Constellations of Pathology in the Placenta and How They Relate to Clinical Conditions

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56.1 Introduction

Histopathologic assessment of the placenta involves quantitative and qualitative examination for the presence of various individual features on gross and microscopic evaluation. These features may be grouped together in different ways. From a pathologic perspective, individual placental features may be combined into the different diagnoses as described in this book. In addition, these features may be viewed from a clinical perspective as being associated with specific pregnancy conditions such as maternal hypertension, fetal growth restriction or sepsis. In this chapter, we propose that these features may be grouped, as stars can be, into constellations, such that a pattern can be seen and useful information obtained.

However, due to the variation present in the mother, the fetus and the placenta and the complex interplay between them, few pregnancies exhibit a full range of maternal/fetal symptoms/signs and associated placental characteristics. Thus, for optimal clinico-pathologic interpretation, a full clinical history is required to provide context for the interpretation of results of the histopathological examination of the placenta. Ideally, before conveying information to patients, results should have been interpreted by a multidisciplinary team (e.g. obstetrician, pathologist, geneticist, midwife).

To illustrate the concept of clinico-pathologic correlation, we have highlighted the clinical and pathologic features of two disorders, namely, hypertensive disorders of pregnancy and preterm birth with preterm rupture of membranes. This is not meant to be a comprehensive analysis of the wide range of all pregnancy complications that have recognized clinical and pathologic features. Rather these are examples of how information regarding the patterns of abnormality may be important when providing information for

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parents about the causes of disorders leading to pregnancy complications, their likely etiopathologic pathways, the estimated recurrence risks and possible interventional strategies to be considered in future pregnancies.

56.2 Hypertensive Disorders of Pregnancy

The hypertensive disorders in pregnancy form a major problem in obstetric care affecting 5–10% of pregnancies and have a spectrum of disease severity. Hypertensive disease in pregnancy is currently classified according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) into chronic hypertension, gestational hypertension, preeclampsia and white coat hypertension (which will not be explored further in this chapter). Chronic hypertension is defined as hypertension (systolic blood pressure of >140 mmHg and/or diastolic blood pressure >90 mmHg) before mid-pregnancy (<20 weeks). Gestational hypertension and preeclampsia are defined as new-onset hypertensive disease after 20 weeks of pregnancy [1]. Although chronic hypertension and gestational hypertension are generally considered to be less severe hypertensive disorders, they can progress to preeclampsia in up to 25% of cases [2] and can carry a risk of (severe) maternal and/or fetal complications [3]. In the absence of preeclampsia, gestational hypertension is associated with increased fetal weight rather than fetal growth restriction.

Preeclampsia is defined by hypertension combined with organ failure based on endovascular disease. Classically, the latter was defined by proteinuria of at least 300 mg/24 h. However, although this restrictive definition is practical for research purposes, it does not sufficiently cover the wide variation of the clinical syndrome of preeclampsia. Consequently, preeclampsia was redefined by ISSHP in 2014 to include symptoms of endovascular disease in other organs as well as proteinuria (Table 56.1). This definition incorporates the more severe forms of preeclampsia (including eclampsia and HELLP syndrome) [1] and covers the broad variety of symptoms. The broad spectrum of abnormalities evident in preeclampsia emphasizes the need to provide detailed clinical information to the pathologist, such that relevant clinical diagnoses are not overlooked in placental pathology interpretation.

56.2.1 Clinical Management of Preeclampsia

Preeclampsia carries high maternal and fetal risks for adverse outcomes [4, 5]. The disease can be critical enough to necessitate termination of pregnancy for maternal reasons.

In the remote from term period, considerations of fetal and maternal well-being may conflict with respect to delivery decisions. If severe preeclampsia occurs in the previable period, perinatal death is the usual consequence. In the viable preterm period, a temporizing management strategy may be employed in high-care settings, provided that the severity of symptoms and signs does not dictate imminent delivery. This approach reduces the rate of neonatal complications without compromising maternal outcome [6]. Prolongation of pregnancy places the mother at risk with a small but significant chance

Table 56.1 Definition of preeclampsia (ISSHP 2014)

Gestational hypertension plus one of the following:	
1. Proteinuria	Spot urine protein/creatinine >30 mg/mmol (0.3 mg/mg) or at least 300 mg in a 24-h portion, or at least 1 g/L (“2+”) on dipstick testing
2. Other maternal organ dysfunctions	Renal insufficiency, liver involvement (elevated transaminases; at least twice upper limit of normal ± right upper quadrant or epigastric abdominal pain), neurological complications (including eclampsia), haematological complications (platelet count below 150,000/dL, DIC, haemolysis)
3. Uteroplacental dysfunction	Fetal growth restriction

DIC disseminated intravascular coagulation

of severe maternal morbidity and of unanticipated fetal death on the one hand and of improved neonatal outcome, despite the morbid associations of prematurity, on the other hand. Maternal condition is monitored, blood pressure is reduced by antihypertensive medication, and anticonvulsive medication (magnesium sulphate) is provided to reduce the risk of eclampsia in cases of suspected imminent eclampsia. In the meantime, fetal well-being is monitored by regular ultrasounds including Doppler measurements to determine vascular resistance in the placenta (umbilical artery Doppler), fetal brain (middle cerebral artery Doppler) and when growth restriction is present before 32 weeks' gestation by assessment of blood flow in the ductus venosus [7]. A description of abnormalities in these waveforms would provide the pathologist with additional information about possible placental pathology.

In late pregnancy (≥36 weeks' gestation), an interventionist approach aiming for expedited delivery may be most practical. Severe maternal complications are rare, but consequences from prematurity are also more benign. Even though there are no clinically significant differences in outcomes of babies and mothers, this approach reduces the caesarean section rate, likely by preventing progression to more severe maternal signs/symptoms and interventions that follow from it [8]. If delivery is anticipated before 34 weeks, corticosteroids should be administered for lung maturation.

Hypertensive disorders of pregnancy share many risk factors with cardiovascular diseases in later life. This is shown by an increased risk of maternal chronic hypertension, ischaemic heart disease, cerebrovascular disease, renal disease, diabetes mellitus, thromboembolism, hypothyroidism and even impaired memory [9]. Importantly, conditions which predispose to the development of MVM (which is the most frequent placental abnormality seen in hypertensive disease) include pre-existing maternal disease such as diabetes, hypertension, renal disease, connective tissue disorders such as scleroderma and various autoimmune conditions, most notably the lupus anticoagulant family of disorders (e.g. systemic lupus erythematosus). A history of placental abruption is a risk factor for recurrence, and women who were themselves born SGA have an increased risk of placental abruption [10].

56.3 Fetal Growth Restriction

Hypertensive disorders are an important risk factor for fetal growth restriction (FGR) in early-onset disease, but FGR often occurs independently, particularly in late-term gestation. FGR is defined as the inability of the fetus to reach its optimal/genetic growth potential. The underlying pathophysiology for FGR is that the placenta is not able to provide the adequate exchange (nutrients, oxygen and waste products) to and from the fetus. This organ failure is multifactorial and relates to a wide variety of placental lesions that may be vascular, immunologic, inflammatory or genetic in origin, e.g. VUE, genetic lesions and vascular lesions.

The dominant cause of FGR (particularly in early-onset cases) is impaired flow in the uteroplacental unit, most frequently as a consequence of maternal vascular malperfusion (MVM). Other disruptors to optimal exchange may be found in disturbed placental-fetal unit flow, as in fetal vascular malperfusion (FVM), with increased diffusion distance for exchange as seen in villous maturation disorders, and in inflammatory conditions reducing the optimum diffusion capacity as in chronic histiocytic intervillositis, villitis of unknown aetiology and massive perivillous fibrin deposition. Infections such as rubella, malaria and Zika virus can cause multiple processes that result in FGR, including those acting directly through the placenta: impaired placental vascularization, altered production of growth hormones and immunologic milieu [11]. Lastly, FGR can also be caused by genetic disorders that affect placental function. These include chromosomal abnormalities involving the fetus such as triploidy or trisomy 18, or anomalies confined to the placenta such as confined placental mosaicism [12].

Table 56.2 Consensus definitions of FGR based on non-customised growth charts [13]

Early FGR
Gestational age <32 weeks, in the absence of congenital anomalies
AC/EFW <p3 or AEDF in the umbilical artery
Or at least two out of three of the following:
1. AC/EFW <p10 *combined with*
2. PI in the uterine artery >p95 and/or
3. PI in the umbilical artery >p95
Late FGR
Gestational age >32 weeks, in the absence of congenital anomalies
AC/EFW <p3
Or at least two out of three of the following:
1. AC/EFW <p10
2. crossing centiles of more than 2 quartiles on growth centiles
3. CPR <p5

AC abdominal circumference, *EFW* estimated fetal weight, *PI* pulsatility index, *CPR* cerebroplacental ratio

It is difficult to define abnormal growth for the individual fetus. FGR cannot simply be defined by dichotomising growth between normal and abnormal based on a threshold of size on a reference chart [13] (Table 56.2). In general there are two approaches to compare fetal size to reference values. The first approach is to relate optimal fetal size to size for a given gestational age in a healthy population. The INTERGROWTH-21st studies have shown that the variation of fetal growth between populations of different ethnic backgrounds is smaller than the variation within populations [14]. The second approach is to customise for maternal individual factors, as surrogate markers for genetic growth potential like maternal height, weight and ethnicity, to assess expected fetal or neonatal sizes [15]. Irrespective of which clinical approach is taken, deviation of growth centile or growth below a certain threshold of the reference is defined as abnormal. However, it does not stop there. FGR is a functional placental problem and a sound definition also encompasses functional variables. The current international definition was developed in international expert consensus, both for clinical practice and research purposes.

56.3.1 Clinical Management of Fetal Growth Restriction

Not only is it difficult to determine the benchmark of optimal growth, there is also considerable difficulty in how to monitor fetal growth during pregnancy. Fetal growth is measured by biometric measurements obtained by ultrasound and is hampered by several variations stemming from variability in observer, software, maternal and fetal characteristics. Additionally, due to the fact that growth is not a static but a dynamic process, complete assessment requires more than one measurement. In many countries, routine obstetric care does not involve multiple ultrasounds, and an ultrasound is performed only when signs or symptoms of pregnancy complications such as preeclampsia occur or when FGR is suspected. Although sequential measurements are required to measure growth, it is possible to estimate whether fetal growth is optimal or not on a single occasion by a combination of biometric measurements and measurements of functional parameters. These include Doppler flow profiles of uterine artery, umbilical artery and ductus venosus [7] in early FGR (<32 weeks of gestation) and middle cerebral artery flow [16] in late FGR (>32 weeks of gestation) [13]. Due to overlap with the syndrome of preeclampsia and associated maternal vascular malperfusion, similar research is performed to arrive at functional predictive and/or diagnostic parameters in the area of angiogenic and anti-angiogenic factors and of radical oxygen species (ROS) biomarkers [17]. Nevertheless, a summary of ultrasound findings and, if relevant, a clinical diagnosis of FGR should be provided to the pathologist prior to examination of the placenta.

Currently, the only known intervention is optimal timing of delivery [18]. For prevention of FGR, aspirin is used as this is associated with a reduction in severe early-onset preeclampsia and FGR in high-risk populations. Many prevention and intervention strategies are under research at the moment, such as sildenafil, growth factor substitution and statins [19].

56.4 Pathologic Changes Related to Preeclampsia and FGR

The gross and microscopic changes are discussed in more detail in the individual chapters and are summarized in Table 56.3.

Preeclampsia and FGR are two complications of pregnancy to which the term "Great Obstetrical Syndromes" has been applied. The others are preterm labour, preterm premature rupture of membranes, late spontaneous abortion and placental abruption [20]. They are characterised by disease of the placental vascular bed and are a feature of early-onset (<34 weeks, rather than late onset, >34 weeks) preeclampsia. There is suboptimal, notably shallow, implantation leading to maternal vascular malperfusion (MVM) and ischaemia. The lesions seen are arterial lesions (unconverted spiral arteries) leading to acute atherosis (which are prone to thrombosis) and prone to damage resulting in abruption. Reduced uteroplacental blood flow can lead to infarction of placenta. Depending on the timing of the insult, there may be recent or remote or combination of lesions. Placental weight and/or size may be affected. As a result of these changes, placental adaptation can be seen in the form of accelerated villous maturation. Secondary lesions frequently coexist: hypoxic stress to the fetus secondary to MVM may be manifested as meconium staining of the membranes and as an increase in nucleated red blood cells within the fetal circulation. A threefold increase in the incidence of fetal vascular malperfusion (FVM) has been documented in cases with MVM compared with controls [21].

Other placental findings frequently reported in preeclampsia include VUE. There is a view that VUE, together with other inflammatory lesions in the placenta such as chronic histiocytic intervillositis and massive perivillous fibrin deposition, has an alloimmune basis. If so, this could be a maladaptation of the immunological interplay between the mother and fetus. Shallow implantation may in part reflect poor preconditioning of the endometrium prior to conception, with a significant immunologic contribution.

Placental findings in preeclampsia can be varied, and the placenta can, indeed, display no overt pathological features, particularly in late-onset disease. Furthermore, it is possible that clinical

Table 56.3 Pathophysiology and constellation of pathology findings in preeclampsia

Pathophysiological event	Pathological effect and findings
Maladaptation of immune response to pregnancy	Inadequate extravillous trophoblast migration Villitis of unknown aetiology Chronic deciduitis Chronic chorioamnionitis
Inadequate extravillous trophoblast migration	Unconverted placental bed spiral arteries Intraluminal endovascular trophoblast in third trimester Increased multinucleate trophoblast cells in basal plate
Absence of physiological vascular change	Acute atherosis
Acute atherosis	Uteroplacental thrombosis Infarction Abruption
Decreased uteroplacental vascular perfusion	Accelerated villous maturation (increased syncytial knots) Membrane chorionic microcysts Laminar necrosis of membranes Diffuse decidual leukocytoclastic necrosis
Intrauterine (intervillous) hypoxia	Persistence of villous cytotrophoblast Presence of fetal nucleated red blood cells in villous vessels Chorangiosis Meconium effects

intervention may alter the pathological manifestations, the most obvious being that early delivery will have altered the natural history of the disease.

56.5 Preterm Birth and Preterm Rupture of Membranes

Preterm birth, the delivery of an infant before 37 completed weeks' gestation, has an incidence of approximately 10% in high-income countries. The earlier the gestation at delivery, the worse the prognosis. Preterm birth is responsible for the majority of neonatal mortality and morbidity worldwide and may occur spontaneously (~66%) or be iatrogenic (~33%), with intervention indicated by deteriorating maternal or fetal conditions (e.g. preeclampsia or FGR). Spontaneous preterm birth may be due to preterm labour or following preterm prelabour rupture of membranes (PPROM). Risk factors for preterm birth include a history of spontaneous preterm birth, short cervix, Afro-Caribbean ethnicity, short inter-pregnancy interval, multiple gestations and uterine anomalies (e.g. bicornuate uterus) [22].

The pathways leading to spontaneous preterm birth are incompletely understood and are beyond the scope of this chapter. Inflammation plays a key role in normal labour as well as abnormal labour, and shifts to pro-inflammatory profiles are thought to be key in sensitizing the myometrium to become contractile. One third of cases of preterm labour are associated with intra-amniotic infection that is usually subclinical, i.e. there are no clinical features of chorioamnionitis or systemic sepsis. When microorganisms are involved, the infectious, usually bacterial, organisms are thought to enter the uterus from the maternal genital tract. Why this happens in some women is unknown; it may be that cervical shortening and microbiome alterations in the vaginal mucosa are key processes leading to ascending intrauterine bacterial infection. It is thought that activation of inflammation, particularly lytic enzymes, weakens the extraplacental membranes, resulting in rupture.

Several strategies to prevent preterm birth have been investigated, including administration of progesterone and cervical cerclage placement. Although widely used in high-income settings, tocolysis is not associated with improvement in neonatal survival and is not used where there are concerns for fetal or maternal well-being (e.g. in the presence of antepartum haemorrhage/sepsis). When preterm birth is anticipated, a course of corticosteroids for lung maturation is indicated, as this reduces neonatal mortality and morbidity prior to 34 weeks. The primary reason to use tocolysis is to gain time for the steroids to have an effect. In the presence of PPROM, women may receive antibiotic treatment (usually erythromycin), which has been demonstrated to prolong pregnancy and to reduce short-term infection [23]. In the case of PPROM, women are screened for signs of infection, using clinical signs and body temperature and on indication of a mixture of genital tract microbiological swabs, white cell count and C-reactive protein. If fever and/or a rise in inflammatory markers is present, without another focus than the intrauterine environment (chorioamnionitis), delivery is indicated. Where a fetal response is detected and an organism identified, this information should be given to the perinatal/neonatal team caring for the baby in order for antibiotic therapy to be modified as appropriate.

56.6 Pathologic Changes Related to Preterm Labour

The predominant identifiable pathologic condition associated with preterm labour and PPROM is amniotic fluid infection. However, often no responsible organism can be identified, and in low-risk women at term, histologic chorioamnionitis was much more common than infection [24]. Amniotic fluid infection refers to infectious organisms which usually inhabit the perineum and/or vagina, which gain access to the uterine cavity, with or without associated membrane rupture. The amniotic fluid infection constellation is restricted to cases that meet the histologic criteria

for chorioamnionitis, with or without clinical chorioamnionitis, but that are due to ascending infection. While there are pregnancies with clinical but no histologic chorioamnionitis and cases of histologic chorioamnionitis without identifiable infectious organisms, discussion of those conditions is not within the scope of the amniotic fluid constellation disorder. Clinical chorioamnionitis is diagnosed with maternal uterine tenderness and fever and/or maternal tachycardia, usually together with PPROM and/or contractions. The diagnosis is difficult, especially during (preterm) delivery, when many women have epidural anaesthesia that reduces uterine sensation and increases maternal temperature by interfering with the hypothalamic thermal regulation centre and subsequently increases maternal heart rate and fetal heart rate.

Amniotic fluid infection is suspected in the presence of a number of predisposing conditions, which are identified by clinical history and potentially by ultrasound [25]. These include premature/prolonged membrane rupture, preterm labour, prolonged labour, prolonged intrapartum cervical dilatation, ± intact membranes, cervical shortening (spontaneous and/or due to prior surgical intervention), prior history of chorioamnionitis, multifetal gestation, history of urinary tract infection(s), history of vaginal colonization (bacterial vaginosis, Group B streptococcus, Candida), young maternal age and primigravid pregnancy [26].

56.6.1 Macroscopic Placental Changes

The placenta may have an opaque fetal surface, with the opacity extending to the extraplacental membranes. The placenta and membranes may also be discoloured (yellow, tan, off-white, green-tinged). The extraplacental membranes may be diffluent (slimy). There may be many pinpoint white umbilical discolorations (surface microabscesses) in the event of umbilical inflammation, and there may be evidence of marginal/retroplacental bleeding (which can be termed "inflammatory abruption"). In addition to these visual changes, the placenta may have a foul odour.

56.6.2 Microscopic Placental Changes

There may be evidence of an inflammatory response in both the maternal and fetal compartments. The maternal inflammatory response progresses temporally from acute subchorionitis, acute chorionitis and acute chorioamnionitis, culminating in necrotizing acute chorioamnionitis ± deciduitis. The maternal changes may be accompanied by a fetal inflammatory response which may be evident as umbilical vasculitis ± perivasculitis and/or chorionic vasculitis ± perivasculitis. In addition, there may be normoblastaemia, meconium, meconium-associated vascular necrosis, vasculitis-associated chorionic/umbilical thrombi and villous oedema.

56.6.3 Prognosis, Predictive Factors and Potential Recurrence Risks

The prognosis for fetuses/neonates affected by amniotic fluid infection depends on a range of factors including gestational age, organism virulence, duration of infection, extent of fetal vasculitis, superimposed vasculitis-associated fetal thrombosis and coexisting complications such as meconium aspiration and the presence of congenital/neonatal sepsis. Predictive factors with respect to an increased risk of adverse fetal or neonatal outcome include the presence of fetal vasculitis, particularly when advanced [27], prematurity, concomitant meconium and congenital/neonatal sepsis [25].

Recurrence risks for amniotic fluid infection are those in which the predisposing conditions persist from one pregnancy to another. These include cervical shortening due to a prior surgical intervention, a prior history of chorioamnionitis, a history of urinary tract infection(s) and a history of vaginal colonization by organisms known to be associated with ascending infection.

56.7 Conclusion

The critical role of the placenta in determining the likelihood of pregnancy outcome means that placental examination is one of the most useful investigations to perform in the presence of a potential or known adverse outcome. Placental abnormalities are observed in 11–65% of stillbirths, and examination of the placenta reduces the likelihood of unexplained stillbirth [28]. Critically, the value of placental examination is optimized with information shared among obstetric and neonatal teams and the pathologist. Understanding the clinical presentation, results of investigations and how this data fits informs placental phenotypes is important, so that placental abnormalities can be placed in context and their potential significance appreciated [29].

Clinical interaction is critical to ensure that relevant diagnoses are recorded and appropriate interventions are considered in future pregnancies. It is anticipated that understanding the interrelationship between clinical factors and placental phenotypes (such as with placental constellation disorders) will facilitate this process. Links between clinical and placental conditions in which key pathologic lesions are identified and the information is conveyed to clinicians, while spurious lesions or incidental findings are recorded but do not prompt inappropriate diagnoses or action, are the aim of clinically informative placental diagnosis.

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