Placenta 33 (2012) 1026–1035

Contents lists available at SciVerse ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

A new, clinically oriented, unifying and simple placental classification system

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ARTICLE INFO

Article history:
Accepted 5 October 2012

Keywords:
Placenta
Pathology
Morphology
Classification system
Clinical relevance

ABSTRACT

Objective: At present there is no internationally accepted, clinically easy understandable, comprehensive morphological placental classification. This hampers international benchmarking and comparisons, and clinical research.

Study design: Internationally published criteria on morphological placental pathology were collected, standardized and focused into a comprehensive diagnosis category system. The idea was to create a clinically relevant placental pathology scheme related to major pathological processes. A system of nine main diagnostic categories (normal placenta included) was constructed. Pathologists and obstetricians discussed the mutual understanding of the wording in the reporting. The previously published diagnostic criteria were merged, structured and standardized. Through an interobserver correlation study on 315 placentas from intrauterine deaths and 31 controls (placentas from live births) the microscopic criteria in this classification system were tested on user-friendliness and reproducibility.

Results: The clinical feedback has been very positive, focusing on the understandability and usefulness in patient follow-up. The interobserver agreement in the microscopic correlation study was in general good. The differences in agreement mainly reflected the degree of preciseness of the microscopic criteria, exemplified by excellent correlation in diagnosing acute chorioamnionitis. Maternal and fetal circulatory disorders need grading criteria and studies are needed to get more insight and clinical correlations of villitis and maturation disorders.

Conclusion: The clinically oriented, unifying and simple placental pathology classification system may work as a platform for standardization and international benchmarking. Further research is needed to define diagnostic criteria in staging and grading of some main diagnostic categories.

1. Introduction

Major advances in basal research on trophoblast- and placental-issues have resulted in a better understanding of placental function and dysfunction [1–4]. Valuable standardization of a clinically oriented examination of placenta, and structured clinical pathologic correlation studies [5–8] have resulted in better definitions and sets of criteria. Advances in perinatal medicine and introduction of antenatal steroids for lung maturation and surfactant replacement therapy have dramatically improved the immediate outcome for the preterm born baby [2,9]. Intrauterine growth restriction is associated with perinatal mortality as well as perinatal and long-term morbidity [10,11]. It is generally accepted that fetal growth restriction (FGR) is a marker of placental dysfunction [10–15]. Various methods to diagnose intrauterine growth restriction have been developed, including ultrasound measurements of fetal growth, fetal and maternal circulation, and maternal perception of fetal movements [16]. A better understanding of placental morphology in functioning and dysfunctional placentas has resulted in an increased interest in and request for placental examination [2,8]. The lack of a standardized, international accepted placental classification is, however, partly reflected in the fact that placental causes of intrauterine death (IUFD) are reported to vary from 28 to 85% [17,18]. The aim of this study was to construct a standardized and clinically easy understandable placental classification system and to test the microscopic criteria for interobserver reproducibility.

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http://dx.doi.org/10.1016/j.placenta.2012.10.002

2. Method for constructing the classification system

In constructing the clinically oriented, unifying and simple placental classification system, pathologists and obstetricians discussed various ways to overcome the challenges of a written report. The aim was a reporting that should be biologically adequate and clinically easy-to-grasp, standardized to be relevant for national and international comparisons and benchmarking, and a platform for further research. In these interdisciplinary discussions, we used the routine placental diagnostics to work out guidelines for diagnostic wording and comments.

Internationally published criteria on morphological placental pathology were collected and discussed, partly including the Norwegian group of perinatal and placental pathologists. In multi headed microscopes findings in placental sections were identified. Discrepancies in the understanding of the findings, and the wording of criteria were discussed. This process resulted in merged, structured and standardized wording of the diagnostic criteria.

3. Material for the interobserver correlation study

The placentas were collected from two major hospitals in the Oslo region (Oslo University hospital Ullevål and Akershus University hospital) from a total of 332s and third trimester intrauterine deaths (IUFD) in single pregnancies, registered in the period 1990–2003. IUFD was defined as fetal death in gestational week 22 + 6 or more, or fetal weight above 500 g. Seventeen placentas were excluded: four due to gestational age less than 22 weeks, and ten because of lacking data about gestational age. In three cases the specimens were not found in the archives. 315 placentas were thus examined according to the new classification system. Thirty-one single placentas from live births in the same period were used as controls. These placentas had been sent to morphological examination on various clinical indications, form variations, or umbilical cord variations with false knots. Cases and controls were clinically well defined as part of a previous study (the Venous Thrombosis in Pregnancy (VIP) study [19]). Verified chromosomal abnormalities had been excluded. The placentas had routinely been examined macroscopically, sectioned and diagnosed by general pathologists in the two university hospitals, without standardized protocols for macroscopic examination and sampling. In general, however, sections had been sampled from the umbilical cord and membranes in addition to two to five sections from placental tissue with or without focal parenchymal lesions. The tissue sections had been routinely fixed in buffered formalin, processed and embedded in paraffin blocks. 3.5 μm sections had been routinely stained with Hematoxylin–Eosin (HE).

4. Method for the interobserver correlation study

The original HE sections were used for the review. The sections were de-identified and blinded prior to individual reexamination according to merged microscopic criteria and the classification scheme by two experienced placental pathologists (GT and BR). Gestational age was the only available information. Evaluation of correlation and reproducibility was carried out [20].

5. Statistics

The interobserver agreement was calculated by un-weighted kappa analysis as a measurement of interobserver reproducibility. Summed interobserver reproducibility of the study, and kappa values to each diagnostic category was calculated in the case and control material. Kappa values relate to the strength of agreement. Values lower than 0.20 means poor agreement; 0.21–0.40 fair agreement; 0.41–0.60 moderate agreement; 0.61–0.80 good agreement; 0.81–1.00 very good agreement [20].

6. Ethical considerations

The study was approved by the Regional Committee for Medical Research Ethics, Region East, Norway, with authorization from the Norwegian Ministry of Health and Social Affairs (REK Sør-Øst C: 2009/1462, 03.01.2011).

7. Results

Through discussions between pathologists and obstetricians, a simplified reporting system was constructed, consisting of nine diagnostic categories related to major pathophysiological processes, including one category of normal placenta according to gestational age. Category nine comprises a variety of conditions including those with unknown or debated etiology (Table 1). In reporting placental pathology, the morphological findings preferentially were to be recorded in one main diagnostic category. Alternative findings and diagnoses were to be discussed in an additional comment. The idea with the preferentially chosen diagnosis in reporting placental pathology, is analogous to the algorithm of an autopsy report. This system has been used in routine diagnostics in our pathology department for some years with very positive feedback from clinicians. The merged and structured diagnostic criteria, all previously published internationally, are listed in Table 2.

315 placentas from the stillbirths, distributed by gestational age, had peak numbers in weeks 36–41. The microscopic findings according to the nine diagnostic categories are summarized in Table 3. The overall interobserver agreement between the two perinatal pathologists according to all diagnostic categories was calculated to 0.79, indicating good reproducibility. Three placentas (3/315; 0.95%) were diagnosed as morphologically normal (week 26, 33 and 38), all without agreement. Twelve cases, mainly from weeks 22–27 (12/315; 3.8%) were diagnosed with acute chorioamnionitis; interobserver agreement calculated to 0.91, i.e. very good reproducibility. Only six cases (6/315; 1.9%) were diagnosed with villitis/intervillositis (weeks 24, 25 and 37, 38), calculated kappa value 0.66. Maternal circulatory disorder was the main diagnostic category, diagnosed in 239 cases (239/315; 75.87%), peak number in weeks 38 (23/315) and 40 (24/315). Kappa value was calculated to 0.79. Twelve cases with fetal vasculopathy (12/315; 3.8%), gestational week 24–40, were diagnosed with kappa value 0.59. Placentas with maturation disorders were found in 34 cases (34/315; 10.79%), mainly in weeks 38 (6/315), 39 (4/315) and 40 (5/315), calculated kappa value 0.60. Although placentas from infants with chromosomal anomalies had been excluded, four cases were diagnosed as morphologically suspicious for gene aberrations (4/315; 1.3%), kappa value 0.25. No placentas were diagnosed in category eight, implantation disorders. Five cases (5/315; 1.6%) with edematous villi without other signs of genetic aberration were placed into diagnosis category nine, other disorders, kappa value 0.79 (Table 3).

The control placentas ($n = 31$) from live born children were mainly from gestational weeks 31, 36 and 40. Overall interobserver agreement was calculated to 0.63, indicating good reproducibility. Two placentas, gestational week 36 and 40 (2/31; 6.45%) were diagnosed as microscopically normal by one of the pathologists. Four cases with acute chorioamnionitis were diagnosed by both pathologists (4/31; 13%). One case of villitis/intervillositis was diagnosed without agreement. Maternal circulatory disorders, diagnosed in 23 placentas (23/31; 74%), mainly from gestational weeks 31, 36, 37 and 40, had a calculated kappa value of 0.61 (Table 4). One placenta was diagnosed with maturation disorders

Table 1
A new, clinically oriented, unifying and simple placental classification system, with nine major diagnostic categories, including normal placenta.

Diagnostic category	Diagnostic wording
1.	Placenta with normal morphology, according to gestational age
2.	Placenta with chorioamnionitis
3.	Placenta with villitis and intervillositis
4.	Placenta with maternal circulatory disorders (decidual vasculopathy)
5.	Placenta with fetal circulatory disorders
6.	Placenta with delayed villous maturation
7.	Placenta with findings, suggestive of genetic aberration
8.	Placenta with implantation disorders
9.	Placenta with other lesions

Table 2
Morphological criteria relevant for the diagnostic categories [4,21–29,31,33–42].

1. Normal placenta according to gestational age (31;33)

Maturation signs correlated to gestational age

Villous maturation	Branching from primary to secondary and tertiary villi with smaller diameter
Vascular maturation	Central fetal capillaries to vasculosyncytial membranes. Arterial fibro-muscular hyperplasia in primary villi
Stromal maturation	Dominant embryonic, loose stroma with Hofbauer cells to stroma dominated by fetal capillaries in tertiary villi Fibromuscular stroma in primary villi

Villi in % / Gestational week	**16**	**20**	**24**	**28**	**32**	**36**	**40**
Primary villi (stem villi): Reticular stroma with fetal vessels, paravascular collagen	17	13	10	9	11	10	9
Secondary villi, immature type (immature intermediate villi): Embryonic stroma, many Hofbauer cells	54	51	32	16	10	5	1
Secondary villi, mature type (mature intermediate villi): Cellular stroma, scattered Hofbauer cells	29	35	50	56	52	47	32
Tertiary villi (terminal villi): Stroma with fetal capillaries dominated by vasculosyncytial membranes	0	1	8	19	27	38	58

2. Chorioamnionitis (21;34)

Acute	**Maternal response**	**Fetal response**
Stage 1	Neutrophils in subchorionic/chorionic fibrin Grade 1 or 2	Umbilical phlebitis and /or chorionic vasculitits Grade 1 or 2
Stage 2	Neutrophils in chorionic plate and membranes Grade 1 or 2	Umbilical arteritis and phlebitis Grade 1 or 2
Stage 3	Karyorrhexis and amniocyte necrosis Grade 1 or 2	Umbilical concentric periphlebitis/necrotizing funisitis Grade 1 or 2
Grade 1: slight to moderate		
Grade 2: intense, > 30 neutrophils in chorionic plate and sub-/chorionic micro abscess		

Subacute	Invasion of acute and chronic inflammatory cells between amnion and chorion Necrosis
Chronic	Lymphocytes in the chorionic trophoblast layer or chorioamniotic connective tissue
Stage 1	Amniotropic lymphocytic invasion confined to the chorionic trophoblast layer
Stage 2	Lymphocytic invasion into the chorioamniotic connective tissue
Grade 1	=/>3 foci or patchy inflammation
Grade 2	Diffuse inflammation

Table 2 (*continued*)

3. Villitis and intervillositis (4;22;23;27;28;35)

Chronic villitis, including villitis of unknown etiology (VUE) and infectious etiology			
Microscopic criteria		**Low grade**	**High grade**
Chronic villous inflammation		5-10 villi/focus, multifocal	>10 villi/focus
Associated lesions		Focal groups of fibrous villi Obliterated fetal vessels Extensive perivillous fibrin Active component (neutrophils) Decidual plasmacells	
Intervillositis	**Macroscopic findings**	**Microscopic findings**	
Acute	Green and/or opaque membranes Pale and/or firm yellow basal plate	Neutrophils in villi/intervillous space Fibrin	
Chronic	Small placentas	Diffuse intervillous invasion of lymphocytes, monocyte-macrophages, eosinophils Villous necrosis and perivillous fibrin	
Histiocytic	Small placentas	Diffuse intervillous invasion of histiocytes	

4. Maternal circulatory disorders (decidual vasculopathy) (22-25;31;36;37)

Chronology of infarction/ischemia	**Acute (hours - 2 days)**	**Subacute (>2 days)**	**Chronic (>1 week)**
Villous capillary stasis with/without hemorrhage			
Trophoblastic necrosis and/or villous necrosis			
Fibrin deposition intra-/intervillous			
Trophoblastic proliferation in the infarction borders			
Demarcation of neutrophils			

Maternal malperfusion:	Increased syncytial knots (estimated according to gestational age)		
	Villous agglutination (clusters of adherent distal villi)		
	Increased intervillous fibrin		
	Distal villous hypoplasia		
	Atherosis of decidual arteries		
	Placental weight <10th percentile		
Pathology		**Macroscopy**	**Microscopy**
Cotyledon infarct	Acute	Basal/ intermediate Dark red Sharply demarcated	Intravillous hemorrhage Congestion of villous capillaries Collapse of the intervillous space
	Subacute	Brownish	Trophoblastic necrosis Intra-/intervillous fibrin deposition Demarcation by maternal neutrophils
	Chronic	Yellow to white Sharply demarcated	Pyknosis, karyorrhexis Ghost villi Intervillous fibrinoid
Intervillous thrombe	Acute	Red, often shiny	Intervillous hemorrhage
	Chronic	White Sharply demarcated	Laminated fibrin
Abruptio	Acute	Dark red and soft Clots adhered to maternal surface	Compressed underlying villous tissue Intravillous hemorrhage, Capillary stasis and edema
	Chronic	Brown, basal impression	Chorioamnionic hemosiderin-macrophages
Compensatory changes	**Distal villous hypoplasia**	Focal lack of secondary villi	Sinusoidal transformed capillaries Increased syncytial knots
	Chorangiosis	Little villous stroma	Prevalence of branching angiogenesis (>10 capillaries per tertiary villus in totally 10 villi of three different non-infarcted areas)

(*continued on next page*)

5. Fetal circulatory disorders (22;23;26;38;39)

Patterns of fetal vascular thrombosis (FVT)		
Luminal thrombosis	**Microscopic findings, vessel and vessel wall**	**Microscopic findings, villous stroma**
Acute thrombosis	Fibrin deposits with/without occlusion Endothelial edema Karyorrhexis	Erythrocyte extravasation Iron deposits in the basement membrane
Subacute thrombosis	Thrombe attached vessel wall	Fibrosis in proximal villi
Chronic thrombosis	Thrombe organized Recanalization Calcification	Clusters of distal avascular and fibrous villi close to affected stem villi
Mural thrombosis	**Microscopic findings of the vessel**	
Intimal fibrin cushion	Laminated pale blue fibrin between vascular smooth muscle and endothelium (+/-calcification)	
Hemorrhagic endovasculitis	Rupture of fetal vessels in primary villi with hemorrhage and inflammatory cells. Active lesion: Inflammatory villous infiltrates = hemorrhagic villitis	
Fibrinous vasculosis (endangiopathia obliterans)	Edema in the fetal vessel wall Obliteration/thrombosis	
Endothelial cushion	Localized proliferating fibroblasts (intramural fibrin, erythrocytes) With/without secondary calcification	

6. Delayed villous maturation (4;29;33;40;41)

Microscopy		
Maturation disorder	**Villi**	**Fetal vessels**
Villous maturation arrest (delayed villous maturation, distal villous immaturity)	Focal imbalance of villous branching Predominance of villi with increased diameter Excessive cellular stroma Excessive extracellular matrix	Increased number of centrally localized capillaries Reduced vasculosyncytial membranes

7. Suggestive for genetic aberration (23;42)

Diagnosis	Genetic characteristics	Macroscopic characteristics	Microscopic characteristics
Complete hydatidiform mole	Paternal Diploid (46 xx or 46 xy)	Translucent vesicles	Apolar trophoblastic hyperplasia Intraepithelial microcysts Cellular atypia Hydropic villi with central cisterns Absence of fetally-derived tissue
Partial hydatidiform mole	Triploid (69 xxx, 69 xxy, 69 xyy)	Normal villous tissue intermixed with translucent vesicles	Partly normal, partly complete mole
Trisomi 13	Non-disjunction/or mosaic	Often SUA (single umbilical artery) Hydropic	Scalloping avascular villi Villous inclusions Dysmature villi
Trisomi 18	Non-disjunction/or mosaic	Often SUA Reduced vascularity Very small placentas	Marked increase in villous stromal cells Dysmature villi Villous inclusions Increased syncytial knots
Trisomi 21	Non-disjunction/or mosaic	Sometimes increased weight	Hydropic Atypical trophoblast proliferation
Tetraploidy			Voluminous/poorly vascularized villi Endovillous migration of trophoblast cells
Mesenchymal dysplasia	Possible mosaic	Often large for gestational age	Enlarged primary villi (stem villi) with fibroblastic stroma Increased vascularization Cystic degeneration without trophoblast hyperplasia Multifocal or localized lesions

Table 2 (*continued*)

8. Implantation disorders (22;23;31)

	Macroscopy	Microscopy
Accreta	Various	Villi directly implanted onto the myometrium (no decidua)
Increta	Various	Villi implanted into the myometrium
Percreta	Placenta protruding through the uterine wall	Villi penetrating the whole uterine wall (through serosa)
Extrachorialis/ Circumvallata	Fetal surface less than maternal surface Membranes inserted on the fetal plate Peripheral parenchyma without membranes Fibrin deposition/necrosis	Duplication of the membranes Hemorrhage, hemosiderin/fibrin deposition/necrosis
Other form variation and umbilical cord variation		
	Umbilical cord	**Disc**
Velamentous umbilical cord	Cord insertion in membranes	Normal
Bipartita	Velamentous insertion	Two/three placental discs connected by membranes
Bi-/multilobata	Normal	Two or many placental lobes
Membranacea	Normal	Flat, membrane like disc <5 mm thick Sometimes villous fibrosis
Succenturiata	Umbilical cord insertion on the main placenta	One or more placentas connected by vessel bridges in the membranes

9. Other lesions (22;23;31)

Diagnosis	**Macroscopy**	**Microscopy**
Chorangioma (hamartoma)	Solitary or multifocal Sharply demarcated Reddish	Proliferation of fetal vessels Myxomatous/fibrous stroma
Choriocarcinoma	Hemorrhage, necroses	Solid sheets of atypical cytotrophoblasts Multinucleated syncytium without stroma Syncytiotrophoblast with atypical, hypochromatic nuclei Dense, eosinophilic cytoplasm
Invasive mole (subsequent to molar pregnancies)	Focal bleeding in the myometrium wall	Mole like villi in the myometrium Apolar trophoblastic proliferation

Placental disc	**Partition**	**Vessel anastomosis (risk of TTT)**
Separated	Dichorionic-diamnionic	None
Merged	Dichorionic-diamnionic	Exceptionally
Merged	Monochorionic-diamnionic	Frequently
Merged	Monochorionic-monoamnionic	Always

	Anastomosis	**Macroscopy**		**Microscopy**
Chronic	a-v/a-a in parenchyma rarely v-v on chorionic plate	**Donor**	Parenchyma huge, pale grayish Thin umbilical cord Ultrasound: oligo-hydramnion	Delayed mature villi Fibrous stroma Sclerotic vessels in primary villi, stem villi Regressive trophoblast Inter-/perivillous fibrin deposition Amnion nodosum
		Recipient	Parenchyma small, red-grayish Thick umbilical cord (edema) Ultrasound: poly-hydramnion	Dissociated villous maturation Tertiary villi with increased branching angiogenesis Villous stroma edema
Acute	a-a/v-v on chorionic plate and parenchyma	**Donor**	Pale	Poor vascularization
		Recipient	Red	Rich vascularization

TTT=Twin-Twin Transfusion: a-a=artery-artery anastomosis, v-v=vein-vein anastomosis, a-v=artery-vein anastomosis

	Macroscopy	**Microscopy**
Gitterinfarct	White irregular shaped areas with solid consistency	Inter- and perivillous fibrin masses

(*continued on next page*)

Maternal floor infarct	Yellow rim of pallor involving the villous tissue adjacent to the maternal surface	Netlike organized fibrinoid around viable villi near basal plate	
Chronic deciduitis		Plasmacell invasion and necrosis in the decidua	
Retention phenomena	**<= 1 week**	**few weeks**	**more weeks**
Chorionic epithelium	Eosinophilic syncytium Increased amount of syncytial knots	Karyorrhexis in the syncytium Perivillous fibrin	Loss of nuclei in epithelial cells Perivillous fibrin Intervillous space obturated
Villous stroma	Minor stroma condensation	Swelling of collagen High collagen amount Hydropic/mucoid degeneration	
Collagen tissue cells	Pyknosis	Pyknosis Cell proliferation	Loss of nuclei in stroma cells

by one of the pathologists. No placentas were diagnosed in categories seven, eight or nine.

8. Discussion

Placenta has been called the diary of pregnancy, written by mother and child. A placental examination can reveal the etiology of adverse events like stillbirths, preterm delivery, FGR and neurodevelopmental impairment, and can indicate whether the pathological process was acute or chronic. Importantly, conditions with a recurrence risk can be identified, thus resulting in adequate follow-up and treatment in a subsequent pregnancy.

The challenges to pathologists in the diagnosis of placental structural findings are numerous. They partly lie in the complexity of the organ with a continuous development and adaptation throughout the pregnancy. At term, all placentas will exhibit structural changes. The clinical relevance and implication of the structural changes will depend on the location and size of the lesions and on the reserve capacity of the placenta. A relevant diagnosis thus depends upon macroscopic as well as microscopic findings, and additionally must relate to normal variations according to gestational age. Relevant clinical information is crucial for the macroscopic examination, sampling of relevant sections for microscopy (standardized ones plus relevant extras) and weighing the clinical relevance of processes seen in the sections by microscopy. In diagnosing and reporting of changes in the clinical setting, the challenge also lies in the formulation of an easily understood diagnosis and a subsequent clinically oriented comment or discussion of differential diagnoses and assumed relevance of the findings. As in all areas of pathology, commonly accepted macroscopic and microscopic criteria, guidelines of supplementary examinations like immunohistochemistry and molecular markers, and harmonization of the wording of the diagnosis are important for international correlations and benchmarking, and for further research. The lack of an internationally accepted diagnostic placental classification often has led to a plethora of diagnostic setups, often in long prose descriptions of morphology. Such reports have often made it difficult for clinicians to grasp the essence of the structural findings. In the clinical setting, relevant placental findings can constructively be discussed at perinatal audits and clinical-pathological meetings locally. The introduction of this classification system with standardization of the written reports with one main, process-related diagnosis and a following discussion/comment has been welcomed by obstetricians and midwifes. It has increased the interest for placental examinations. For statistics and further research, the SNOMED coding system (Systematized Nomenclature of Medicine) was used. In addition to topography (T) and morphology (M), an EP code (etiology, pathogenesis) for main diagnostic category was developed locally, as exemplified in Table 5. This coding system could easily be adapted into other comprehensive pregnancy related coding systems, like the CODAC-system (Causes of death and associated conditions).

In the interobserver correlation study, the focus was on the microscopic criteria. The only clinical information available for the pathologists while reviewing the sections, was gestational age. The results in the correlation study thus have no bearing as to the cause of the stillbirths. The interobserver correlation study only intended to test reproducibility of the microscopic criteria and to identify areas with need for further research. Interobserver reproducibility varied between 0.25 and 0.91, that is fair to very good agreement

Table 3
Placental main diagnostic categories in microscopic review of 315 cases of intrauterine fetal deaths. 1 = normal, 2 = chorioamnionitis, 3 = villitis and intervillositis, 4 = maternal circulatory disorders, 5 = fetal circulatory disorders, 6 = delayed villous maturation, 7 = suggestive for genetic aberration, 8 = implantation disorders, 9 = other lesions.

Diagnostic category	Gestational week																						
	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	Total
1	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	3
2	1	2	1	3	2	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	12
3	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	2	2	0	0	0	0	0	6
4	0	8	11	7	7	13	5	13	9	10	12	10	6	8	17	14	23	15	24	19	7	1	239
5	0	0	2	1	0	1	0	0	1	0	1	1	1	0	1	0	1	1	1	0	0	0	12
6	0	0	1	1	1	0	3	0	1	1	0	1	0	3	2	2	6	4	5	2	1	0	34
7	1	0	0	0	0	1	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	4
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	1	0	1	1	0	0	0	1	1	0	0	0	0	0	0	0	5
Total	2	10	16	13	11	16	9	13	12	12	13	14	7	13	21	19	33	20	30	21	8	2	315

Table 4
Placental main diagnostic categories in microscopic review of 31 control cases of live born children. 1 = normal, 2 = chorioamnionitis, 3 = villitis and intervillositis, 4 = maternal circulatory disorders, 5 = fetal circulatory disorders, 6 = delayed villous maturation, 7 = suggestive for genetic aberration, 8 = implantation disorders, 9 = other lesions.

Diagnostic category	Gestational week																					
	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	Total
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	2
2	0	0	1	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	4
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
4	0	1	0	1	0	0	1	2	0	4	1	0	0	1	3	3	1	0	3	1	1	23
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	0	1	1	1	0	1	1	2	0	5	2	0	0	1	4	3	2	1	4	1	1	31

[20]. Acute chorioamnionitis, with well defined microscopic criteria related to localization, staging and grading according to fetal and maternal response to inflammation [21], had very good agreement (kappa value 0,91 to 1), a consequence in part of Redlines well defined criteria [21]. The major diagnostic category "maternal circulatory disorders" had a good interobserver agreement of 0.79. Microscopic criteria like increased syncytial knots, villous agglutination, intervillous fibrin deposition and infarcts are well known and well defined findings in placental hypoxia [4,22–25]. More specific criteria of staging and grading are however lacking, both in general and in relation to advanced gestational age. In our material, increased syncytial knots and intervillous fibrin deposition were seen in nearly every placenta. Many sections included infarcts. This might explain the good interobserver agreement in our study.

Fetal placental circulatory disorders had a kappa value 0.59, meaning moderate interobserver agreement. Interobserver agreement of each of the criteria of fetal vessel pathology made by Redline et al. had kappa values between 0.34 and 0.78 [26]. Again there is the challenge of grading and weighing fetal placental circulatory disorders versus other diagnostic categories, pinpointing the importance of discussion in the comments. Fetal vasculopathy was assumed to be secondary to maternal circulatory disorders when the latter were dominant in the sections. Avascular villi were seen in placentas with and without prominent hypoxic changes. They were diagnosed as maternal vascular underperfusion only when other features of that entity were present and other features of fetal vascular obstruction were absent. Retention phenomena (diagnostic category 9) were differentiated from avascularity in fetal vasculopathy. Focal vessel wall changes like endothelial edema and endothelial cushions were assumed to be local vessel wall injury caused by hypoxia.

Focal lymphocyte invasion in the villous stroma, disrupted trophoblastic epithelium, destructed fetal vessel walls and increased number of Hofbauer cells in the stroma were conclusive for chronic villitis. Invasion of neutrophils, lymphocytes or histiocytic cells in the intervillous space were interpreted as acute or chronic intervillositis. Villitis and intervillositis are graded into high and low grade. The high grade lesions correlate with intrauterine death, fetal growth restriction and recurrence risk [27,28]. Six cases were diagnosed as villitis and intervillositis, good interobserver agreement. Lymphocytic villous invasion close to hematomas or infarcts was read as related to the maternal circulatory lesion. In 13

Table 5
Examples of pathology reports. Relevant clinical information is crucial. Macroscopic description includes net weight and measurements, and information of placental lesions or variations. Routine sections include two from the umbilical cord (one near child, one near placenta), membrane roll, normal looking full thickness placenta, and two from maternal plate/decidua. Extra sections from lesions. Microscopic findings include those of importance for the main diagnosis and other findings to be discussed in the comment. The code includes SNOMED system and a local coding system stating the main diagnostic category.

Case 1	
Clinical information	35 year old woman with preeclampsia. Acute C-section in gestational week 38. Child weight 2300 g, Apgar score: 7–9.
Macroscopy	Placental weight (net) 263 g, basal plate 15 × 13.5 cm. 65 cm long umbilical cord, central insertion, diameter 1,8 cm. Focal parenchymal lesions (chronic infarcts) <5%. Few calcifications. Routine sections.
Microscopy	Numerous syncytial knots, focal villous agglutinations and increased fibrinoid in intervillous space. Areas with small villous diameter and many vasculosyncytial membranes. Villous groups with chronic inflammation in the stroma, near the decidua with lymphocytes and calcification.
Diagnosis	Placenta with maternal circulatory disorders.
Comment	Placenta is low in weight and disc area compared to gestational age. Microscopy reveals ischemic changes consistent with maternal underperfusion in addition to areas with compensatory villous capillary proliferation. Normal fetal vessels in stem villi. Chronic villitis near the basal plate is seen as a secondary reaction to maternal circulatory disorders.
Codes: SNOMED + local	T 88,000, M 36,050, M 43,000, EP 74,000.
Case 2	
Clinical information	37 year old woman with diabetes mellitus type 1. IUFD in gestational week 38 + 6. Girl, 3350 g, 50 cm.
Macroscopy	Placental weight (net) 553 g. Eccentric umbilical cord insertion, 53 cm. Basal plate 17 × 18 cm. No focal parenchymal lesion. Routine sections.
Microscopy	Umbilical cord and membranes without any inflammation. Immature secondary villi with centrally localized fetal vessels and few vasculosyncytial membranes. Normal fetal vessels in stem villi. Increased intervillous fibrinoid. Focal trophoblastic condensation.
Diagnosis	Placenta with delayed villous maturation.
Comment	Placental villous microscopy, consistent with maturation arrest is probably related to maternal diabetes type 1, so that the IUFD is related to delayed placental maturation.
Codes: SNOMED + local	T 88,000, M 75,000, EP 76,000.

cases the diagnosis villitis was competing with maternal circulatory disorders. Morphological changes indicative for viral inclusions were not found either in case placentas or control placentas.

The microscopic criteria of villous morphology in relation to gestational age, and differentiation between primary and compensatory changes of maturation is poorly defined and not internationally accepted. A standardization of maturation disorder criteria thus does not exist. Little is known about the correlation of maturation disorders and clinical outcome [29,30]. Combining the microscopic criteria published by Becker [33], Vogel [31] and Kaufmann [4], normal maturation was defined in relation to gestational age by villous branching architecture (stem, secondary and tertiary villi), villous stroma changes (embryonic, reticular, cellular or fibrous), and micro vascular changes (transformation of the villous capillaries into sinusoids and development of the vasculosyncytial membranes). In the merged microscopic criteria, secondary and/or tertiary villi with increased number of fetal vessels are interpreted as a compensatory accelerated maturation, secondary to maternal circulatory disorders. Retarded maturation, inadequate to gestational age was categorized into main diagnostic category six, 'delayed villous maturation'. These findings were in part focal, partly explaining the variation in the registered main diagnosis. Again there was the problem of staging and grading.

Placentas from infants with verified chromosomal defects had been excluded from this material. Morphological changes like trophoblastic invaginations, intravillous inclusions and large edematous villi [32], reported as 'suggestive of genetic aberration' were, however, found in four cases, fair reproducibility. Edematous or dysmature villi are not defined in number or extent and thus competed with retention phenomena and maturation delay.

The five cases with edematous villi without other signs of gene aberration were placed into group nine, 'other lesions', kappa value 0.79, meaning good interobserver agreement. Only using morphology without available clinical data, hydrops and/or fetal anemia was suspected. No diagnosis of implantation disorders was made in this clinical series.

There are several limitations in the interobserver correlation study. The study could preferable have included more pathologists from other hospitals. The microscopic criteria were tested on retrospective material of placentas from fetal deaths. The sections had been sampled in a non-standardized way and essential sections from macroscopically normal looking placentas to evaluate maturation disorders were often missing. Placentas from normal pregnancies could preferably have been included.

In conclusion, this clinically oriented, unifying and simple placental pathology classification system has been welcomed by the obstetricians. The diagnostic categories are useful to the clinicians because they accentuate care assessment. Generally, the merged microscopic criteria showed moderate to very good interobserver agreement. Criteria without specification of stages and grades were more vulnerable for lack of reproducibility. Substantial further research is needed to define diagnostic criteria in the staging and grading in major diagnosis categories as maternal and fetal circulatory disorders and maturation disorders.

Acknowledgment

We acknowledge the support and discussion with our group of Norwegian perinatal and placental pathologists, representing every health region in Norway. We especially mention Ricardo Laurini. Without the practical support by research technician Marina Novikova and the financial support by Ekstrastiftelsen Helse og Rehabilitering (H&R) and Landsforening for Uvented Barnedød (LUB), this study could not have been done.

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