Virchows Arch (2004) 445:9–16
DOI 10.1007/s00428-004-1032-2

REVIEW ARTICLE

Thomas Stallmach · Gundula Hebisch

Placental pathology: its impact on explaining prenatal and perinatal death

Received: 27 November 2003 / Accepted: 15 April 2004 / Published online: 11 May 2004

Abstract This review considers six main situations in which pathologists are expected to report and interpret placental messages for obstetricians, neonatologists and, indirectly, parents: (1) abortion is the body's corrective response to the embryonic defect suggested by malformed chorionic villi; (2) infection causing chorionic villous inflammation is specific and haematogenous; pathogen identification is mandatory, in contrast to chorioamnionitis caused by increased local immunosuppression allowing indiscriminate bacterial entry; (3) prematurity and (4) intrauterine growth restriction are often associated with pregnancy-specific disease (pre-eclampsia) or pre-existing maternal conditions (systemic lupus); parental studies may improve outcome in subsequent pregnancies; (5) intrauterine death near term is often due to placental dysmaturity featuring a severely reduced number of syncytiocapillary membranes; it accounts for the death in utero of 3 in 1000 pregnancies; detection helps to minimise recurrence in subsequent pregnancies; (6) twins are best confirmed as monozygous by the absence of chorionic tissue in the dividing membranes; most monochorionic twins have vascular connections whose detailed analysis is requested only if there are inter-twin differences in growth and colour. From a formal point of view, many more bits of pathology than discussed in this review can be found in placentas and, with the advances in ultrasonography, might even be seen prior to birth. The extent of such a disturbance might ultimately affect fetal growth, which is amenable to prenatal detection offering the chances for an appropriate management. In contrast, dysmaturity is a great challenge as no predictive tests are as yet available.

Keywords Placenta · Pathology · Abortion · Infection · Intrauterine growth restriction

T. Stallmach (✉)
Department of Pathology,
Zurich University Hospital,
Schmelzbergstrasse 12, 8091 Zurich, Switzerland
e-mail: thomas.stallmach@usz.ch
Tel.: +41-1-2552101
Fax: +41-1-2554416

G. Hebisch
Department of Obstetrics and Gynecology,
Zurich University Hospital,
Schmelzbergstrasse 12, 8091 Zurich, Switzerland

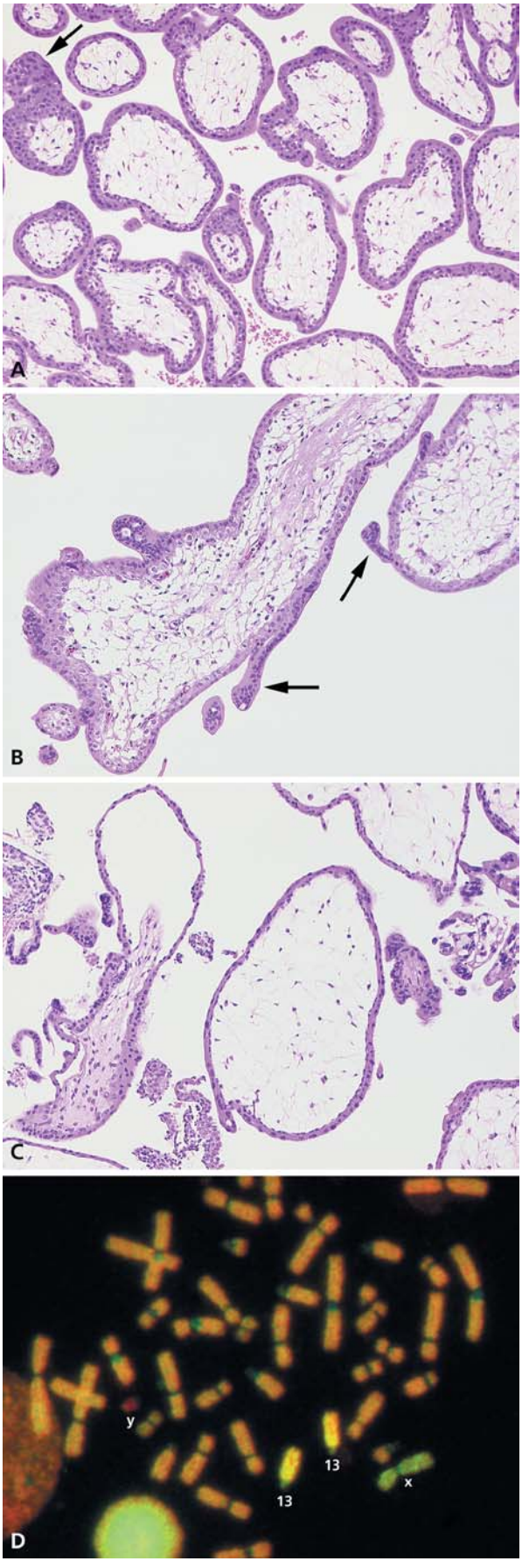
Introduction

Examination of the placenta by the pathologist is mandatory in cases of abortion, fetal malformation, infection, growth restriction, pre-eclampsia, late intrauterine death, intra-partum hypoxia (documented deterioration of the cardiotocogram or low pH immediately post-partum) and complicated twin pregnancy (feto-fetal transfusion syndrome, differences in body weight, zygosity). The pathologist needs a written request from the clinician, with information to include (at a minimum) the week of gestation, fetal weight, maternal health during pregnancy and the indications for referral (ideally in the form of the questions that the clinician would like to have answered).

Abortion (miscarriage)

Some 50% of all conceptions are thought to end in early abortion, many unnoticed. Timing life from the sperm's entry into the egg, John Opitz [17] said: "Most men die before birth, not after birth". Human reproductive failure is characterised less by resorption (as in mice) than by the expulsion of the products of conception. For the pathologist who receives the decidua with a line of demarcation and placenta, the single most important question is: are the chorionic villi normal? If 'No', it can be assumed that abortion has corrected an earlier mistake.

Chromosomal analysis of early and very early abortion tissue reveals a high proportion of pathological karyotypes [4, 12, 26], including tetraploidy, triploidy and trisomy of all chromosomes (with the sole exception to date of trisomy 1). Via an unknown mechanism, the maternal



organism detects and aborts these chromosomal pathologies. Although such karyotypes are compatible with limited trophoblastic and chorionic development, the architecture of the resulting chorionic villi, stratification of trophoblast layers, vascularisation and stromal density are abnormal (Fig. 1). Generally speaking, abnormal chorionic villi are mostly due to an abnormal karyotype, i.e. a genetic abnormality that—with very rare exceptions—is sporadic. Prolongation of such a pregnancy is neither desirable nor feasible. Precise characterisation of the chromosomal abnormality, e.g. trisomy of which chromosome, requires living cells for fibroblast culture and karyotype analysis. Alternatively, formalin-fixed, paraffin-embedded material can be subjected to comparative genomic hybridisation to detect the surplus DNA derived from the extra chromosome [5, 7] (Fig. 1d). Both methods are laborious and expensive, and the information retrieved is not required by the individual patient. If the parents wish for another child, there is no clearly defined need for a period of contraception.

If the chorionic villi are normal, on the other hand, this is bad news for the mother, since the assumption must be that she has aborted a potentially normal child. The reasons are not usually evident from the histology. Recurrence can be common. Many clinicians consider further exploration or a period of contraception helpful [25]. Recurrent abortion is defined by three consecutive early abortions of identical type, ideally with the chorionic villi showing the same disturbed architecture. Only then is parental karyotype analysis indicated. It occasionally detects a balanced chromosomal abnormality in one parent as the repeated cause of imbalance in the conceptus [1].

Infection

Irrespective of the cause of pregnancy failure, abortion material reveals inflammation as part of the desquamation process of devitalised tissues. In contrast, inflammation

Fig. 1 Early chorionic villus morphology and karyotype. **A** Normal chorionic villi show uniform branching architecture, trophoblast layering and stromal density. Polar proliferations of cytotrophoblast (*arrow*) are normal in early pregnancy. Haematoxylin and eosin (H&E), ×80. **B** Malformed villi are often large with irregular contours and syncytiotrophoblast piling (*arrow*). H&E, ×80. **C** The great diversity of abortifacient abnormal karyotypes is reflected in a variety of patterns of chorionic villus malformation. In this example, the dominant feature is stromal heterogeneity. H&E, ×80. **D** Ideogram of comparative genomic hybridisation analysis of DNA from a paraffin block with malformed chorionic villi (probe). The extracted DNA has a female karyotype and is hybridised on a normal male metaphase preparation: the Y chromosome is *red* because no corresponding DNA is present in the probe DNA (*green*). The X chromosome is *green* because of a surplus of X-derived DNA in the probe (ratio 2:1). Both chromosomes 13 are *bright yellow* compared with all other chromosomes because of a surplus of chromosome 13-derived probe DNA (ratio 3:2). The technology establishes the karyotype in different areas of the placenta with different morphology in cases of suspected mosaicism, but is not recommended for routine use. (Source: Scharpf P, doctoral thesis, Zurich 2002)

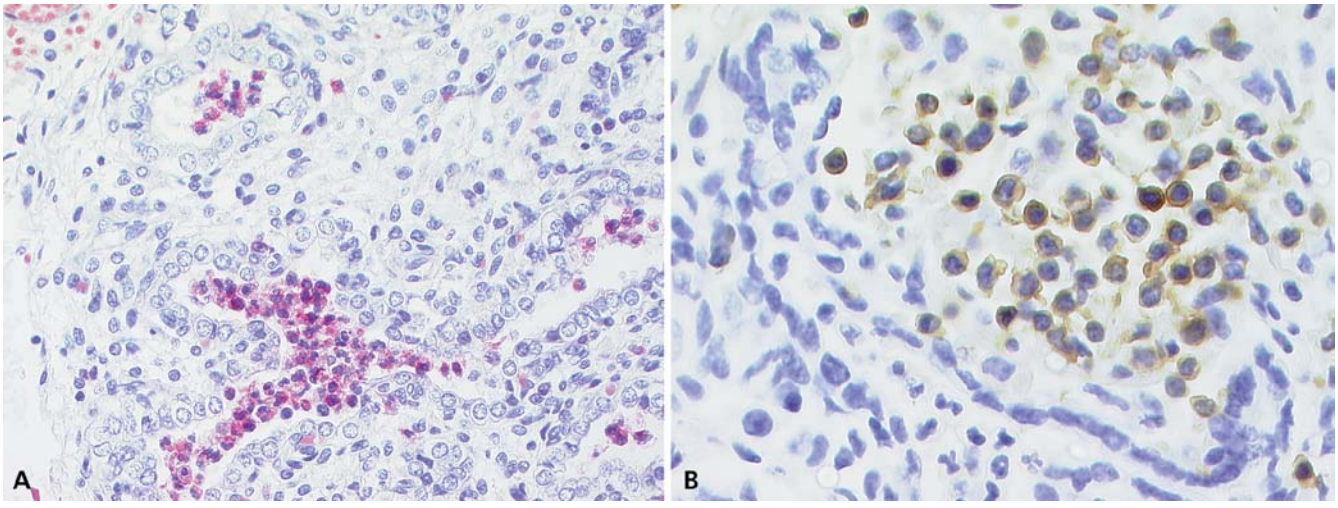


Fig. 2 Fetal lung with amniotic infection syndrome (chorioamnionitis). **A** Segmented maternal granulocytes aspirated into the alveoli from amniotic fluid. This should not be diagnosed as 'pneumonia'. The absence of aspirated granulocytes in otherwise unequivocal chorioamnionitis indicates oligohydramnios. Chloroacetate esterase stain, ×250. **B** Longstanding chorioamnionitis produces bronchus-associated lymphatic tissue. Lymphocytes labelled with CD45 antibody, ×400

due to infection becomes more prevalent from 16 weeks of pregnancy onwards.

There are two main scenarios. The first is that of so-called ascending amniotic infection [19], which is recognised by neutrophilic infiltrates in the membranes, chorionic plate and umbilical cord. At autopsy, the fetus—even when submitted without the placenta—readily reveals the diagnosis by increased hepatic granulopoiesis, ingested and aspirated granulocytes and the formation of bronchus-associated lymphatic tissue in the lungs (Fig. 2). The most sensitive finding is the presence of segmented neutrophilic (maternal) granulocytes within the fetal alveoli. However, care should be taken to discriminate apoptotic fetal cells from the alveolar lining. Furthermore, granulocyte aspiration and ingestion can be completely missing following oligohydramnios (preceding premature rupture of the membranes). Increased granulopoiesis within the fetal liver sinusoids, i.e. more than 15 granulopoietic cells per high power field (excluding the portal tract, where brisk granulopoiesis is physiological) visualised with a chloracetate esterase stain, is, thus, a more reliable indicator [22]. The formation of bronchus-associated lymphatic tissue can be most striking, however, and is seen in fetuses exposed to chorioamnionitis for several days [9]. Organism culture and special stains are not required. However, if the cord shows macroscopic yellow spots or histological evidence of superficial necrotising inflammation, there is a high suspicion of fungal infection, and periodic acid-Schiff staining for Candida is indicated.

The alternative scenario is haematogenous infection of the fetus, indicated by inflammation within the chorionic villi. In bacterial infections, granulocytes predominate while lympho-plasmocytic infiltration usually signifies cytomegalovirus (CMV) infection in developed countries. Whereas most viral infections can only access the fetus after primary infection of the mother during pregnancy [parvovirus infection, varicella (chickenpox), rubella (German measles) and toxoplasmosis], reactivation of latent maternal CMV infection can severely damage the fetus.

Haematogenous infection of the fetus is a mandatory indication for pathogen identification [3, 15]. It is the example *par excellence* of infectious disease. Chorioamnionitis, however, is not, since its most likely primary cause is an imbalance between fetal trophoblast invasion and maternal adaptation. Presumably, this results in a surplus of local immunosuppression and facilitates the ascension of bacteria from the vagina. Infection, then, can be caused by any of the bacteria present in the urogenital and intestinal tract, obviating in general the need to identify them as "pathogens".

Prematurity

Very immature newborns (24–28 weeks of gestation) are often the product of medical intervention designed to rescue either the fetus from adverse in utero conditions or the mother from the consequences of pre-eclampsia. Pregnancy is usually terminated by caesarean section timed by risk-factor assessment following the induction of fetal lung maturation using cortisone given to the mother.

Placentas should be sent for examination to document the antenatal diagnosis. Amniotic infection (see above), at some stage, induces labour, which cannot be stopped. Maternal inflammatory parameters (fever, C-reactive protein) and contraction intensity often correlate quite well with the intensity of placental inflammation, provided that at least two strips of extraplacental membranes, two to three segments of umbilical cord and three blocks from the placenta are examined [14, 29].

In contrast, pre-eclampsia does not induce uterine contractions. Termination is usually indicated on maternal

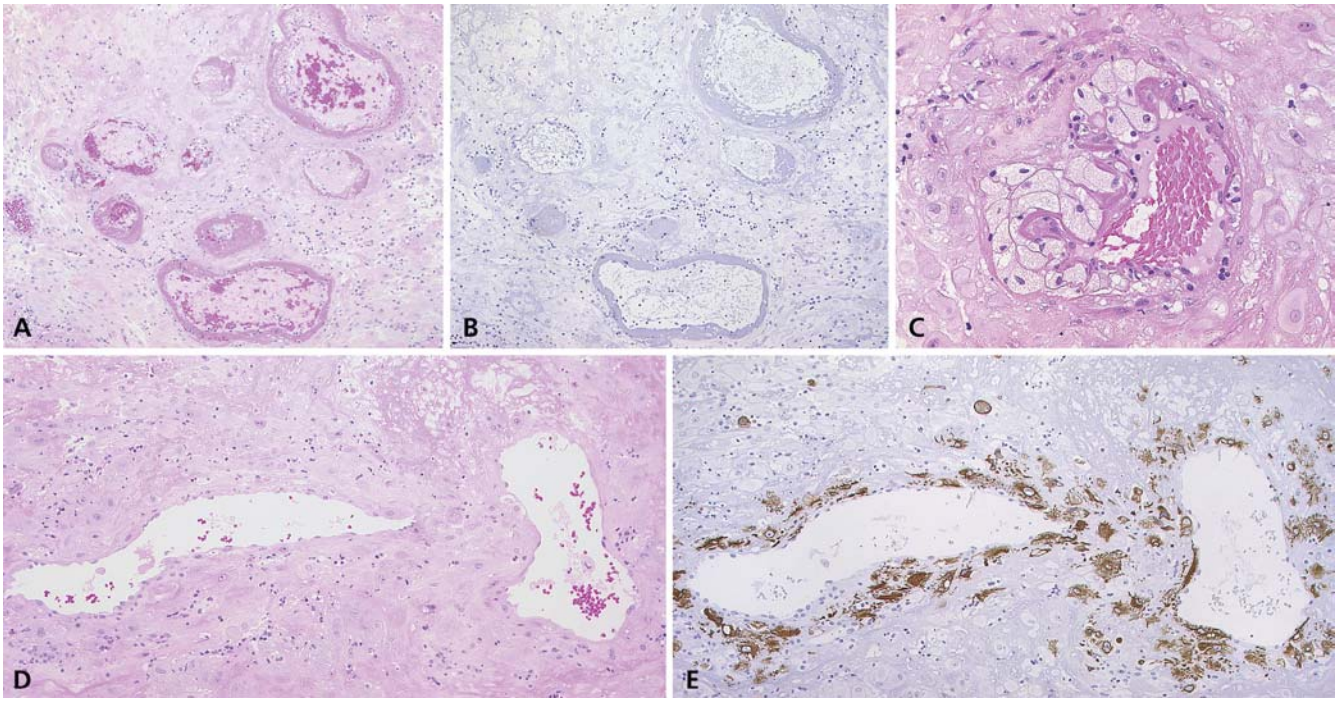


Fig. 3 Spiral artery pathology. **A** Acute atherosis is characterised by greater arterial density and a narrower arterial lumen on cross-section (compare the physiological transformation in **D**) and distinctive, strongly eosinophilic, hyaline replacement of the media. Haematoxylin and eosin (H&E), ×100. **B** In acute atherosis, the vessel wall is devoid of trophoblast cells (compare with **E**). Multinucleated trophoblast cells (none shown) may sometimes be present at a distance from the pathological vessels. Pancytokeratin, ×100. **C** High-power cross-sections in acute atherosis revealing segments with intimal foam cells. H&E, ×250. **D** Physiologically transformed spiral arteries are less coiled (fewer aggregated cross-sections); the muscle coat is replaced by (less eosinophilic) fibrinoid material (compare with acute atherosis in **A**). H&E, ×100. **E** Physiologically transformed spiral artery containing fetal trophoblast cells labelled with pancytokeratin antibody, ×100

grounds (oedema, proteinuria, hypertension and coagulation abnormalities). Pre-eclamptic placentas are usually below the fifth percentile for weight and size and display circulatory abnormalities in the intervillous space (infarcts of different age and size, thromboses). Very characteristic findings are seen in the underlying decidua, which is often inadequately represented in the usual placental blocks. When more of the basal plate tissue is retained, or the tissue submitted derives from curettage of the placental bed, a lack of trophoblast invasion can be seen [23]. Sometimes this goes along with a relative increase of multinucleated trophoblast cells clustered, albeit at some distance, around spiral arteries. These arteries themselves are narrow and show acute atherosis (Fig. 3). Similar placental findings can be present in mothers after organ (mostly kidney) transplantation and mothers with underlying autoimmune disease (lupus erythematosus).

Pre-eclampsia seems to be an aetiologically heterogeneous disorder. Late onset disease, greater than 34 weeks [30], usually does not restrict fetal growth [18], and, in most cases, the characteristic findings within and around spiral arteries are missing. There may be signs of intervillous circulatory disturbance; however, this increases anyway, to some extent, towards term. Meaningful research in this field has to take into account that clinical pre-eclampsia comprises at least two different conditions.

Intrauterine growth restriction

Serial fetal ultrasonography can now detect deviations from a growth curve that is initially unremarkable. Although this usually indicates a placental problem, there are multiple conditions that can restrict fetal growth (Table 1). The fetal growth curve evidences placental malfunction in the nutritional supply line and—as in children and adults—some time is required before death ensues. Given proper monitoring, fetal starvation is usually only fatal if it starts very early in pregnancy, when the risks of extreme prematurity put severe restrictions on caesarean section. The placenta of a growth-restricted child is almost always small (below the fifth percentile). However, if small size is the only placental abnormality, the term "placental insufficiency" is inappropriate, as the placenta will be small like any other fetal organ if the child is small for a non-placental reason. Thus, any genetic condition (e.g. uniparental disomy) or toxin (e.g. heavy smoking) that restricts fetal growth will also cause a small placenta. To identify a small placenta as a primary cause of fetal growth restriction, additional findings are required, e.g. impaired maternal blood flow through the intervillous space (infarcts) or impaired fetal blood flow through the cord and allantoic vessels or chorionic villi (fetal thrombotic vasculopathy) [13, 20]. Rarely, the combination of impaired maternal and fetal circulation

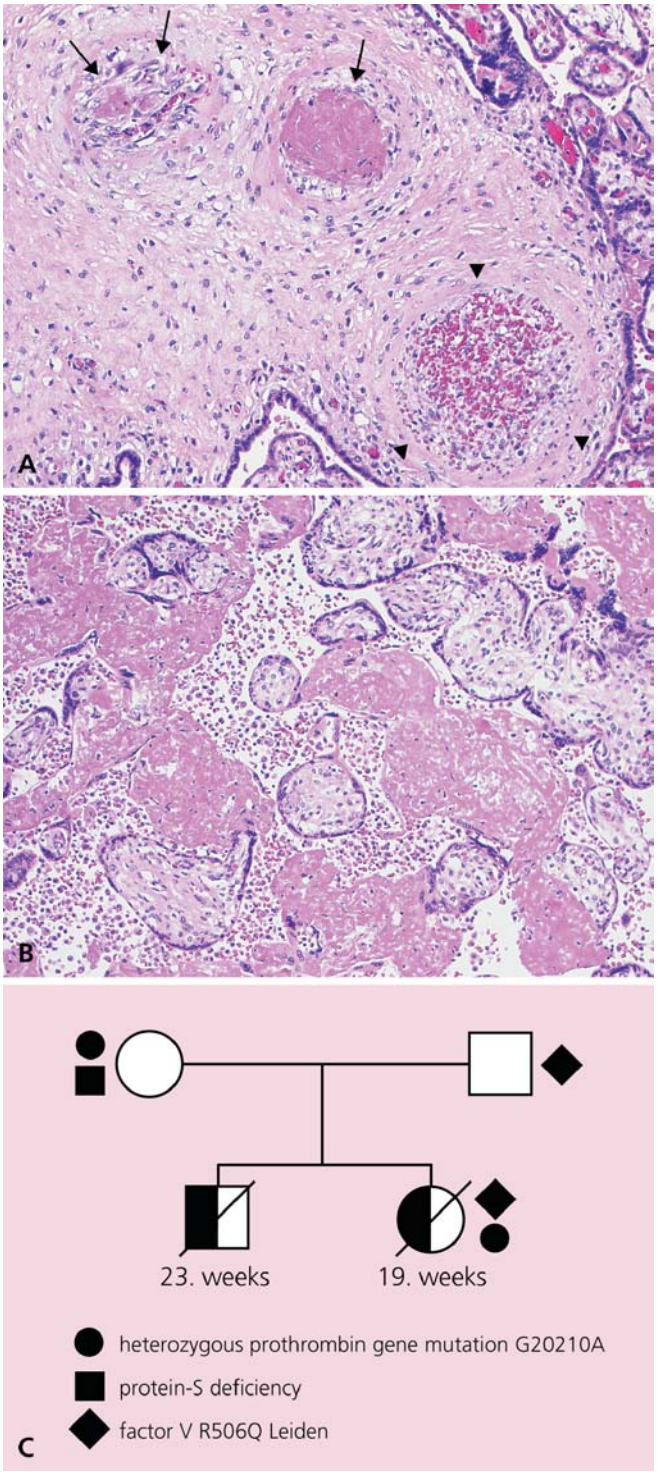


Fig. 4 Impaired fetomaternal circulation in the placenta. **A** Fetal thrombotic vasculopathy in a stem villus with two patterns: fresh thrombosis (*arrow*) followed by obliterating intimal proliferation (*two arrows*) and so-called haemorrhagic endovasculitis (*arrowheads*). **B** Obliteration of the maternal intervillous blood space by fibrin. Intervillous granulocytes and monocytes accompany the florid thrombotic process (haematogenous infection may show the same infiltrate but within the chorionic villi). **C** Genetic analysis of the female fetus fed by the above placenta and of the parents. Semi-shaded symbols denote two fetuses affected by a severely impaired placental circulation. No genetic analysis was performed of the first death at 23 weeks in 1981. *Small symbols* denote the genes analysed. The 19-week fetus is the double heterozygote infant of a family segregating a prothrombin gene mutation, factor V (Leiden) and protein S deficiency

Table 1 Possible causes of intrauterine growth restriction

(A)	Physical environment, mind, drugs
	Poor maternal nutritional status (low pre-pregnancy weight, vegetarians)
	Residence at high altitude (>5000 m above sea level)
	Stress factors (mental, physical, emotional)
	Drugs (nicotine, alcohol, medical and illegal drugs)
(B)	Pre-existing disease
	Cardiovascular (heart defects, heart insufficiency)
	Respiratory diseases (asthma)
	Haematological diseases (chronic anaemia, haemoglobinopathies)
	Gastrointestinal disorders (M. Crohn, ulcerative colitis)
	Renal transplantation, haemodialysis
	Chronic infections
	Immunological disorders (systemic lupus erythematodes, anti-phospholipid-antibody syndrome)
(C)	Pregnancy-specific disorders
	Hypertensive disorders of pregnancy (pre-eclampsia, HELLP syndrome)
	Chronic vaginal haemorrhage, retroplacental haematoma
	Multiple pregnancy
(D)	Fetal cause
	Fetal malformation (aneuploidy, single gene disorders, sporadic)
	Fetal infections (toxoplasmosis, CMV, others)
	Placental mosaicism and uniparental disomy

may reveal a combination of different—and perhaps as yet unknown—thrombophilic traits inherited by the fetus [6, 10, 28] (Fig. 4).

The functional reserve capacity of the placenta is usually given as 30%. However, live-born severely growth-restricted children are occasionally observed with placentas containing barely 30% of functional tissue. This makes it difficult to ascribe the in utero death of a severely dystrophic fetus merely to loss of functional placental tissue and starvation. The cause of death is rather a sudden additional pathology, e.g. focal abruptio from the decidua. Hence, the need for meticulous inspection to identify and report abruptio, even if focal and discrete.

Autopsy organ dimensions and weights in a small, non-malformed fetus can reveal two patterns. If all measures are similarly small, the placenta is a most unlikely cause. If the brain and feet are of normal size while the heart and kidney are small, and organs such as liver, spleen and thymus are very small, the asymmetry suggests insufficiency of the placental supply line. The risk of recurrence depends on the underlying condition causing the placental growth retardation and circulatory deficit. Even if unexplained, recurrence is readily detected by monitoring fetal growth during the next pregnancy. Some centres give prophylactic anticoagulation using heparin or aspirin alone or in combination [2, 11].

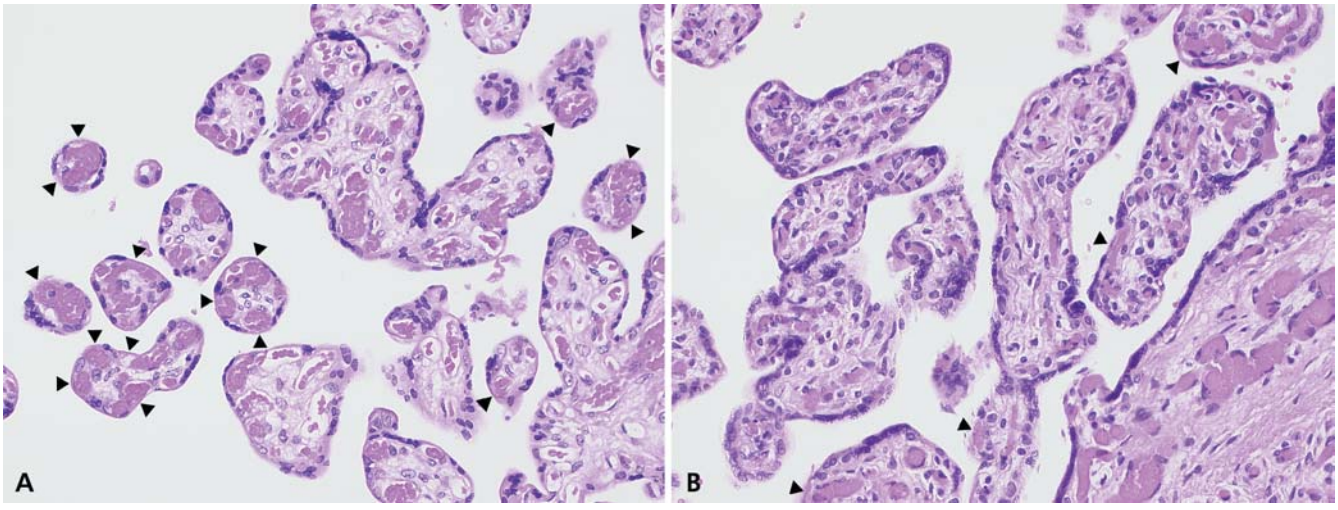


Fig. 5 Chorionic villus maturation in late pregnancy. **A** Normal maturation leads to a dominance of terminal villi with several syncytiocapillary membranes (*arrowheads*) per cross-section from 36 weeks onwards. Haematoxylin and eosin (H&E), ×250. **B** A dysmature term placenta has many fewer syncytiocapillary membranes (*arrowheads*); chorionic villi may be plumper. H&E, ×250

Intrauterine death near term

Of 1000 pregnancies that have progressed uneventfully to fetal viability, 3–4 will result in the catastrophe of sudden and silent in utero death. This represents one-half of perinatal mortality in highly developed countries. "Sudden" means the absence of warning, even in retrospect, from either maternal symptoms or fetal measurements. Given these circumstances, it is conceivable that the fetus has died from hypoxia, as either a single or repeated event. This makes it clear that the placental delivery of oxygen is not coupled to that of nutrients. A well-accepted cause is sudden premature abruptio; however, this produces symptoms in the mother and is, thus, not silent. In most other cases, mothers only present days after the child has died in utero because they have noticed the lack of fetal movements. Labour has to be induced to deliver the macerated child. At autopsy, so-called hypoxic haemorrhages are seen in the pleura, pericardium and meninges, and the approximate interval between death in utero and delivery can be estimated from the histology of the heart and lung [8].

The most common cause is placental dysmaturity or placental maturation defect [24]. Such placentas are of normal size or even large, but with a pale cut surface. In some cases of dysmaturity, the indication for examination by the pathologist is the midwife's observation that the placenta is pale. The pallor is due to defective formation of both the sinusoidal vessels in the terminal villi and the syncytiocapillary membranes. Sinusoidal vessels with broad contact and a short diffusion distance to maternal blood have been equated with impaired placental respiratory function and, thus, the risk of asphyxia. In its smallest and most mature terminal villi, a normal late pregnancy placenta ($\geq$35 weeks) has an average of three sinusoidal contacts with the surrounding maternal blood (Fig. 5). A dysmature placenta has an average of one such structure per terminal villus. About 5% of unselected placentas examined without indication reveal this pattern, and, up to now, there is no clue as to its cause. Although only 2% of fetuses with a dysmature placenta will actually die, this risk is 70-fold that of a fetus with a normal placenta [24]. A mother who has lost a child due to placental dysmaturity has a tenfold higher risk of recurrence compared with baseline. No predictive markers are presently available: placental dysfunction is manifested only as a terminal acute event. To minimise recurrence in a subsequent pregnancy, one option is to induce labour at completed 37 weeks, although this must be balanced against the risks of premature birth.

The concept of dysmaturity as a cause of fetal death is not yet widely accepted. A counter-argument is that fetuses dying from this supposed hypoxia are a minority. The answer is very simple: most fetuses are rescued by birth, as their placenta is required to function for only a few weeks more. Pathologists know how difficult it is to predict final decompensation in a diseased organ. For example, severely glomerulonephritic kidneys can force haemodialysis within a few weeks, but they can also stay functional for another couple of years.

Twin pregnancy

With very rare exceptions [21], a monochorionic twin pregnancy identifies the newborns as "identical" (monozygous). Thus, the fusion of placental tissues is considered an indication for histological examination of the dividing membrane. If the membrane contains chorionic tissue, it means that the twins lived in separate chorionic cavities. They still might be "identical". However, the rate of complications is low. In contrast, lack of chorionic tissue in the dividing membrane signifies a monochorionic cavity, which in most cases goes along with feto-

fetal vascular connections. If both twins are alive and similar in weight and colour (haemoglobin, haematocrit), there is no need for elaborate study of vessel connections. Intrauterine death and discrepancies of weight and colour, on the other hand, indicate the need to examine the chorionic plate for large connections. This can usually be performed within a few minutes by insufflation of the artery and vein of either umbilical cord using an air-filled syringe. Arteriovenous fistulas in the depths of the cotyledons are betrayed by small branches of arteries or veins coming from disparate sides and leading into the same area of the chorionic plate. These fistulas are usually multiple, although unbalanced in net blood flow [16, 27]. The imbalance is rescued by large connections, mostly arterio-arterial anastomoses, within the chorionic plate. However, these have their own intrinsic risk. If due to other causes, the condition of one twin deteriorates (eventually going along with a drop in its blood pressure), its circulation is overtransfused by the stronger pumping action (effecting a higher blood pressure) of the co-twin's heart.

Feto-fetal vascular connections are sometimes destroyed by laser coagulation. If this therapy is incomplete, it risks destabilising a previously labile balance in reciprocal transfusion. Some clinicians are, therefore, concerned to confirm successful coagulation of all connecting vessels after birth by examination of the placenta.

Conclusion

Examination of a placenta is clearly indicated in every pregnancy failure, as it can reveal underlying systemic causes and/or the risk of recurrence. Placentas should also be examined from children who survive birth but have an unexplained low Apgar score, infection or growth retardation. The routine storage of all placentas for at least 3 days is recommended, should the need for examination be dictated by subsequent deterioration in the newborn. From a formal point of view, many more bits of pathology than discussed in this review can be found in placentas and, with the advances in ultrasonography, might even be seen prior to birth, e.g. a "cyst" representing a subchorial haematoma. The extent of such a disturbance might ultimately affect fetal growth, which is amenable to prenatal detection offering the chances for an appropriate management. More to be feared is sudden deterioration, mostly by abruptio of the placenta. Dysmaturity causing sudden death due to hypoxia is the greatest challenge, as there are no premonitory signs and no predictive tests as yet available.

References

1. Badawy SZA, Westpfal EM (2000) Frequency of etiological factors and cost effectiveness of the work up for patients with history of recurrent pregnancy loss. Early Pregnancy 4:253–260
2. Bar J, Mashiah R, Cohen-Sacher B, Hod M, Orvieto R, Ben-Rafael Z, Lahav J (2001) Effect of thrombophylaxis on uterine and fetal circulation in pregnant women with a history of pregnancy complications. Thromb Res 101:235–241
3. Bruder E, Ersch J, Hebisch G, Ehrbar T, Klimkait T, Stallmach T (2000) Fetal varicella syndrome: disruption of neural development and persistent inflammation of non-neural tissues. Virchows Arch 437:440–444
4. Creasy MR, Crolla JA, Alberman ED (1976) A cytogenetic study of human spontaneous abortions using banding techniques. Hum Genet 31:177–196
5. Daniely M, Aviram-Goldring A, Barkai G, Goldman B (1998) Detection of chromosomal aberration in fetuses arising from recurrent spontaneous abortion by comparative genomic hybridization. Hum Reprod 13:805–809
6. Formstone CJ, Hallam PJ, Tuddenham EGD, Voke J, Layton M, Nicolaides K, Hann IM, Cooper DN (1996) Severe perinatal thrombosis in double and triple heterozygous offspring of a family segregating two independent protein S mutations and a protein C mutation. Blood 87:3731–3737
7. Fritz B, Hallermann C, Olert J, Fuchs B, Bruns M, Aslan M, Schmidt S, Coerdt W, Müntefering H, Rehder H (2001) Cytogenetic analyses of culture failures by comparative genomic hybridization (CGH)—re-evaluation of chromosome aberration rates in early spontaneous abortions. Eur J Hum Genet 9:539–547
8. Genest DR, Williams MA, Green MF (1992) Estimating the time of death in stillborn fetuses: I. Histologic evaluation of fetal organs; an autopsy study of 150 stillborns. Obstet Gynecol 80:575–584
9. Gould SJ, Isaacson PG (1993) Bronchus-associated lymphoid tissue (BALT) in human fetal and infant lung. J Pathol 169:229–234
10. Hebisch G, Bernasconi MT, Gmuer J, Huch A, Stallmach T (2001) Pregnancy-associated recurrent hemolytic uremic syndrome with fetal thrombotic vasculopathy in the placenta. Am J Obstet Gynecol 185:1265–1266
11. Heilmann L, von Tempelhoff GF, Pollow K (2003) Antiphospholipid syndrome in obstetrics. Clin Appl Thromb Hemost 9:143–150
12. Kajii T, Ferrier A, Niikawa N, Takahara H, Ohama K, Avirachan S (1980) Anatomical and chromosomal anomalies in 639 spontaneous abortuses. Hum Genet 55:87
13. Kraus FT, Acheen VI (1999) Fetal thrombotic vasculopathy in the placenta: cerebral thrombi and infarcts, coagulopathies, and cerebral palsy. Hum Pathol 30:759–769
14. Langston C, Kaplan C, Macpherson T, Manci E, Peevy K, Clark B, Murtagh C, Cox S, Glenn G (1997) Practice guideline for examination of the placenta: developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists. Arch Pathol Lab Med 121:449–476
15. Meyer A, Stallmach T, Goldenberger D, Altwegg M (1997) Lethal maternal sepsis caused by Campylobacter jejuni: pathogen preserved in placenta and identified by molecular methods. Mod Pathol 10:1253–1256
16. Nikkels PG, van Gemert MJ, Sollie-Szarynska KM, Molendijk H, Timmer B, Machin GA (2002) Rapid onset of severe twin–twin transfusion syndrome caused by placental venous thrombosis. Pediatr Dev Pathol 5:310–314
17. Opitz JM (1987) The Farber lecture. Prenatal and perinatal death: the future of developmental pathology. Pediatr Pathol 7:363–394
18. Rasmussen S, Irgens LM (2003) Fetal growth and body proportion in preeclampsia. Obstet Gynecol 101:575–83
19. Redline RW, Faye-Petersen O, Heller D, Qureshi F, Savell V, Vogler C (2003) Amniotic infection syndrome: nosology and

reproducibility of placental reaction patterns. Pediatr Dev Pathol 6:435–448
20. Sander CM, Gilliland D, Akers C, McGrath A, Bismar TA, Swart-Hills LA (2002) Live births with placental hemorrhagic endovasculitis. Interledional relationships and perinatal outcomes. Arch Pathol Lab Med 126:157–164
21. Souter VL, Kapur RP, Nyholt DR, Skogerboe K, Myerson D, Ton CC, Opheim KE, Easterling TR, Shields LE, Montgomery GW, Glass IA (2003) A Report of dizygous monochorionic twins. N Engl J Med 349:154–158
22. Stallmach T, Károlyi L (1994) Augmentation of fetal granulopoiesis with chorioamnionitis during the second trimester of gestation. Hum Pathol 25:244–247
23. Stallmach T, Hebisch G, Orban P, Lü X (1999) Aberrant positioning of trophoblast and lymphocytes in the feto-maternal interface of growth-retarded fetuses. Virchows Arch 434:207–211
24. Stallmach T, Hebisch G, Meier K, Dudenhausen JW, Vogel M (2001) Rescue by birth: defective placental maturation and late fetal mortality. Obstet Gynecol 97:505–509
25. Stephansson O, Dickman PW, Cnattingius (2003) The influence of interpregnancy interval on the subsequent risk of stillbirth and early neonatal death. Obstet Gynecol 102:101–108
26. Stern JJ, Dorfmann AD, Gutierrez-Najar AJ, Cerrillo M, Coulam CB (1996) Frequency of abnormal karyotypes among abortuses from women with and without a history of recurrent spontaneous abortion. Fertil Steril 65:250–253
27. Umur A, van Gemert MJ, Nikkels PG, Ross MG (2002) Monochorionic twins and twin–twin transfusion syndrome: the protective role of arterio-arterial anastomoses. Phys Med Biol 49:57–64
28. Vern TZ, Alles AJ, Kowal-Vern A, Longtine J, Roberts DJ (2000) Frequency of factor V (Leiden) and prothrombin G20210A in placentas and their relationship with placental lesions. Hum Pathol 31:1036–1043
29. Vogel M (1996) Atlas der morphologischen Plazentadiagnostik. 2. Auflage. Springer, Berlin Heidelberg New York
30. von Dadelszen P, Magee LA, Roberts JM (2003) Subclassification of preeclampsia. Hypertens Pregnancy 22:143–148