commonly in early pregnancy—whereas fetal circulatory disorders such as thrombosis, avascular villi and edema were more common in later pregnancy [152].

Maternally perceived decreased fetal movement is associated with an increased risk of stillbirth and fetal growth restriction. Placentas from mothers who report decreased fetal movement were shown to have increased maternal vascular malperfusion lesions [155].

4.8.3 Fetal Abnormalities

4.8.3.1 Chromosomal Abnormalities

Placental changes in chromosomal abnormalities are described in the chapter on miscarriages and early pregnancy loss (Chap. 7).

4.8.3.2 Inborn Errors of Metabolism

Pathological changes in the placenta have been observed in a number of metabolic storage disorders and in some cases have been the only clue to the diagnosis, especially

in cases of fetal hydrops. Involvement of the various cell types in the placenta is tabled (**Table 4.4**). Electron microscopy on one or two villi from chorionic villus sampling can provide expedient antenatal diagnosis. Ultrastructural evidence of accumulation of metabolites was found in specimens from pregnancies complicated by Niemann–Pick, Hurler's, Pompe's and sialic acid storage diseases as early as 10 weeks gestation. Morphologic techniques to diagnose inborn error of metabolism are now superseded by molecular genotyping [156].

4.8.3.3 Fetal Hydrops and Non-immune Hydrops

A range of findings may be found in placentas from maternofetal rhesus incompatibility or isoimmunization due to ABO or anti-Kell antibodies. Grossly, the placenta may appear normal or be of normal size and weight but show pallor or be bulky, heavy and edematous and pale. Intervillous thrombosis appears to be a frequent finding. Histologically, the placenta may be normal but may show characteristic changes, particularly in severe maternofetal rhesus disease. There is usually villous immaturity and the stroma may be edematous. Nucleated red blood cells are aggregated in the fetal vessels cursorily resembling extramedullary hematopoiesis. With the development of antenatal diagnosis and treatment, many of the changes described are often not seen.

With non-immune hydrops, the placenta is usually hydropic and, histologically, resembles that seen in immune hydrops (**Fig. 4.52**).

4.8.3.4 Fetal Growth Restriction

Many studies on the placenta in fetal growth restriction are actually based on birth-weight charts that indicate that the infant is small-for-gestational age or small-for-dates, with the inference that it has suffered intrauterine growth restriction. Thus, some small-for-gestational age infants may not actually have intrauterine growth restriction while some babies with intrauterine growth restriction may not be small-for-gestational age or may even be large for dates [157]. Further, the lower limit for small-for-gestational age may be defined differently: less than 3rd, 5th, or 10th centile or <2 standard deviations below the mean.

Birthweight is affected by constitutional (e.g., genetic factors, chromosome abnormality) and environmental (e.g., infection, maternal malnutrition or diabetes, drugs such as alcohol or illicit drugs, placental milieu such as multiple pregnancy or poor uteroplacental perfusion in pre-eclampsia) factors. Many factors are related to poor fetal growth (see Chap. 2) but when no cause is found it is tempting to attribute the cause of fetal growth restriction to "placental insufficiency," a term that has been deprecated. Gruenwald argues that as the placenta is a fetal organ it cannot be responsible for poor fetal growth but its growth and development will be affected by factors suppressing or promoting fetal growth [158].

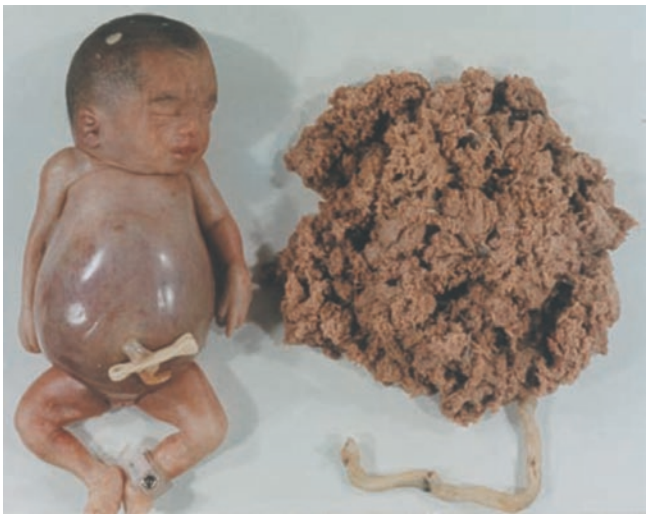

Fig. 4.52 Hydropic fetus with its bulky pale placenta in thalassemia major

Table 4.4 Involvement of various cell types revealed by light and electron microscopy. Adapted [156]

Disease	Trophoblast	Fibroblast	Endothelial cell
Sialic acid storage	+ syn and cyto	+	+
G_{M1} gangliosidosis	+ syn and cyto	+	+
β-glucuronidase deficiency	+ (patchy)	+	+
Neuramidase deficiency	+ syn and cyto	+	+
I-cell disease	+ syn	+	+
Mucopolysaccharidosis I and II	–	+	+
Pompe's disease	+ (cyto)	+	+
aspartylglucosaminuria	+ (cyto, but rare)	+	+
Wolman's disease	–	+ (macrophages)	+
Niemann–Pick A	+ (patchy)	+ (macrophages)	?
Niemann–Pick C	–	–	–
Tay–Sachs disease	+ (syn)	–	–
Mucolipidosis	–	–	+

+ = present; – = absent; syn = syncytiotrophoblast; cyto = cytotrophoblast

The placenta may be small. Placental findings related to specific infections may be apparent while those related to poor uteroplacental circulation may be seen also (see previous). Also, as noted earlier, villitis of unknown etiology can be present, the severity of which correlates with the severity of the growth restriction. Some placentas may have no obvious histologic abnormality.

Confined placental mosaicism has been found to be associated with some cases of fetal growth restriction [159] and, also paradoxically, with large-for-gestational age infants [160]. Acute atherosis was reported only in placentas with fetal growth restriction associated with confined placental mosaicism, but not in placentas with growth-restricted infants without confined placental mosaicism [161].

4.8.3.5 Fetal Hypoxia

Three vexed questions arise in relation to fetal hypoxia: whether there is evidence of fetal hypoxia, the duration of the lesion, and whether the lesion is causal. An excess of nucleated fetal red blood cells in the fetal vessels of the placenta in the absence of other causes that might cause increased hematopoietic activity is now accepted as a marker of fetal hypoxia [80, 162]. However, nucleated fetal red blood cells are present in quite a high proportion of placentas from term pregnancies but rarely more than one per 1000 erythrocytes, and their detection may be insensitive. Unfortunately, the presence of nucleated fetal red blood cells does not provide any reliable information about the timing of the fetal hypoxia. The response time for erythropoietin production and the type and amount of response to acute or chronic hypoxic states are all unknown, while release of fetal red blood cells sequestrated in the liver or spleen also hamper any attempt at estimating the time frame of fetal hypoxia.

Meconium staining of the placenta and membranes (see previous) is now no longer acceptable as a marker for fetal hypoxia. Fetal hypoxia commonly occurs in association with uteroplacental ischemia due to defective placentation and the associated histological changes may be detectable in the placenta. High expression of CD15 immunostaining in fetoplacental arteries and veins appears to serve as a marker for severe non-acute fetal hypoxia by highlighting delayed villous maturation [163], and correlated well with amniotic fluid erythropoietin [164].

4.8.3.6 Fetal Tumors

Metastases from fetal tumors, especially neuroblastoma and leukemia, are well documented. Single cases of placental metastases from fetal hepatoblastoma and malignant melanoma have been reported. The placenta appears large, pale and edematous. Histological examination reveals tumor cells plugging villous capillaries.

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