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Pathologic findings of the placenta and clinical implications – recommendations for placental examination

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Summary

The placenta is a unique and complex organ that combines the circulatory systems of two or more individuals within a single dynamic organ with a set, short lifespan. A diverse spectrum of disorders, including infections as well as metabolic, genetic, circulatory, and maturation defects, may affect its function. Pathology investigation of the placenta is key for identifying several pathogenic processes in both the mother and the foetus. Aberrant placentation, maternal and foetal vascular compromise, infection, inflammatory immunologic conditions, and disorders of maturation are elements of newly proposed classification schemes.

The clinical impact of placental examination consists of diagnosing maternal and foetal disease, identifying the potential for recurrence, correlating clinical pathological findings with distinct morphologic features, and identifying the aetiology responsible for growth restriction or foetal death.

Gestational trophoblastic disease occurs more frequently in the first trimester; however, in very rare cases, it can affect the term or third-trimester placenta.

The application of reproducible nomenclature is expected to facilitate progress in the diagnosis and treatment of obstetric and foetal disorders with placental manifestation.

Therefore, this review aims to facilitate communication between obstetricians, neonatologists, and pathologists involved in this diagnostic process.

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Introduction

The placenta is a unique and complex organ that combines the circulatory systems of two or more individuals within a single dynamic organ with a set, short lifespan. A diverse spectrum of disorders, including infections as well as metabolic, genetic, circulatory, and maturation defects, may affect its function. The pathologic investigation of the placenta yields a wealth of information crucial for optimal patient treatment. Since the early descriptive days of placental pathology, enormous progress has been made towards an improved understanding of the pathogenesis and impact of morphologic phenotypes in relation to clinical conditions.

After the pioneering work of the College of American Pathologists based on the results of an interdisciplinary task force [1], several national and regional professional societies (e.g. the German Society for Pathology, The Royal Society of Pathologists, the American Academy of Pediatrics, the Section on Neonatal Perinatal Medicine, and the Society for Pediatric Pathology) published guidelines with indications for placental examination [2–4]. However, these guidelines come from countries with unique healthcare systems, or they are published in German. Therefore, a tailored set of guidelines is needed for our country as well.

Many clinicians in the field of perinatal medicine have reservations towards this examination, which may be based on historical doubts about the value of placental examination and the lack of a general application of the standards of the examination [5].

The Amsterdam Classification has developed more informative techniques and defined criteria to yield more useful results [6, 7], the significance of which has been documented (for example, in [8]). The comprehensive Human Placenta Projects of the NIH have also expressed the increased perception of the placenta as a source of infor-

mation [9, 10]. Deficits and consequences of inadequate communication between clinicians and pathologists are apparent; to overcome these issues, mutually defined clinical data are needed in the requests for examinations, along with consistent nomenclature in examination reports [6, 11]. Patients expect a full and competent work-up of their health problems. Therefore, obstetricians and neonatologists may demand high-quality placental pathology examinations that provide relevant clinical information (see table 1) that includes information on the responsible pathologist at the receiving institution. Pathology reports should be standardised according to the new guidelines. The spectrum of thorough work-up has become so large that pathology departments should consider involving team members with special interests and expertise in placental examination [12, 13]. Without fulfilling of these two essential requirements, widespread acceptance of recommendations for placental examination cannot be expected.

Placental investigation aims to identify and classify previously unsuspected maternal or foetal disease requiring immediate attention, conditions with a high recurrence risk in subsequent pregnancies, implications for future pregnancy or patient management, and specific explanations for adverse pregnancy outcomes. This review focuses on the clinical indications for placental pathological examination and newly proposed classification schemes for placental pathology, endeavouring to unify nomenclature for facilitated communication between pathologists, obstetricians, and neonatologists. Thus, this review elucidates the contribution of placental investigation, ultimately benefiting the long-term interest of our patients, namely mothers and children.

This publication aims to provide standardised recommendations for placental investigation according to several indications, adapted to the literature [1–4, 13–15]. It offers a comprehensive list with specific clinical parameters for submitting a placenta for pathological examination (table S1 in the appendix). This list could be displayed in various areas in labour and delivery rooms to remind clinicians to submit placentas for examination. Some guidelines grade the strength of recommendation for different indications; however, this may be controversial in some cases, such as preterm births and other indications [2–4]. For practical purposes, it is more relevant to note that "placental pathology is most likely to provide explanatory data in these situations":

- Acute and unexpected adverse outcomes (birth asphyxia, depressed 5-minute APGAR score, neonatal encephalopathy, sick neonate in the neonatal intensive care unit (NICU), and critically ill mother)
- Chronic and unexplained adverse outcomes (foetal growth restriction; discordant twin growth; stillbirth; foetal, neonatal, or maternal death; recurrent foetal loss; and spontaneous preterm delivery) [13].

Table 1:
Information required for the pathologist for placenta investigation.

1. Mother: age, parity, gestational age, and maternal pathology (diabetes mellitus, gestational diabetes, hypertensive disease, or other systemic maternal disease)
2. Newborn: sex, birth weight, length, head circumference, pH of umbilical artery, and APGAR values
3. Mode of delivery
3. Course of pregnancy (uneventful, uterine bleeding, infection, peripartum fever, or abnormal amount of amniotic fluid)
5. Results of foetal examinations (no abnormalities; abnormal laboratory or sonographic findings, including Doppler flowmetry)
6. Multiple pregnancy: twin-specific identification of umbilical cord (for instance white clamp for twin A, blue clamp for twin B); chorionicity from ultrasound examination.
7. Questions for the pathologist
8. Addresses of recipients for copies of the pathology report, such as the neonatology department or referring external physicians (with the approval of the mother).

Handling of the placenta after delivery in the delivery room and information needed by the examining pathologist

When the placenta is still in the labour and delivery room, it is weighed with the membranes but manually cleaned of gross blood clots. This is recommended for practical reasons. The umbilical cord is lifted without tension from the placental disc so that the cord is not weighed. The result is recorded as the fresh weight of the placenta (table S2 in the appendix). In every obstetrical setting equipped with a balance, this value is easy to measure, and its documentation in the patient's chart is mandatory. This practice corresponds to the traditional documentation of deliveries by physicians and midwives. For multiple births, the total weight of all placentas is recorded, and in cases of separate placentas, their respective weights may also be documented.

The umbilical cord is measured, including the placental and newborn components. Notes on abnormalities in placental shape or colour, the umbilical cord, and the membranes are made, including appropriate photographs.

When a pathological examination is indicated, oral informed consent must be obtained from the mother and documented in the file. According to Swiss legislation, in exceptional cases, competent and comprehensive information must be obtained before genetic analyses are performed, and written informed consent is mandatory. Information about this kind of additional analysis should be given at a suitable time before delivery or during postpartum, but not on the labour and delivery floor.

If the placenta is sent for histopathological examination, it should be submitted fresh and untrimmed to the pathology department. The placenta is then weighed without the membranes or umbilical cord, as most percentile curves for placentas are based on the trimmed weight.

The placenta may be stored unfixed at a temperature of 4–8 °C for 3–4 days, according to local possibilities and agreements either in the obstetrical or the pathology department, depending on available storage capacities and agreements between the departments regarding the storage of tissue that will not be submitted for histological exams. Some newborns present with problems several days after an apparently normal delivery, at which point a submission can still be made [17]. Histopathologic and molecular genetic examinations may be performed on placentas fixed after up to 7 days without a loss of information. However, for optimal RNA extraction, placental tissue should be snap-frozen or placed in an RNA protection medium as soon as possible, ideally within 30 minutes of delivery. The effect of longer intervals on other aspects, such as the proteom-

ic profile, remains to be established, although initial data suggest potential significant effects [12]. For genetic counselling, "trio" sequencing (i.e. the analysis of the genomes of both parents and the foetus), a state-of-the-art technique, can be performed if sufficient resources are available [16].

Upon submission for pathology investigation, the routine macroscopic examination by the pathology laboratory, including the trimmed weight of the placenta, is performed according to the standards of the Swiss Pathology Society (table S3 in the appendix). The documentation includes the degree of coiling of the umbilical cord (normally 2–3 coils per 10 cm, i.e., a spiral or coiling index of 0.2) [3, 18–20]. Placental sampling follows the guidelines defined by the Swiss Pathology Society [21] in agreement with the Amsterdam Placental Workshop Group Consensus [6].

Mothers may opt for the personal use of their placenta. If the mother wishes to keep the placenta (whether a pathological examination is unnecessary or whether an explained examination is refused), it must be left to the mother

Definition of placental lesions (Amsterdam Classification)

In recent years, progress in placental investigation has been made, and a standardised, reproducible, and biologically based classification system has been gradually accepted. To establish an updated and agreed-upon protocol for diagnostic criteria for placenta lesions, a group of placental and perinatal pathologists as well as foetal-maternal medicine specialists from across the world gathered in Amsterdam in 2014. The consensus criteria were published in 2016 [6] and constitute the current optimal international standard for diagnostic placental evaluation. Beyond the immediate diagnostic application, the proposed classification system is also expected to improve the comparability of studies. The classification categories are listed in detail in table 2.

Placental vascular processes

Maternal vascular malperfusion

The normal placenta is characterised by low-velocity, high-volume blood flow. Maternal vascular malperfusion

Table 2:
Classification of placental pathologies.

Placental vascular processes			
Maternal stromal-vascular lesions	Developmental	Superficial implantation/decidual arteriopathy	
		Increased immature extravillous trophoblast	
	Malperfusion	Global/partial	Early: distal villous hypoplasia
			Late: accelerated villous maturation
		Segmental/ complete	Villous infarct(s)
	Loss of integrity	Abruptio placentae (arterial)	
		Marginal abruption (venous)	Acute
			Chronic
Foetal stromal-vascular lesions	Developmental	Villous capillary lesions	
		Delayed villous maturation (maturation defect)	
		Dysmorphic villi	
	Malperfusion	Global/partial	Obstructive lesions of umbilical cord
			Recent intramural fibrin in large foetoplacental vessels
			Small foci of avascular or karyorrhectic villi
		Segmental/complete	Chorionic plate or stem villous thrombi
			Large foci of avascular or karyorrhectic villi
	Loss of integrity	Large vessel rupture (foetal haemorrhage)	
		Small vessel rupture (foeto-maternal haemorrhage)	
		Villous oedema	
Placental inflammatory-immune processes			
Infectious inflammatory lesions	Acute	Maternal inflammatory response: chorioamnionitis, subchorionitis	
		Foetal inflammatory response: chorionic/ umbilical vasculitis	
	Chronic	Villitis (CMV, others)	
		Intervillositis (Malaria, others)	
Immune/ idiopathic inflammatory lesions	Villitis of unknown aetiology and related/ associated lesions	Chronic villitis	
		Chronic chorioamnionitis	
		Lymphoplasmacytic deciduitis	
		Eosinophil T-cell foetal vasculitis	
	Chronic histiocytic intervillositis		
Other placental processes			
Massive perivillous fibrin (oid) deposition (maternal floor infarction)			
Abnormal placental shape or umbilical insertion site			
Morbidly adherent placenta (PAS, placenta accreta spectrum)			
Meconium-associated changes			
Increased circulating nucleated red blood cells			

is understood as a consequence of abnormal spiral artery blood flow. This event often starts early in pregnancy because of developmental abnormalities leading to decidual arteriopathy (necrosis of decidual arteries). Global partial maternal vascular malperfusion results in accelerated villous maturation, as reflected by increased syncytial knots, increased intervillous fibrin, and decreased villous branching, leading to villous paucity. Over 30% of all distal villi affected are termed distal villous hypoplasia. Segmental complete maternal vascular malperfusion causes villous infarcts overlying occluded spiral arteries. Any infarction in a preterm placenta and any infarction affecting >5% of the placenta volume at term should be described.

Loss of maternal vascular integrity

Abruptio placentae is typically associated with preeclampsia due to atherosis/decidual arteriopathy or ischaemia-reperfusion in a central location with indentation of the basal plate and extension into the intervillous space. Marginal abruption is caused by the rupture of maternal veins at the periphery of the placenta. It may follow an acute or chronic course.

Delayed villous maturation

Delayed villous maturation is characterised by a monotonous villous population (at least 10 villi in at least 30% of one full-thickness parenchymal slide) with reduced numbers of vasculosyncytial membranes, a persistent continuous cytotrophoblast layer, and centrally placed capillaries. Focal delayed villous maturation is found in one parenchymal slide, whereas diffuse villous maturation is present in two or more parenchymal slides.

Fetal vascular malperfusion

Global partial foetal vascular malperfusion is understood as being associated with potentially obstructive umbilical cord lesions, such as hypercoiling, stricture, abnormal umbilical cord insertion site, and long-standing entanglements, and is histologically characterised by scattered small foci of avascular villi and mural fibrin deposition in large foetoplacental veins. Segmental complete occlusion of large foetoplacental vessels by thrombi leads to larger foci of villi with stromal-vascular karyorrhexis. Furthermore, delayed villous maturation might also contribute to foetal hypoxemia due to reduced oxygen and nutrition supply.

Loss of foetal vascular integrity may result in haemorrhage or oedema of placental villi. Patchy oedema of distal villi is correlated with severe acidaemia in babies born at term [22] (figures 1 and 2).

Placental inflammatory-immune conditions

The placenta mediates between two organisms and the environment. This leads to increased susceptibility to infection and occasional immune-mediated allograft-type responses. Inflammation is the main abnormal non-vascular finding.

Acute inflammatory response in ascending infection and infection with haematogenous spread is described in detail below. Most importantly, villitis of unknown aetiology (VUE) consists of the chronic cellular inflammation of the villous stroma and sometimes the intervillous space and stem villus vessels. It is currently regarded as a maternal graft-versus-host-type reaction to foetal antigens. Approximately 5–10% of term placentas contain foci of villitis of unknown aetiology [15]. High-grade villitis of unknown aetiology, defined as at least one focus involving >10 contiguous villi, carries a significant recurrence risk (see below).

Other placental processes

Massive perivillous fibrin(oid) deposition is considered an autoimmune-mediated process that contributes to a severe decrease in the exchange surface of the villi, leading to severe growth restriction or intrauterine demise [23]. The placenta might show a large variety of form anomalies because of a disrupted placentation process (myomas, scars, allo-foetal immune reaction). In addition, the placenta accreta spectrum (discussed at the end of this review) is associated with these conditions. Meconium is toxic to the amnion as well as fibroblasts and the smooth muscle cells of vessels [24]. The increase in nucleated red blood cells might raise the suspicion of foetal anaemia, prompting further investigations (e.g. ParvoB19 virus infection or foeto-maternal transfusion).

Clinical implications of placental findings

Impact on the development of the foetus concerning the failure of maturation and circulation in the placenta and neonatal/obstetrical management implications

Severe maternal vascular malperfusion is observed more frequently with maternal and obstetric disorders and can be the first indicator of maternal autoimmune disease. Investigations should include the evaluation of maternal cardiovascular status, glucose tolerance, thrombophilia, and renal function. These factors are associated with significant perinatal morbidity and mortality, including intrauterine growth restriction, foetal and neonatal demise, and foetal/neonatal neurocompromise (seizures and cerebral palsy). In addition, they have a recurrence risk ranging from 34% to 100%, and preventive measures can improve foetal and maternal outcomes in subsequent pregnancies [23]. The prophylactic use of acetylic salicylic acid, uterine artery Doppler, early third-trimester placental ultrasound, and indicated late-preterm and early-term deliveries in subsequent pregnancies may be recommended [15, 25].

In histologic chorioamnionitis with resulting spontaneous preterm delivery, neonatal antibiosis may be initiated, and the treatment of maternal conditions with an eventual causal relationship (e.g. periodontal or endometrial disease) may be considered [15].

Villitis of unknown aetiology, maternal floor infarction, and chronic histiocytic intervillositis should trigger maternal testing for autoimmune diseases, and low-molecular-weight heparin or intravenous immunoglobulin and heparin may be considered [15, 26]. Furthermore, a link between chronic histiocytic intervillositis and foetal and neonatal alloimmune thrombocytopenia, including the role of human platelet antigens, has been established. There-

fore, the diagnosis of chronic histiocytic intervillositis should prompt a respective haematologic workup of the child [27, 28].

Findings for maternal antifoetal rejection in subsets of massive perivillous fibrin deposition/maternal floor infarction could lead to further diagnostic and therapeutic options in future [29].

Foetal vascular malperfusion, especially foetal thrombotic vasculopathy, is a red flag to exclude disorders of thrombophilia, including inherited disorders (e.g. factor V Leiden), maternal connective tissue disorders (anti-cardiolipin antibodies), and other causes of systemic thromboses, such as DIC. It also alerts clinicians that a thorough neonatal exam should be performed to exclude systemic thrombi in the brain, lungs, heart, or kidneys [2].

Term infants with high-grade foetal vascular pathology are at an increased risk of developing seizure disorders, developmental disability, and static neuromuscular conditions, such as cerebral palsy [30].

Delayed villous maturation is correlated with a decreased foetoplacental weight ratio; excessive villous stroma and centrally positioned capillaries lacking vasculosyncytial membranes, as seen in diabetes; foetal growth restriction; and chronic umbilical cord obstruction [14, 15]. Therefore, in subsequent pregnancies, delayed villous maturation should prompt testing for pregestational diabetes in early pregnancy, screening for gestational diabetes in the second trimester, serial ultrasound for foetal growth and amniotic fluid, and consideration of delivery before 40 weeks [15, 31].

Disorders of placental circulation associated with foetal brain lesions

If maternal placental perfusion or foetal circulation is affected, the placenta strives to modulate the effects of un-

Figure 1: Macroscopic placenta findings. A: Placenta bipartita with marginal cord insertion. B: Velamentous cord insertion. C: Hypercoiling of the umbilical cord. D: Candida funisitis. E: Retroplacental haematoma. F: Umbilical vessel thrombosis.

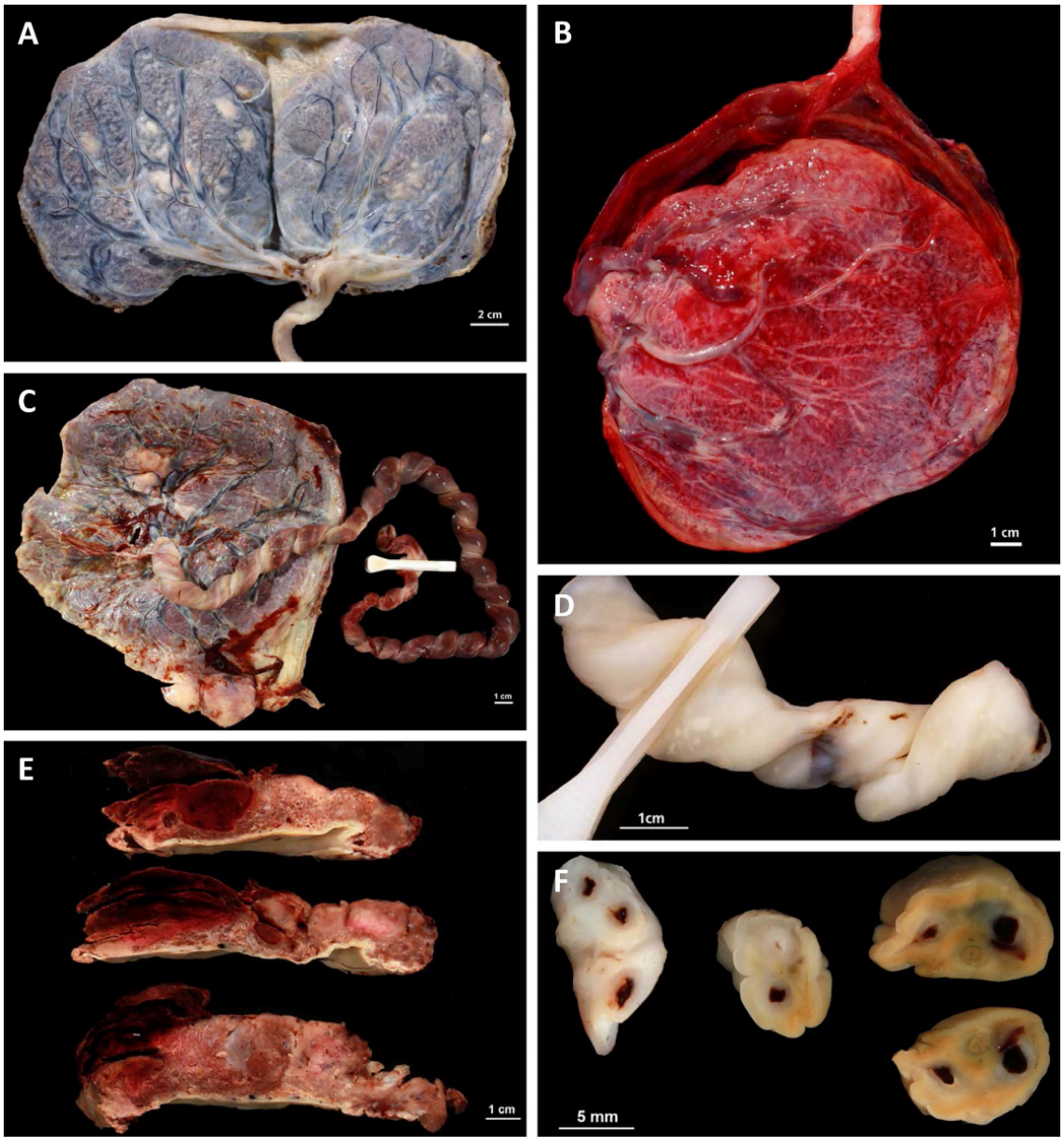
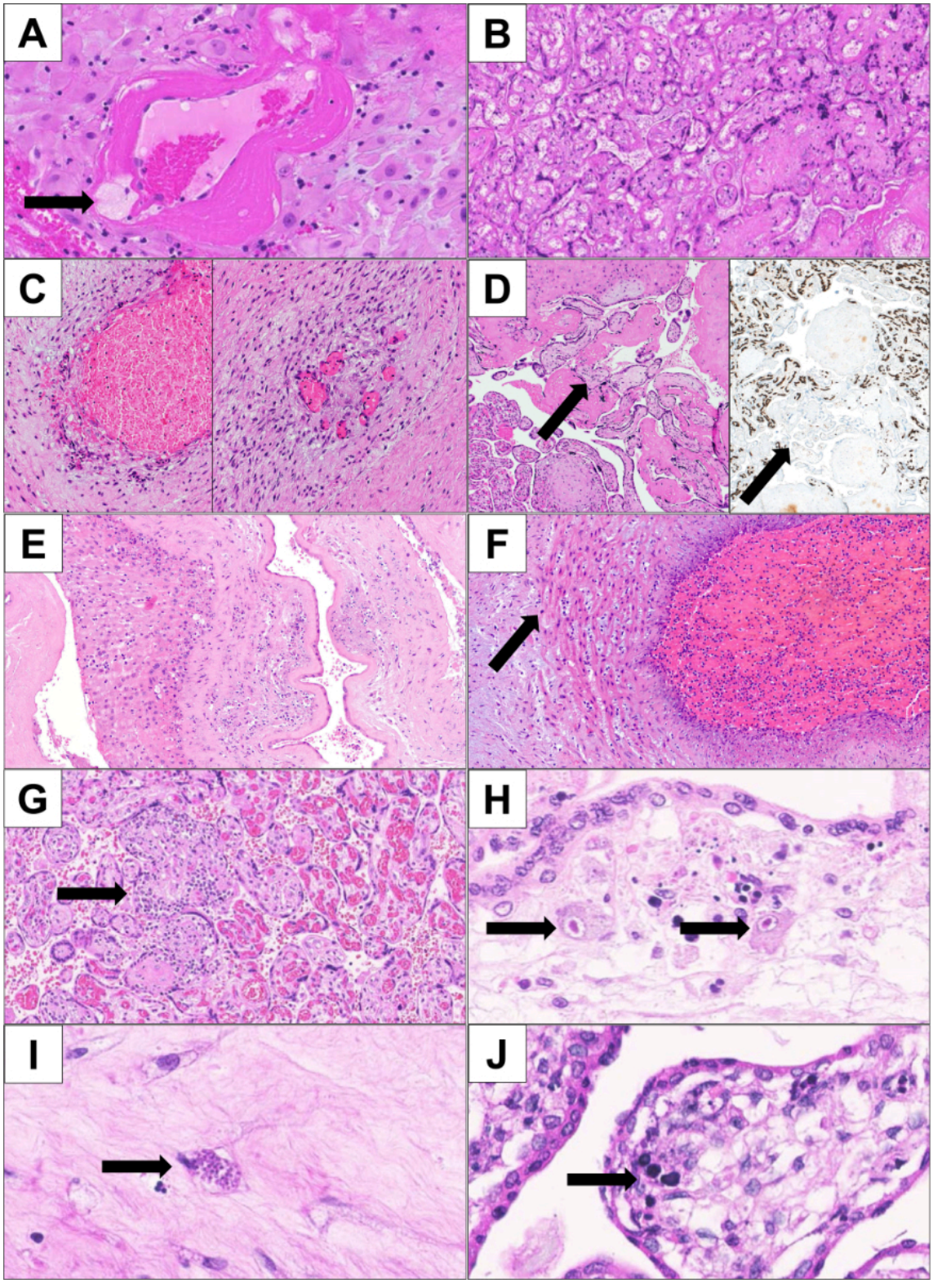


Figure 2: Histological placenta findings.
A: Decidual arteriopathy demonstrated by fibrinoid necrosis of the vessel wall and the presence of foam cells (arrow) (HE, 200×).
B: Infarct (HE, 40×).
C: Endangiopathia obliterans showing early changes (left; loss of endothelial integrity and erythrocyte extravasation) and late changes (right; fibroblast ingrowth and intraluminal septation) (HE, 100×).
D: Focus of avascular villi (arrow); the loss of capillaries is also visualised by immunohistochemical staining of the endothelial marker CD34 (right) (HE: 100×; immunohisto-chemistry for CD34: 40×).
E: Acute chorioamnionitis of the free membranes in ascending intrauterine infection (HE; 100×).
F: Foetal response to ascending infection: omphalovasculitis and debuting funisitis (HE, 200×).
G: Villitis of unknown aetiology (VUE) (the arrow shows lymphoid destructive aggregates in a villus) (HE, 100x).
H: CMV (the arrow shows two characteristic “owl eye” endothelial cells infected by CMV (HE, 400×).
I: *Toxoplasma gondii* (the arrow points to a toxoplasma cyst in the chorionic plate) (HE, 400×).
J: Parvovirus B19 (the arrow shows two characteristic “lampion” cells) (HE, 400×).



derlying disease. In a large cohort of term infants developing cerebral palsy, severe foetoplacental large-vessel lesions have profound effects on foetoplacental physiology and can be associated with the release of inflammatory mediators into the foetal circulation in 34% of patients [32]. Chronic processes that decrease the placental reserve are maternal vascular malperfusion, high-grade chronic villitis, increased perivillous fibrin deposition, chronic abruption, and distal villous immaturity; these are found in 23% of patients [32]. The placental indicators of protracted foetal hypoxia are increased circulating nucleated red blood cells and villous chorangiosis, which are present in 15% of patients [32]. In birth trauma or failed assisted vaginal delivery, placental findings may be lacking [32]. Multiple placental lesions are particularly important; in one study, 63% of patients had clinical or pathologic evidence of umbilical cord compromise [32]. Foetal vascular malperfusion, which is clinically correlated with chronic partial/intermittent umbilical cord obstruction due to hypercoiling, stricture, abnormal placental insertion sites, and long-standing foetal entanglements, has been associated with CNS injury [33, 34]. The histological features are venous dilatation, mural fibrin deposition of larger foetoplacental veins, and scattered foci of avascular villi, indicative of poor circulation of the distal villi. Extensive avascular villi have been termed foetal thrombotic vasculopathy and have been found to be associated with CNS injury and other adverse outcomes [14, 15] (figures 1 and 2).

Placental infection

Organisms present within the placental membranes may cause an inflammatory response called chorioamnionitis. This generally occurs during the second and third trimesters of gestation and constitutes the most common trigger of premature birth [35] [36]. The microbiological organisms involved are typically bacteria from the gastrointestinal and genitourinary tract, leading to an ascending infection [37–39]. The inflammatory response originates from both the mother and the foetus and is typically predominantly composed of neutrophil granulocytes.

The maternal inflammatory response leads to the migration of neutrophilic granulocytes from the intervillosum towards the chorionic plate and forms the earliest detectable inflammatory response in the form of subchorionitis. The ensuing migration towards the amniotic stroma forms the full picture of chorioamnionitis. The formation of subchorionic abscesses has been associated with adverse outcomes [40].

The foetal inflammatory response constitutes granulocyte infiltration of foetal vessels in the chorionic plate and umbilical cord [36]. Levels of circulating foetal interleukin 6 are found in inflammatory response with umbilical arteritis [41].

Microbiologic exams include a swab from the placenta in all premature children and cases of prolonged membrane rupture. The swabs are typically taken by obstetricians and should be obtained from both the maternal and the foetal sides of the membranes. For the neonatologist, atypical microbiological organisms (e.g. chlamydia) are especially relevant for further therapeutic decisions regarding the appropriate antibiotic therapy. In addition to bacterial ascending infection, haematogenous viral infections such as CMV, Zika, or COVID placentitis may arise.

CMV placentitis is characterised by marked chronic lymphohistiocytic villitis with a prominence of plasma cells and the deposition of haemosiderin in the villous stroma. Several endothelial cells might show typical cytomorphologic changes (“cytomegaly”). CMV infection is a leading cause of congenital deafness; therefore, detecting the transmission of CMV to the child in cases of CMV placentitis

Table 3:
What to look for in the placenta as the cause of specific adverse outcomes (modified from [15]).

Preterm foetal death	Maternal vascular malperfusion
	Global/ partial foetal vascular malperfusion
	Abruption
	Placental insufficiency
	Umbilical cord complications
Spontaneous preterm birth before 37 weeks of gestation	Acute chorioamnionitis
	Marginal abruption
	Mild maternal malperfusion
Foetal growth restriction/ indicated preterm birth before 37 weeks of gestation	Global/ partial maternal malperfusion (accelerated maturation)
	Chronic villitis and intervillositis [79]
	Foetal vascular malperfusion
	Foetal stromal-vascular developmental lesions
	Placental insufficiency
	Umbilical cord complications
Term foetal death	Abruption placentae
	Global/partial foetal vascular malperfusion (umbilical cord accident)
	Foeto-maternal haemorrhage
	Delayed villous maturation
	Placental insufficiency
	Umbilical cord complications
CNS injury at term	Complete/segmental foetal vascular malperfusion
	Global/partial foetal vascular malperfusion (umbilical cord accident)
	Chronic villitis with obliterative foetal vasculopathy
	Acute chorioamnionitis with severe foetal cellular inflammatory response
	Multiple placental lesions

might help preserve the hearing capability of the infected child if they are adequately treated for CMV.

Parvovirus B19 affects the foetal erythroid cells leading to severe anaemia and hydrops fetalis. In the placenta, Parvovirus B19-infected cells appear as enlarged cells with ground glass nuclear inclusions. CMV diagnosis can be confirmed by immunohistochemical stains. Chronic villitis might also be present.

In *Toxoplasma gondii* infection, cysts containing the tachyzoites might be found in the subamnionic or subchorionic tissue and beneath the surface of the umbilical cord. In case of ruptured cysts, a granulomatous reaction may occur.

In the first waves of COVID-19 in 2020, most reported findings were non-specific findings, such as signs of maternal and foetal malperfusion or growth retardation; however, in 2021, several authors reported on intrauterine foetal demise (IUFD) in the wave of the Delta variant, showing a triad of prominent histiocytic intervillositis accompanied by extensive necrosis of the syncytiotrophoblast and fibrin deposition. Further studies showed that SARS-CoV-2 could be detected in syncytotrophoblastic and cytotrophoblastic cells, the villous stroma, and possibly Hofbauer cells [42]. IUFD could be correlated with these findings on the basis of acute placental insufficiency. Transmission of SARS-CoV-2 to the child has not been reported in most cases. Interestingly, in the wave of the Omicron variant, to date, no more cases of SARS-CoV-2-related placentitis have been reported [43, 44].

Recurrence risk of placental lesions in subsequent pregnancies

Chronic histiocytic intervillositis is rare, but it may recur in 75–90% of subsequent pregnancies [45] [46]. Similarly, massive perivillous fibrin deposition or maternal floor infarction may recur in 40–60% of subsequent pregnancies [15]. Commonly, high-grade villitis of unknown aetiology (25–50%), placenta accreta (25–30%), severe maternal malperfusion (10–25%), and spontaneous preterm birth with chorioamnionitis (10-25%) carry a significant risk of recurrence in subsequent pregnancies [47–50].

Foetal growth restriction and placental causes

Foetal growth restriction (also called intrauterine growth restriction) means that a foetus was unable to reach its genetic growth potential because of interfering factors during pregnancy.

Foetal growth restriction has various definitions that vary between countries. To reach a consensus, the results of a Delphi process were published in 2016. The complexity of the phenomenon of foetal growth restriction is expressed in the mention of several foetal growth parameters as well as functional parameters (perfusion of the umbilical arteries) [51]. Foetal growth restriction is characterised by an increasing drop in sonographic growth parameters, especially the abdominal circumference, along with a foetal estimated weight below the expected values in serial measurements from early pregnancy. This observation is diagnostically more important than falling below a certain percentile (e.g. the 10^{th} or 3^{rd} percentile), as defined in various guidelines for the small-for-gestational-age (SGA) foetus or SGA newborn. This means that foetal growth restriction can also be present in a “normal weight” newborn. Conversely, an SGA newborn may have exhausted its genetic growth potential. Early-onset foetal growth restriction (<32 w) is distinguished from late-onset foetal growth restriction (≥32 w), with some authors defining the two ranges as ≤34 weeks vs. >34 weeks or <34 weeks vs. ≥34 weeks [52, 53].

Foetal growth restriction can be caused by maternal, foetal, or “genuinely” placental factors. Different factors may occur simultaneously.Descriptions of placental causes of foetal growth restriction in the literature are characterised by varying categorisations of findings by pathologists, such as vascular, macroscopic, or microscopic and congenital, acquired, or secondary abnormalities [53]. In turn, the assignment of “typical” histologic findings to specific clinical images is compromised because pathologists are typically informed about the clinical situation (i.e. not blinded) and most study designs are retrospective (based on case-series rather than case-control data) [12, 53].

Indication for placental examination in foetal growth restriction

Foetal growth restriction of any severity is an indication for placental examination. Many newborns with (intrauterine) foetal growth restriction come from pregnancies with pathologies that per se constitute an indication for placental examination, such as prematurity, maternal or other foetal pathology, or macroscopic abnormality of the placenta.

If the newborn’s weight is ≥10^{th} (≥3^{rd}) percentile (see table S1 in the appendix), foetal growth restriction cases that were not conspicuous antepartum are likely to remain undetected and, in the absence of any other indication, do not lead to placental examination.

Observations of the placenta in foetal growth restriction

The pathophysiologic processes in the placenta in foetal growth restriction are the result of complex trophoblast dysfunction. Trophoblasts in foetal growth restriction placentas exhibit reduced proliferation, increased apoptotic death, altered metabolism, senescence, and impaired invasive capacity. These cell-level changes underlie the gross anatomical changes seen in the foetal growth restriction, such as the deficient remodelling of the uterine spiral arteries supplying the placenta during early pregnancy [53, 54].

In cases of foetal growth restriction, the placenta shows a reduction in volume, surface area, and vascularisation of the intermediate and terminal villi [53]. Typically, placental weight and birth weight are highly correlated. Sonographic imaging in the first and the second trimester demonstrating a small placenta has predictive value regarding the development of foetal growth restriction. However, imaging using MRI in the third trimester may present foetal growth restriction placentas with a thickened globular appearance as opposed to the typical flattened disc seen in normal pregnancy, and the severity of growth restriction is significantly correlated with the percentage of placental volume affected by this morphology (literature cited by [54]).

Abnormal placental shapes (such as extrachorial or bilobate placentas) are associated with foetal growth restriction. Placental location on the lateral wall also carries a risk of foetal growth restriction up to four times higher compared with placental location on the anterior or posterior wall, but the data are conflicting [53].

Macroscopic vascular anomalies

Isolated small thromboses and infarcts may be found in placentas of uncomplicated pregnancies. Larger infarcts, often associated with intervillous thromboses and extensive fibrin deposition, are found in most pregnancies complicated by pre-eclampsia and foetal growth restriction. The frequently observed macroscopic vascular anomalies (lesions) in foetal growth restriction placentas are listed in table 4.

Microscopic lesions

Many different microscopic placental lesions have been described in pregnancies complicated by foetal growth restriction (table 5). Most are non-specific and have been found in villous tissue from uncomplicated pregnancies, and the terminology used to describe them is highly variable. The distribution of these lesions depends on whether the restricted foetal growth is isolated or associated with pre-eclampsia; additionally, the distribution depends on gestational age at onset, with late onset leading to a more heterogeneous group with less characteristic histological changes [53].

- Villous developmental defects mainly include villous hypoplasia, delayed and accelerated villous maturation, and chorangiosis. The entire anatomy of the villi is involved, not just the terminal vasculature.
- Foetal vascular malperfusion may impair placental function and contribute to foetal growth restriction.
- Maternal vascular malperfusion with atherosis of the spiral arteries is characterised by fibrinoid necrosis of the arterial wall, subendothelial lipid-filled foam cells, and perivascular lymphocytic infiltration; it progressively leads to the macroscopic vascular lesions described previously [53].
- Noninfectious villitis, also called villitis of unknown aetiology (VUE), has been described as a pattern of placental injury occurring predominantly in term placentas. Prevalence rates vary greatly in the literature, with 5–15% in uncomplicated pregnancies and 15–100% in pregnancies complicated by foetal growth restriction [53].
- Confined placental mosaicism and placental mesenchymal dysplasia also contribute to foetal growth restriction.

Umbilical cord anomalies

Foetal growth restriction has been associated with abnormalities of the umbilical cord insertion, which in turn are often associated with abnormalities in placental shape. The absence of one of two umbilical arteries (SUA) is associated with foetal growth restriction; however, the strength of the association is controversial [53].

Placental changes in mothers with diabetes

Typically, the dysregulation of maternal glucose homeostasis first appears during pregnancy. However, diabetes type 1 and 2 (T1DM and T2DM) also occur in pregnant women, which means that the diabetes was already present before the onset of pregnancy (pregestational diabetes). Gestational diabetes mellitus (GDM) is considered transient insulin resistance most likely due to pregnancy hormones and resolves after delivery; however, the risk of developing diabetes type 2 after pregnancy is elevated in these women [55].

In contrast to pregestational diabetes, gestational diabetes mellitus is not associated with an increased risk of birth defects. Rather, a possible weak association is attributable to overweight and obesity or unrecognised pregestational diabetes [56].

Gestational diabetes mellitus is associated with foetal and neonatal complications, such as macrosomia and hypoglycaemia, but also maternal complications, such as hypertension, pre-eclampsia, and an increased risk of caesarean delivery. Existing placental histomorphology studies of maternal diabetes present varied and inconsistent findings regarding placental abnormalities [57]. However, the changes most often described in gestational diabetes melli-

Table 4:
Pathophysiology and prenatal diagnosis of placental macroscopic vascular anomalies found in cases of foetal growth restriction [53].

Type of anomaly	Pathophysiology	Prenatal ultrasound imaging
Intervillous thrombosis	Focal coagulation of maternal blood inside the intervillous space	Echogenic cystic lesions or hypoechoic areas on ultrasound
Breus' mole	Extensive subchorial thrombosis involving at least 50% of the chorionic plate	Large echogenic lesions under the foetal placental plate
Infarcts	Villous necrosis due to obstruction of the uteroplacental artery	Complex echogenic intraplacental masses close to the basal plate
Maternal floor infarction	Lesion combining parabasal villous necrosis, fibrin deposition, thrombosis, and haematoma	Diffuse hyperechogenic lesions increasing with advancing gestation

Table 5:
Pathophysiology of placental microscopic lesions found in cases of foetal growth restriction [53].

Type of lesion	Pathophysiology
Villous developmental defects (hypoplasia, dysmaturity, or capillary dysplasia)	Malperfusion of the intervillous space by maternal blood
Atherosis of spiral arteries	Failure of spiral artery remodelling in the placental basal plate
Villitis of unknown aetiology	Oxidative stress secondary to ischemia-reperfusion of the intervillous space

tus are increases in placental weight, the frequency of immature villi, the mean number of redundant connections preterminal villi, the volume of parenchymal tissue, and the incidence of fibrinoid necrosis and chorangiosis [58–65]. When comparing pregestational diabetes (T1DM) with gestational diabetes mellitus, similar changes in the studied parameters of placental villi in the two conditions were observed, but the deviation of the morphometric parameters of placental villi was most pronounced in T1DM. The area and perimeter of the villi were reduced by 17% and 12%, respectively, in women with T1DM compared with 15% and 8%, respectively, in women with gestational diabetes mellitus [66]. In addition, placentas from women with T2DM had higher rates of decidual vasculopathy than those from women with gestational diabetes mellituswhen women with pre-eclampsia and diffuse chorangiosis were excluded, but they showed a lower rate of villous immaturity after full adjustment, indicating already-chronic damage of the maternal microvasculature in mothers with T2DM [67]. Interestingly, the correction of hyperglycaemia does not protect against placental abnormalities; several studies have shown that placental histopathologic changes exist even in pregnant women with well-controlled diabetes [58, 64, 68].

In summary, diabetes mellitus in pregnant women alters placental morphology, and morphological differences between different types of diabetes seem to exist, although the results of existing studies are not consistent.

Disorders of placental shape and placentation

A normally shaped placenta consists of a roundish disk-like organ with central or paracentral umbilical cord insertion. Abnormal placental shapes include placental lobation and elongation as well as peripheral, marginal, and membranous umbilical cord insertion. Placental shape anomalies are thought to result from disturbed development with a potential predisposition to preterm birth, foetal growth restriction, or adult cardiovascular disease [14, 69]. Accessory lobes are defined by entirely separate placental tissue foci within membranes. Placenta lobata denotes a placenta with over 50% septal incision. An elongated placenta is longer than broad, but the parameters are not yet clearly defined [14]. Peripheral umbilical cord insertion is defined as insertion less than three centimetres from the placental margin, whereas a marginal insertion is within two centimetres. Pathogenetically, currently, aberrant vasculogenesis of major chorionic vessels is implicated and correlated with adverse outcomes [70, 71].

Placenta accreta

The term placenta accreta has heterogeneous definitions [72]. Pathologists have differentiated three subtypes [73]. The most frequent form, placenta accreta, represents 75% of all cases and is defined as a lack of a decidua and direct contact between the chorion villi and the myometrium. Placenta increta is defined as an invasion or extension of the chorionic villi into the myometrium and represents approximately 18% of all reported cases. Placenta percreta is defined as a complete penetration of the myometrium and serosa. This form represents only 7% of cases. Abnormally invasive placentation is not due to the further invasion of extravillous trophoblast into the uterine wall; it likely arises due to scar dehiscence, allowing the development of chorionic villi deep within the uterine wall, including within its peripheral circulation [57]. The classification depends highly on the pathologist's interpretation, the received specimens, and the sections taken [74]. In the instance of suspicion of placenta accreta, an average of five sections of basal plate are routinely taken from the placenta. Milder forms, in which only muscular fibres are involved, are termed basal plate myometrium (BPMYO) and represent clinical occult placenta accreta; alternatively, they might be a marker of previous abnormal placentation [75]. Placenta accreta has also been subdivided into total, partial, and focal, depending on the amount of placental tissue involved [76].

However, it is not known which threshold amount and/or depth of myometrial invasion must be reached to increase the risk of subsequent placenta accreta [74].

The recurrence rate of placenta accreta is as high as 18–28% [48, 77]. Results concerning the morbidity in subsequent pregnancies are inconsistent. Vinogard et al. described a history of previous placenta accreta as an independent risk factor for postpartum haemorrhage even without placenta accreta in the current pregnancy (adj. OR = 4.1, 95% CI 1.5–11.5). Additional risk factors were placenta accreta (adj. OR = 22.0, 95% CI 14.0–36.0) and placenta praevia (adj. OR = 7.6, 95% CI 4.4–13.2) in the current pregnancy. Interestingly, they described a reduced risk of pre-eclampsia with a history of placenta accreta (RR 0.51, 95% CI 0.26–0.98).

The presence of basal plate myometrium in a previous pregnancy is associated with an increased risk of a morbidly adherent placenta (MAP) in subsequent pregnancies; 76% of women with an MAP had basal plate myometrium in a previous pregnancy. However, basal plate myometrium was detected in 40% of women without an MAP. The histological finding of basal plate myometrium from previous placenta accreta in the context of clinical data increases the positive predictive value of MAP in the subsequent pregnancy by up to 85% [74].

In a retrospective study, Roeca et al. suggested that the risk for major morbidity after a prior pathologically diagnosed placenta accreta depends on the clinical context; 29% of women who had a placenta accreta and suffered from any morbidity during their index pregnancy had a major morbidity in the subsequent pregnancy [78].

No morbidities have been reported in patients in whom the index pregnancy had placenta accreta without any clinical signs, although careful assessment and management of these patients are warranted. Moreover, even a simple history of placenta accreta without recurrent disease is associated with an increased risk of obstetric complications in future pregnancies [76].

Conclusion

This article illustrates the consequences and possibilities of placental pathologic investigation. Table S1 in the appendix was created to serve as a short reminder for daily work in the labour and delivery room regarding when to send the placenta for histopathological evaluation. Many pathologic conditions of both the mother and the foetus can be addressed with modern therapies. They are associat-

ed with a specific histologic pattern of the placenta, which can be interpreted with higher accuracy. These morphologic changes can also be correlated with the clinical context, which further results in a more targeted therapy because the underlying cause is evident. This also has prognostic and predictive implications and the potential for more effective and faster clinical management, including risk stratification and further investigations.

There is a need for standardised guidelines and reproducible nomenclature are needed, as summarised in this review, serving as a powerful tool for clinicians to act in a reasonable and personalised way that prioritises the patients.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

Table S1:
Recommendations for histopathological examination of the placenta (adapted from [2–4]).

A: Maternal indications		
Indication	**Restrictions/comments**	**Common underlying placental findings**
Preterm delivery <37 0/7 weeks gestation		Acute chorioamnionitis, marginal abruption, mild global/partial maternal malperfusion (accelerated maturation)
Systemic disorders, gestational or underlying, with concern for mother or infant (e.g., pregestational or poorly controlled gestational diabetes mellitus, severe hypertensive disorders, autoimmune disorders, collagen disorders, severe anaemia [<90 g/l], malignant diseases)	Malignant diseases: excl. cured malignancies according to clinical definitions/conventions	
Unexplained or recurrent pregnancy complications	E.g., late spontaneous abortion (14 0/7 to 21 6/7 weeks gestation[1]) or early spontaneous abortion	Global/partial maternal vascular malperfusion (accelerated maturation), global/partial fetal vascular malperfusion (umbilical cord accident), abruptio placentae, maternal floor infarction, chronic histiocytic intervillositis
Amnion infection syndrome, peripartum fever >38.5 °C	Incl. clinical suspicion of chorioamnionitis	Acute: maternal (chorioamnionitis, subchorionitis) or fetal inflammatory response (chorionic/umbilical vasculitis). – Chronic: villitis (e.g., CMV), intervillositis. – Potential identification of specific agent
Abruptio placentae	Incl. suspicion of abruption during delivery	Loss of vascular integrity: abruptio placentae (central, arterial); marginal abruption (venous); chronicity (circumvallate membrane insertion, organizing marginal blood clots, hemosiderin deposition)
Excessive uterine bleeding of unknown aetiology during 2nd and 3rd trimester		
Thick or prolonged (viscid) meconium		Meconium-associated changes (meconium phagocytosis as sign of chronic or recurrent hypoxia) delayed villous maturation (maturation defect)
History of maternal substance abuse	If suspected relevance for fetal development	
Suspicion of placental injury following invasive procedure	If suspected relevance for fetal development	Hematoma (timing)
Maternal abdominal trauma in pregnancy	If suspected relevance for fetal development	Hematoma (timing)
Maternal death		
B: Fetal-neonatal indications		
Indication	**Restrictions/comments**	**Common underlying placental findings**
Stillbirth or neonatal death	Stillbirth ≥22 0/7 weeks gestation	Preterm fetal death: global/partial maternal vascular malperfusion (accelerated maturation), global/partial fetal vascular malperfusion (UC accident), abruptio placentae; term fetal death: abruptio placentae, global/partial fetal vascular malperfusion (UC accident), fetomaternal haemorrhage, delayed villous maturation
Fetal growth restriction (FGR) or small for gestational age (SGA) (<10. p.)[2]		Global/partial maternal malperfusion (accelerated maturation), chronic villitis of unknown aetiology (VUE), complete/segmental fetal vascular malperfusion (fetal thrombotic vasculopathy), fetal stromal-vascular developmental lesions
Embryo-fetal infection, incl. suspicion of infection TORCH infections, Zika, COVID-19		Acute: maternal (chorioamnionitis, subchorionitis) or fetal inflammatory response (chorionic/umbilical vasculitis). – Chronic: villitis (e.g., CMV), intervillositis. – Potential identification of specific agent
Hydrops fetalis of unknown aetiology		
Major congenital anomalies	May be omitted if known aneuploidy	
Dysmorphic phenotype of unknown aetiology		
Suspicion of diabetic fetopathy	Independent of birthweight and maternal diagnosis of DM or GDM; incl. distribution of body fat, face, repeated hypoglycaemia, polyglobulia	
Haemolytic disease due to maternal alloimmunisation	May be omitted in mild disease manifestation during pregnancy and early postpartum	
Admission to NICU		
Compromised clinical condition e.g., non-reassuring fetal heart rate requiring urgent or immediate delivery	pH umbilical artery <7.0, Apgar score ≤6 at 5 min or ventilatory assistance >10 min	In case of antepartum hypoxemic episodes: possible strongly clotting blood and/or impression of basal plate; maternal or fetal stromal-vascular lesions, esp. malperfusion; meconium-associated changes
Neonatal haematocrit <35%		Erythroblastosis in fetal vessels
Infection or sepsis	Restricted to 72 h postpartum	
Neonatal seizures		
Suspected meconium aspiration syndrome		Meconium-associated changes (e.g., meconium phagocytosis, meconium associated myonecrosis and ulceration of the umbilical cord)
Anomalies not diagnosed antepartum		
Complications associated with multiple gestation, e.g., weight difference >20% (base: larger fetus)[3]		Distribution of placental area, feto-fetal vascular anastomoses
Multiple pregnancy with same sex and macroscopically fused placentas	May be omitted if chorionicity was determined by ultrasound antenatally	Chorionicity (confirmation of monozygosity), feto-fetal vascular anastomoses
Neonate with known or suspected malignancy	Placental metastases affect prognosis and have the potential to metastasize to the mother	For diagnoses of pathologic causes of adverse outcome, critical values and findings associated with maternal and neonatal long-term morbidity
C: Placental indications		
Indication	**Restrictions/comments**	**Common underlying placental findings**

Unusual findings in any aspect of the placenta gross examination by experienced examiner e.g., abnormal weight of placenta[4]	If neonatal pathology present (birth weight <10. or >90. p. or disturbed adaptation)	Small placenta, e.g., maternal vascular malperfusion; large placenta, e.g., oedema of chorionic villi; delayed villous maturation (maturation defect); partial hydatidiform mole; placental mesenchymal dysplasia
Structural abnormalities or masses involving the placental disc, umbilical cord or membranes	Cord: incl. thrombosis, abnormal coloration, malodour, single artery, absence of Wharton's jelly; excl. true and false knots of cord, amniotic band syndrome, accessory lobe, uncomplicated velamentous cord	Abnormal colour of cord, e.g., fungal infection; abnormal colour of placenta (pale): disturbed maturation of villi
Morbidly adherent placenta		
History of a placenta with pathology known to recur		
Termination of pregnancy for obstetrical or maternal indications		

[1] Recommended definition of late abortion: 14 0/7 to 21 6/7 weeks gestation. Limits are not uniform in literature.

[2] All charts used in Swiss University Hospitals are accepted.

[3] Birth weight discordance: (larger twin weight − smaller twin weight)/larger twin weight × 100 [74]. The ≥ 20% level for defining birth weight discordance agrees with the ACOG-SMFM recommendation [75]. A Delphi procedure consensus recommends a ≥ 25% difference for the sonographically estimated fetal weight [76].

[4] Weighing the placenta and measuring the length of the cord are not as standardized in the obstetric department as in a department of pathology after trimming, i.e., cutting the membranes and cord. Results from standardized techniques should be declared as such. If the placental weight is taken as criterion, use of the 10th and 90th percentile of the weight distribution curves is recommended for untrimmed placentas published by [77] and for trimmed placentas published by [78].

Table S2:
Normal weights of untrimmed placentas (from: Thompson JM, Irgens LM, Skjaerven R, Rasmussen S. Placenta weight percentile curves for singleton deliveries. BJOG. 2007 Jun;114(6):715-20. https://doi.org/10.1111/j.1471-0528.2007.01327.x [80], reprint with permission by the publisher).

Gestational weeks	**Male infants**					**Female infants**				
	3rd p.	10th p.	50th p.	90th p.	97th p.	3rd p.	10th p.	50th p.	90th p.	97th p.
24	150	180	260	380	460	130	160	240	350	400
25	150	180	270	400	470	130	170	260	370	430
26	150	190	290	420	490	140	180	270	400	460
27	160	200	310	450	520	150	190	300	430	490
28	170	220	340	480	550	170	210	320	460	530
29	190	240	360	510	590	190	230	350	500	570
30	210	270	400	550	630	210	260	390	540	610
31	240	290	430	590	670	240	290	420	570	660
32	260	320	460	620	710	260	320	450	610	700
33	290	350	500	660	750	290	350	490	650	740
34	320	380	530	700	790	320	380	520	690	780
35	350	410	560	740	830	350	410	560	730	820
36	370	440	590	770	870	370	440	590	760	860
37	400	460	620	810	900	400	460	610	800	890
38	420	490	650	840	930	420	480	640	820	920
39	440	510	670	860	960	440	500	660	840	950
40	460	530	690	880	980	460	520	670	860	960
41	470	540	700	890	990	470	530	680	870	970
42	480	540	700	900	1000	470	530	690	870	980
43	480	540	700	890	1000	470	530	680	870	980
44	470	540	690	880	980	460	520	670	860	960

Table S3:
Normal weights of trimmed placentas (from: Vogel M, Turowski G. Clinical Pathology of the Placenta. Berlin: De Gruyter; 2019, https://doi.org/10.1515/9783110452600, [81], reprint with permission of the publisher).

Gestational week	**Trimmed placental weight**		
	10^{th} p.	50^{th} p.	90^{th} p.
15/16	45	70	115
17	50	100	125
18	65	105	155
19	90	125	160
20	105	140	165
21	110	145	215
22	115	165	230
23	120	180	240
24	120	205	250
25	145	210	300
26	155	230	300
27	165	220	305
28	170	255	345
29	185	295	350
30	225	285	375
31	230	335	420
32	265	320	400
33	295	370	465
34	285	365	490
35	300	390	495
36	340	435	555
37	345	470	550
38	375	460	605
39	395	490	620
40	405	500	625
41	415	515	650
42	410	495	625