Pathophysiology of Placental-Derived Fetal Growth Restriction

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Condensation: Deficient remodelling of the uterine arteries and resultant malperfusion compromise placental function through infarction, reduced villous surface area and vascularisation, and dysregulation of transporter activity.

Abstract

Placental-related fetal growth restriction arises primarily due to deficient remodelling of the uterine spiral arteries supplying the placenta during early pregnancy. The resultant malperfusion induces cell stress within the placental tissues, leading to selective suppression of protein synthesis and reduced cell proliferation. These effects are compounded in more severe cases by increased infarction and fibrin deposition. Consequently, there is a reduction in villous volume and surface area for maternal-fetal exchange. Extensive dysregulation of imprinted and non-imprinted gene expression occurs, affecting placental transporter, endocrine, metabolic and immune functions. Secondary changes involving dedifferentiation of smooth muscle cells surrounding the fetal arteries within placental stem villi correlate with absent or reversed end-diastolic umbilical artery blood flow, and with a reduction in birthweight. Many of the morphological changes, principally the intra-placental vascular lesions, can be imaged using ultrasound or MRI scanning, enabling their development and progression to be followed in *vivo.* The changes are more severe in cases of growth restriction associated with pre-eclampsia compared to those with growth restriction alone, consistent with the greater degree of maternal vasculopathy reported in the former. The higher level of stress may activate pro-inflammatory and apoptotic pathways within the syncytiotrophoblast, releasing factors that cause the maternal endothelial cell activation that distinguishes between the two conditions. Congenital anomalies of the umbilical cord and placental shape are the only placental-related

conditions that are not associated with maldevelopment of the utero-placental circulation, and their impact on fetal growth is limited.

Key Words: Placenta; fetal growth restriction; ultrasound imaging

Introduction

The kinetics of placental and fetal growth are closely interrelated, and are important features predicting post-natal health and in particular cardiovascular adaptations in childhood. [1, 2] Fetal growth is dependent on nutrient availability, which in turn is related to the maternal diet, utero-placental blood supply, placental villous development and the capacity of the villous trophoblast and feto-placental circulation to transport these nutrients. At birth, the feto-placental weight ratio gives a retrospective indication of the efficiency of the placenta to support growth of the fetus, and estimates the potential risks for chronic diseases in later life through developmental programming. [2, 3]

Fetal growth restriction (FGR) is defined as the failure of the fetus to achieve its genetically determined growth potential. [4] FGR can have many causes, but the majority of cases that are not associated with fetal congenital malformations, fetal genetic anomalies or infectious aetiology are thought to arise from compromise of the uterine circulation to the placenta. Sufficient dilatation of the utero-placental circulation together with rapid villous angiogenesis are the key factors necessary for adequate placental development and function, and subsequent fetal growth.

The etio-pathology of FGR due to abnormal development of the utero-placental circulation and its impact on placental development and structure has been studied for more than five decades. [5] Ultrasound imaging, and in particular color Doppler imaging, has allowed the study of both the umbilico- and utero-placental circulations from the first trimester of gestation onwards. [6, 7] These techniques have been used extensively in the screening of placental-related complications of pregnancy, such as pre-eclampsia, [8, 9] and the management of a fetus presenting with primary or secondary FGR. [10] More recently, 3-dimensional (3D) Doppler

imaging [11, 12] and magnetic resonance imaging (MRI) [13] have been used to study the development of the placental and fetal circulations, but their use in clinical practice has remained limited.

Placental-related complications of pregnancy that lead to FGR have their pathophysiological roots in the early stages of placentation and can manifest themselves from the end of the first trimester of pregnancy when the definitive placenta is forming. [14, 15] Considerable remodelling of the placenta takes place towards the end of the first trimester/start of the second trimester, associated with onset of the maternal arterial circulation when the placenta becomes fully hemochorial. Events at this time potentially impact the final size of the placenta, and hence it functional capacity. This concept is supported by findings *in-utero* showing that pregnancies complicated with FGR, with or without accompanying pre-eclampsia later in pregnancy, have a smaller placenta volume and higher uterine resistance to blood flows compared to healthy controls from the beginning of the second trimester. [9]

The relationships between abnormal placental development and fetal growth restriction are complex. Isolating the placental causes of FGR can be difficult as many clinical studies are small, retrospective and often multivariate with confounding factors such as maternal smoking and ethnicity. Also, many potential stressors converge on the same intracellular pathways, and separating the influence of, for example, glucose as compared to oxygen deprivation during periods of ischemia is impossible.

In order to provide a coherent account of how the FGR phenotype may arise we first consider the development of the normal placenta before discussing the molecular and clinical pathologies.

Early development of the placenta

Initial development of the placenta takes place within the superficial layer of the endometrium, and by the end of the third week post-conception villi have formed over the entire chorionic sac. This precocious growth is supported and stimulated by secretions from the underlying endometrial glands (Figure 1), [16, 17] so-called histotrophic nutrition. The carbohydrate and lipid rich secretions are delivered through openings in the developing basal plate into the intervillous space, from where they are taken up by the syncytiotrophoblast. As well as providing nutrients, the secretions contain numerous growth factors that stimulate placental cell proliferation *in vitro,* and most likely play an important role in regulating development and differentiation *in vivo*. [18-20] The absence of significant maternal blood flow at this stage means that initial development takes place in a low oxygen concentration, which is physiological and should not be considered hypoxic. [21] This environment is thought to protect the embryo from damaging reactive oxygen species during the period of organogenesis, but may also serve to maintain stem cell potential. [22] Once the main organs have differentiated there is a need for a greater supply of oxygen to support faster fetal growth, [23] and hence there must be a switch from histotrophic nutrition to hemotrophic supply from the maternal circulation.

Development of the utero-placental circulation

The human hemochorial form of placentation poses major haemodynamic challenges. In particular, a high volume of maternal arterial blood flow has to be delivered to the placenta at a sufficiently low pressure and velocity to prevent mechanical damage to the delicate villous trees. [24] In normal pregnancies, the

arcuate and radial arterial components of the uterine vasculature dilate under the combined effects of estrogen, progesterone, human chorionic gonadotropin and other hormones and factors secreted by the placenta. The dilation accommodates the increased uterine flow of pregnancy, and is so marked that by around 20 weeks of gestation the diameter of the arcuate arteries is equal to that of the uterine artery. [25] The more distal elements of the utero-placental vasculature undergo additional extensive remodelling under the influence of extravillous trophoblast cells that migrate out from the placenta during early pregnancy. This remodelling involves the loss of smooth muscle cells and elastin from the arterial walls, and their replacement by fibrinoid material. [26] As a result, these segments of the utero-placental vasculature become inert flaccid conduits, incapable of vasoconstriction. The extravillous trophoblast cells arise from the anchoring villi that are attached to the developing basal plate, and pass down the lumens of the spiral arteries as endovascular trophoblast, and through the decidual stroma as interstitial trophoblast. The migration of endovascular trophoblast is so extensive during the first trimester that the cells effectively ‘plug’ the mouths of the spiral arteries, restricting flow to a slow seepage of plasma through a network of intercellular spaces (Figure 2). [27, 28] The plugs begin to break down towards the end of the first trimester, and it is only after approximately 10 weeks of gestation that the maternal arterial circulation to the intervillous space is fully established, as confirmed by measurements of the rise in intraplacental oxygen concentration. [29, 30] The interstitial trophoblast cells interact with the maternal immune system, in particular the uterine natural killer cells. Together, the extravillous trophoblast and natural killer cells are thought to release proteases and cytokines that stimulate de-differentiation and loss of the smooth muscle cells within the arterial walls. [31, 32] Thus, a degree of activation of the natural

killer cells is necessary, and genetic studies have revealed that these immune interactions may regulate birth weight across the microsomic-macrosomic range. [33]

The arterial remodelling extends as far as the inner third of the myometrium, and so encompasses the hypercontractile segment of a spiral artery lying in the junctional zone. Consequently, there are two principal effects of the remodelling; firstly, dilation of the mouth of the artery reduces the velocity and pulsatility of the maternal inflow into the placental intervillous space, and secondly the loss of smooth muscle reduces the risk of spontaneous vasoconstriction. [24]

Remodelling of the spiral arteries extends into the second trimester, and possibly even longer. Ultrasound assessment of a cohort of 58 normotensive women revealed that blood flow from the mouths of the spiral arteries is pulsatile in all cases up to 20 weeks, and that pulsatility decreases thereafter with advancing gestational age. [34] By 34 weeks, 37% of women showed no pulsatile inflow into the placenta.

Placental remodelling

The early or primitive placenta undergoes extensive remodelling towards the end of the first trimester. Regression of villi starts over the superficial pole of the gestational sac (Figure 3A) and gradually extends until only those villi covering the deep pole in contact with the placental bed remain as the definitive discoid placenta. This profound remodelling raises questions regarding how and when the size and shape of the placental disc are determined, and whether further expansion and recruitment of spiral arteries can occur in later pregnancy under adverse conditions. The remodelling is associated with onset of the maternal circulation to the placenta, which starts most commonly in the peripheral regions and extends to the central zone over the next few weeks. [35] This pattern inversely reflects the degree of

extravillous trophoblast invasion across the placental bed, which is greatest in the central region where it has been established the longest. [36] Hence, 'plugging' of the arteries by endovascular trophoblast is more extensive in the center than in the periphery. The early onset of blood flow in the periphery causes a locally high level of oxidative stress (Figure 3B), which induces activation of the apoptotic cascade. Consequently, the villi regress, leaving only avascular, hypocellular 'ghosts' that are incorporated into the smooth membranes (Figures 3C and D). [35] At the same time, expression and activity of the principal antioxidant enzymes within the placenta increase, [37] and so villi in the central zone have greater defences when the maternal blood flow reaches them.

The mature placenta is often described as discoid; however, there is considerable debate as to whether the majority are actually circular or ellipsoid. This may seem a rather academic point, but the risk of chronic disease in adult life has been associated with abnormal shape of the placenta through developmental programming of the major organ systems. [38] This phenomenon may reflect changes in placental function, for increased variability in shape has been linked to reduced placental efficiency as estimated by the ratio of fetal to placental weight. [39, 40] Similarly, eccentricity of the point of insertion of the umbilical cord into the placenta has been linked to reduced efficiency, [41] acting possibly through hemodynamic effects in the feto-placental circulation. We have speculated that excessive or asymmetrical regression of the villi due to aberrant onset of the maternal circulation may lead to abnormal placental shapes and cord insertions, and may reflect local variations in the extent of extravillous trophoblast invasion. [22] Support for this hypothesis comes from the strong correlation between the shape of the placenta at the end of the first trimester and that at term. [42] Clearly, events during the first

trimester are of critical importance, and there is increasing evidence from ultrasound studies that both growth restriction and macrosomia of the placenta are initiated during this period. [43]

Given the regression of the peripheral villi that takes place, it is difficult to envisage how the placental footprint might extend further over the uterine surface during later pregnancy, and in so doing recruit additional spiral arteries. Rather, it seems more plausible that from 10-12 weeks onwards the placenta and the uterine wall expand together. [2, 44] It is possible that more spiral arteries may be tapped within the placental bed during this process, and of course during normal pregnancies elaboration and remodelling of the villous trees will increase the functional capacity to meet fetal demands. [45]

Deficient spiral artery remodelling

Deficiencies in extravillous trophoblast invasion and maternal arterial remodelling have been linked to the pathophysiology of the 'Great Obstetric Syndromes', including growth restriction, through malperfusion of the placenta. [46] Studies have reported a gradient of effects, with absence of remodelling in the junctional zone and myometrial segment being associated with more severe growth restriction compounded with pre-eclampsia. [46-50] Aberrant remodelling of the more proximal radial arteries may also contribute to placental malperfusion in pathological pregnancies. [51] However, it must be recognised that remodelling is a continuum, and that examples of deficiently modified spiral arteries may be seen in normal pregnancies and *vice versa*. [52] In addition, histopathological reporting is generally not performed blinded to the clinical condition, knowledge of which may influence

interpretation of the findings. [53, 54] Nonetheless, within the limitations that placental bed biopsies provide as an overview of the maternal blood supply to the placenta there is general agreement that deficient spiral artery remodelling is causal of the placental changes that predispose to FGR of maternal vascular origin.

There are many possible causes for deficient spiral artery remodelling, and the actual cause will undoubtedly differ from case to case. Inadequate histotrophic nutrition during the first few weeks of pregnancy, [15] or excessive apoptosis within the placental bed [55] could lead to a reduced number of extravillous trophoblast cells. Other studies suggest interstitial trophoblast invasion is normal or even increased in cases of FGR, but that the cells fail to penetrate into the walls of the arteries. [50] The reason for this is not known, but may possibly reflect abnormal interactions with the uterine natural killer cells, leading to excessive inhibition and diminished release of proteases. [56]

The consequences of deficient spiral arterial remodelling are multiple. Firstly, it will impact adversely on the velocity with which the maternal blood enters the placental intervillous space. Mathematical modelling has shown that the normal dilation reduces the velocity by an order of magnitude, from approximately 2-3 $m.s^{-1}$ to around 10 $cm.s^{-1}$. [24] This reduction ensures even perfusion of the villous trees and adequate transit time for exchange. In pathological pregnancies inflow remains high velocity and pulsatile, [34] and causes mechanical damage to the placenta as will be discussed later. Secondly, retention of the vascular smooth muscle in the junctional zone is likely to cause greater intermittent perfusion of the placenta. Angiographic studies performed on the rhesus macaque, which has a similar utero-placental circulation to the human, revealed that even in normal pregnancies blood flow from a spiral artery is intermittent. [57] This effect is independent of uterine contractions, and

thought to be due to spontaneous vasoconstriction of the arteries involved. It might be expected, therefore, that the event will be more frequent in arteries where the junctional segment has not been remodelled, exposing the placenta to recurrent ischemia-reperfusion-type insults. Thirdly, deficient remodelling predisposes the spiral arteries to acute atherotic changes, with accumulation of foam cells and narrowing of the lumen (Figure 4). These changes are seen distal to the junctional segment, and may be induced by the high shear forces experienced or involvement in the ischemia-reperfusion insult, possibly compounded by dyslipidemia in the mother. Their effect will be to severely limit blood flow to the placenta, and so not surprisingly the lesion is associated with poor obstetric outcomes. [46, 58]

Malperfusion of any organ is a powerful inducer of oxidative stress, and the placenta is no exception. Placental oxidative stress has been linked to complications of pregnancy, including pre-eclampsia and FGR. [59-61] Oxidative stress is defined as a condition in which the generation of highly reactive species of oxygen overwhelms a cell's capacity to detoxify them, leading to indiscriminate damage to any biological molecules inn the immediate vicinity, including proteins, lipids and DNA. Consequently, cell function is impaired, and in the most severe cases cell death may be induced. Reactive oxygen species are generated physiologically as an inevitable by-product of aerobic respiration, protein folding, detoxification of drugs and xenobiotics by cytochrome P450, the response of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase to growth factors and cytokines, and various other oxido-reductase and cyclooxygenase enzymes (Figure 5). The principal source under normal conditions is the mitochondria, for during passage of electrons along the complexes of the electron transport chain (ETC) there is leakage on to molecular oxygen, particularly from complexes I and III. [62] The acquisition of an unpaired

electron generates the superoxide free radical, and 2% of oxygen consumed during quiet respiration is converted to superoxide. This acts as a signalling intermediate, regulating the activity of redox-sensitive transcription factors to maintain metabolic homeostasis in accordance with the prevailing oxygen concentration. However, because of its potential harmful actions, excess superoxide is detoxified in the mitochondria by the enzyme superoxide dismutase through conversion to hydrogen peroxide. Being non-polar, hydrogen peroxide can diffuse out from the mitochondria and is then further detoxified by the enzymes catalase and glutathione peroxidase within the cytoplasm (Figure 5).

Under normal conditions there is thus a homeostatic balance between generation and de-toxification of reactive oxygen species (ROS). However, generation of ROS is increased during hypoxia and ischemia-reperfusion, when build-up of electrons on the ETC leads to a greater rate of leakage. [63] Thus, exposure of placental explants to cycles of hypoxia-reoxygenation is a powerful generator of oxidative stress, inducing pro-inflammatory cytokines and even apoptosis. [64-66] Similar changes are seen *in vivo* when placentas are subjected to labor, for there is intermittent maternal perfusion of the intervillous space during uterine contractions. [67] The balance may also be perturbed if activity of the anti-oxidant enzymes is impaired. Transition metals, such as manganese, selenium, copper and zinc, are required at the active site of these enzymes to shuttle electrons, and a dietary lack of micronutrients has been linked to complications of pregnancy. [68] Attempts to redress the balance by administration of antioxidant vitamins have yielded disappointing results. [69] One reason for this lack of success may be that oxidative stress rarely occurs in isolation, and is closely associated with other forms of cell stress, in particular endoplasmic reticulum stress. There are close physical

and functional associations between mitochondria and the ER, mediated principally through calcium signalling, that integrate the two organelles (Figure 6). [70]

The endoplasmic reticulum (ER) is the organelle responsible for the synthesis, folding and post-translational modification of all membrane-bound and secreted proteins. Because misfolded proteins are potentially toxic to cells, there is strict quality-control within the ER comprising of three evolutionary conserved signalling pathways collectively known as the Unfolded Protein Response (UPR). [71, 72]. Regulation operates at various levels, but one of the most rapid and sensitive responses is to block non-essential protein synthesis in order to conserve resources and relieve the burden of nascent proteins on the endoplasmic reticulum folding machinery. This is achieved through phosphorylation of a key regulatory factor, the alpha sub-unit of eukaryotic initiation factor 2 (eIF2α), that limits assembly of ribosomal complexes on the mRNA. Longer-term responses involve increasing the functional capacity of the endoplasmic reticulum by upregulation of chaperone proteins and elaborating more cisternae to meet the synthetic and secretory demands of the cell.

Synthesis and secretion of proteins has to be closely linked to the metabolism of a cell, and regulated in relation to the supply of oxygen and nutrients. Hence, the eIF2α arm of the UPR controlling translation of mRNA can also be activated in response to hypoxia, amino acid deprivation and other stressors. [73-75] In view of this wider involvement in cell homeostasis, the UPR is also referred to as the Integrated Stress Response pathway.

Placental molecular pathology in FGR

1. Growth regulatory pathways

One of the principal features of the placenta in cases of FGR is the reduction in volume, surface area and vascularisation of the intermediate and terminal villi that mediate maternal-fetal exchange. [76-78] This reduction appears to be due to excessive villous regression during placental remodelling, compounded by a slower rate of subsequent growth. [79]

In the case of the placenta, members of the insulin-like growth factor family are particularly important regulators of cell proliferation. [80] Their actions are integrated with oxygen and nutrient supply through the AKT/mTOR signalling pathway, a central regulator of the translation of mRNA into protein. Activity in this pathway influences placental growth, [81] and is downregulated in cases of growth restriction of maternal vascular origin (Figure 7). [82, 83] Although this is often attributed to hypoxia secondary to deficient spiral artery conversion, no measurements have been performed *in vivo* to confirm placental, as opposed to fetal, hypoxia. One situation where there is no doubt the placental tissues are exposed to a low maternal arterial oxygen concentration is during pregnancy at high altitude. It is notable that a similar reduction in mTOR activity is seen in placentas from pregnancies at 3,100m, where it is accompanied by a reduction in placental villous volume and birth weight. [84] The changes can be mimicked by exposing placental cell lines to hypoxia *in vitro,* when there is a reduction in the proliferation rate commensurate with the metabolic activity of the cell type. [84]

The AKT/mTOR pathway also regulates expression and activity of placental transporters that are responsible for transfer amino acids, fatty acids and glucose. Many of these transporters are downregulated in growth restriction, [85-88] which will compound the loss of functional capacity of the placenta caused by the reduction in

villous surface area. Downregulation precedes the growth restriction in response to maternal undernutrition in animal models, [89] suggesting that it is causal of the condition and not a response.

2. Stress response pathways

Given the high endocrine output of the placenta, the syncytiotrophoblast contains large quantities of ER. Activation of the UPR pathways is seen in placentas from high-altitude pregnancies, where is can be viewed as a homeostatic response to match feto-placental growth to oxygen availability. More severe activation is seen in cases of growth restriction caused by maternal vascular compromise, [83, 84] and the degree of activation, both in terms of individual pathways and the number of the pathways involved, is greatest in cases of growth restriction accompanied by pre-eclampsia. This finding is consistent with the placentas being exposed to a more severe maternal vascular insult due to the greater deficiency in spiral artery remodelling described earlier. [83]

The difference in the degree of activation may have pathophysiological significance, for high levels of activation of the UPR are associated with stimulation of the release of pro-inflammatory cytokines, cell senescence and even apoptosis (Figure 6). [90, 91] The NFκB pathway can be stimulated either through the IRE-1/TRAF2 pathway, [90, 92] or more simply through suppression of protein synthesis. The half-life of the inhibitory IκB subunit is shorter than that of NFκB, and so prolonged translational arrest will inevitably lead to an inflammatory response. [93] Pro-inflammatory cytokines and apoptotic debris have all been implicated in causing the maternal endothelial cell activation that characterises pre-eclampsia, and hence, the higher level of activation of the UPR may explain the distinction between FGR

alone and FGR associated with pre-eclampsia (Figure 7). For example, shedding of pro-inflammatory microparticles from the syncytiotrophoblast is seen in pre-eclampsia but not in FGR alone. [94] Exactly when the stress begins during pregnancy is difficult to determine, but we speculate that it originates around the time of onset of the maternal circulation to the placenta towards the end of the first trimester. [15] Perturbation of endoplasmic reticulum function could also account for the change in glycosylation seen in the syncytiotrophoblast of the FGR placenta. [95]

3. Transcriptomic changes

Changes in gene expression have been reported for the growth-restricted placenta employing microarray technology, [96, 97] but in general it has yet to be determined whether the changes are responsive to, or causal of, the growth disorder. Imprinted genes that are expressed in a parent-of-origin fashion play a key role in the regulation of placental growth, and so have been the subject of particular attention. It is notable that *PHLDA2* that inhibits growth, and *MEST* that promotes growth, are upregulated and downregulated respectively in FGR. [98, 99] However, no correlation was found between the level of gene expression and loss of imprinting, suggesting that disorders of imprinting *per se* are not causal of the condition. Indeed, these studies also found widespread changes in non-imprinted genes involved in endocrine signalling, tissue growth, immune modulation, oxidative metabolism, vascular function and metabolite transport. [98] A more recent comprehensive transcriptome-wide profiling of normal and growth restricted placentas using next-generation sequencing revealed five network modules enriched for similar processes, including cellular respiration, amino acid transport, hormone signaling, histone modifications and gene expression, that were associated with birth weight.

[100] Furthermore, the hub genes for each module were significantly associated with growth restriction, and so these networks may play an important role in regulating placental function in these pathological cases.

These changes may reflect differences in gene transcription, but could also potentially arise through epigenetic changes involving microRNAs (miRs). Non-coding RNAs can bind to mRNA, regulating its stability and hence the transcript level. They can also influence translation of the mRNA and so the level of the encoded protein. It has been reported that 97 miRs are upregulated and 44 downregulated in SGA as compared to AGA placentas. [101] Functional studies of *miR-10b*, *-363* and *-149*, which were either significantly increased or trended to increase in the growth restricted placentas, in a trophoblast-like cell line showed that these have a negative impact on their target genes that encode angiogenic factors and amino acid transporters. When trophoblast-like cells were exposed to nutrient restriction, *miRs-10b* and *-149* increased whereas *miR-363* decreased, suggesting that they respond to multiple cues or that different cell types within the placenta respond in different ways during growth restriction.

Placental-specific mRNAs and microRNAs thought to be derived from the syncytiotrophoblast can be detected in the peripheral maternal blood, opening the possibility of their use as diagnostic biomarkers of placental dysfunction. [97, 102]

4. Placental metabolism

Data on placental metabolism in cases of growth restriction are conflicting. Placental mitochondrial content has been reported to be both increased [103] and decreased [104] based on assays of mitochondrial DNA content. [105] These findings have been correlated with the oxygen content in the umbilical vein, but by contrast we observed

no difference in mitochondrial content in the high-altitude placenta as determined by the level of citrase synthase. [106] There was, however, a significant reduction in the protein, but not mRNA level, of the complexes of the electron transport chain, suggesting again a block to protein translation and a reduction in mitochondrial activity. It might be expected, therefore, that placental metabolism becomes more dependent on glycolysis, but there appears to be no change in glycogen content in the growth restricted placenta. [107]

Autophagy-related proteins are regulated by UPR pathways, [108] and have been reported to be increased in FGR placentas where they may reflect excessive levels of organelle stress and recycling, or severe nutrient depletion. [109] Increased autophagy has also been observed in the placental territory of monochorionic twins with selective FGR, where it was inversely proportional to the umbilical blood flow. [110]

5. The feto-placental circulation

Reduced placental surface area and transport are important contributors to placental function and hence fetal growth restriction, but another important factor is the resistance within the umbilical circulation. The absence or even reversal of end-diastolic flow in cases of severe growth restriction as assessed by Doppler ultrasonography will greatly impair the transport of nutrients to the fetus. These findings are not surprisingly associated with fetal hypoxia. Pathological changes have been reported in the resistance arteries within the stem villi of growth restricted placentas, [111-113] but the molecular mechanisms underlying them has only recently been elucidated. The smooth muscle cells surrounding these arteries express the enzyme cystathionine-γ-lyase (CSE) that synthesises hydrogen sulfide, a powerful

vasodilator of the fetal placental vasculature that maintains vascular smooth muscle cells in their differentiated state. [114] This enzyme is reduced at the mRNA and protein levels in placentas associated with absent or reversed end-diastolic flow, and is associated with de-differentiation of the smooth muscle cells, the adoption of a synthetic phenotype, and a reduction in the lumen to wall ratio. [115] These changes can be induced by exposing explants of stem villous arteries to hypoxia-reoxygenation, indicating that the *in vivo* findings are likely secondary to the oxidative stress caused by the placental malperfusion. The severity of the changes correlates with the birth weight, indicating that they may act as an important component of the placental dysfunction in growth restriction (Figure 7).

Clinical placentology in FGR

Many, if not all, placental abnormalities have been found in association with FGR but the results of most histopathological studies are hampered by a number of methodological factors. Most studies are retrospective based on case-series rather than case-control data and many have used different clinical definitions of FGR, mixing cases of fetuses constitutionally small (small-for gestation age or SGA) and/or born prematurely following inaccurate gestational dating or unknown gestational age (low-birth weight or LBW). Specific placental lesions have rarely formed the primary topic of investigation, more often being considered as a coincidental finding or one of several potential causes of FGR. In addition to these selection biases, confounding factors such as maternal smoking, and methodologic disparities such as the location and number of samples taken for histopathologic examination make it difficult to evaluate the data from many studies, in particular from those early histopathologic

studies performed before routine ultrasound became available and at a time when laboratory investigations were limited.

Overall, placental lesions associated with FGR have been divided by pathologists into different categories: vascular and non-vascular, macroscopic and microscopic, congenital and acquired or secondary abnormalities. [116-118] The classification below is based on pathologist standardised diagnostic criteria for each individual lesion and highlights those lesions that can be diagnosed prenatally with ultrasound imaging.

Abnormalities of placentation

Abnormal placental shapes, in particular those with irregular outlines (extrachorial and bilobate placenta) have been associated with poor obstetric outcome, in particular poor fetal growth. [119, 120] These anomalies are difficult to diagnose *in-utero* by ultrasound scanning and are not routinely investigated in pregnancies complicated by FGR.

Placental location, and in particular lateral placentation, are more likely to be associated with FGR. A case-control study of precisely-dated singleton pregnancies found that those complicated by FGR are nearly 4-fold more likely to have had a lateral placentation (odds ratio (OR), 3.8; 95% confidence interval (CI), 1.3-11.2) at 16-20 weeks, compared with anterior or posterior placentation. [121] A population-based, retrospective cohort study of 544,734 singleton live births, including 2744 placenta previa found, after controlling for maternal factors including smoking and gestational age, that previa placentation is associated with a 3.7% rate of FGR (OR 1.24, 95% CI 1.17, 1.32) at birth, independently of the 12% rate of preterm delivery.[122] By contrast, a retrospective cohort study of 59,149 women with singleton

pregnancies undergoing ultrasound between 15 and 22 weeks, found that no difference in the incidence of FGR after adjusting for confounding factors (adjusted OR, 1.1; 95% CI, 0.9-1.5) in the 724 women presenting with placenta previa. [123] The pathophysiology of FGR in cases of abnormal placentation is unknown but one can hypothesized the development of the utero-placental circulation and in particular, the recruitment of spiral arteries, is influenced by the density of the uterine terminal vascular network where the blastocyst implants.

Macroscopic vascular anomalies

Deficient remodelling of the spiral arteries is associated with greater pulsatility of the jets of maternal blood in SGA pregnancies, as expected. [34] More severe vasculopathies of the arteries are associated with a combination of secondary placental macroscopic lesions including intervillous and parabasal thrombi, hematomas, infarcts and extensive fibrin deposition (Figure x). [116, 117] Placental thromboses and infarcts are the most commonly found lesions in pregnancies complicated by FGR with or without pre-eclampsia and both have been reported on ultrasound examinations (Table 1). [124]

Placental thromboses are the consequence of focal coagulation of maternal blood inside the intervillous space, [124, 125] and are found mainly in area lower villous density such as under the fetal or chorionic plate, in the placental marginal areas and in the centre of cotyledons. [116, 117] Isolated small thromboses are of no clinical significance and are commonly found in the placenta of uncomplicated pregnancies. Massive subchorial thromboses, also called Breus' "*mole*", have been reported in pregnancies complicated by FGR and stillbirth. [116, 125-129] A series of 14 cases found that subchorial thrombosis involving 50% or more of the chorionic or fetal plate are

associated with a 70% incidence of FGR in those pregnancies that continue after 24 weeks of gestation. [128] The development of an intervillous thrombosis is often associated with fibrin deposition and these lesions are often described as “echogenic cystic lesions” or hypoechoic areas on ultrasound. [124, 130, 131] The ultrasound features i.e. echogenicity of an intervillous thrombosis will change with advancing gestation as more and more fibrin deposition will appear in its periphery and depending on when, or if, the maternal blood clots in its centre (Figures 2 A & B). Large thromboses have been diagnosed prenatally on MRI.[132]

Placental infarcts are due to the complete obstruction of utero-placental arteries leading to interruption of the maternal blood flow and progressive necrosis of the villous tissue including its fetal circulation of the corresponding cotyledon(s). [116, 117, 124] Isolated small infarcts can be found in uncomplicated pregnancies but larger infarcts often associated with intervillous thromboses and extensive fibrin deposition are found in most pregnancies complicated by pre-eclampsia and FGR. These lesions appearing as complex echogenic intra-placental masses close to the basal plate on ultrasound imaging [133-138] and have also been identified recently on MRI in pregnancies complicated by utero-placental insufficiency and FGR. [139, 140]

Maternal floor infarction (MFI) is an extended lesion combining parabasal villous necrosis, fibrin deposition, thrombosis and hematoma that is associated with a high risk of severe FGR and stillbirth. [116, 117, 141] The disorder is somewhat misnamed, because it is mainly characterized by heavy deposition of fibrin in the decidua beneath the placenta rather than by arterial occlusion and ischemic necrosis of the villi. [142] The fibrin in floor infarcts often extends into the intervillous space, where they envelop villi, causing them to become atrophic. Similarly, massive fibrin depositions, in particular if involving more than 50% of the placental mass are

associated with severe FGR. [138] On ultrasound, these lesions appear as diffuse hyperechogenic lesions increasing in size with advancing gestation. [134, 143, 144]

Placental vascular lesions associated with FGR have been known to present with abnormally high levels of maternal serum (MS) alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) at 15-18 weeks of gestation. [125, 145-147] There is also an association between the vasculopathies of the spiral arterioles leading to pre-eclampsia and FGR, a placental "Jelly-like" ultrasound appearance and high MSAFP levels at 18-28 weeks. [146] The "Jelly-like" appearance of the placenta is characterized on ultrasound by a narrow implantation basis or basal plate diameter, increased thickness and patchy decrease in echogenicity secondary to the fetal plate being pushed up by jet-like blood streams from the spiral arteries (Figure 3 and videos clips). We found recently an association between placenta protein A (PAPP-A) levels in MS, basal surface area measurements at 11-14 weeks of gestation and birthweight centile. [148] All three parameters were lower in pregnancies complicated by pre-eclampsia and FGR. These findings support the concept of an early disruption in the normal establishment of the intervillous circulation starting from the end of the first trimester with a secondary maldevelopment of the villous tissue including intraplacental vascular lesions and presenting clinically with early onset pre-eclampsia and FGR.

Microscopic lesions

Many different microscopic placental lesions have been described in pregnancies complicated by FGR. Most are unspecific, have been found in villous tissue from uncomplicated pregnancies and the terminology used to describe them has been highly variable. The distribution of these lesions depends if the restricted fetal growth

is isolated or associated with pre-eclampsia and on gestational age at onset, with late onset leading to a more heterogeneous group with less characteristic histological changes. [118] Recent histological classifications have been proposed separating, these lesions according to their maternal, fetal, or inflammatory origin, [149] Our understanding of their pathophysiology remains limited by our limited knowledge of the mechanisms triggering them in early pregnancy. The microscopic lesions below have been the most commonly described in pregnancies complicated by FGR with or without pre-eclampsia (Table 2).

Villous developmental defects included mainly villous hypoplasia, delayed and accelerated villous maturation and villous capillary dysplasia. These morphological alterations of the villous architecture are thought to be secondary to underperfusion or malperfusion of the intervillous space by maternal blood, and in particular to fluctuations in the oxygen tension inside the placenta. Villous vascular lesions related to maternal underperfusion are more common in early-onset (≤ 34 weeks) than in late-onset (> 34 weeks) FGR, [150] suggesting a timing effect linked to the extent of the placental defect at the beginning of pregnancy. Giles et al were the first to correlate fetal umbilical artery flow velocity Doppler waveforms with placental villi microvascular anatomy. [151] They correlated the blood flow resistance in the umbilical circulation obtained with Doppler ultrasound with the numbers of small muscular arterioles and tertiary stem villi. They found that the number of small arterial vessels was lower in pregnancies with a high resistance to blood flow and was associated with a higher incidence of FGR than in normal controls or in pregnancies with clinically suspected FGR with normal Doppler features. They found no differences in the number of tertiary stem villi between the group with increased resistance to blood flow and the controls suggesting that only the villous vasculature and not the overall

anatomy of the villous tree was altered in their cases. Other studies have shown correlations among the pathology of the stem villus arteries, the umbilical Doppler waveform and birthweight. [115]. However, more detailed histomorphometric studies have also shown that placentae from FGR cases with abnormal umbilical artery Doppler features have increased number of villous infarcts, fibrin deposition, villous hypoplasia, cytotrophoblast proliferation and thickening of the villous trophoblastic basal membrane. [152-154] This highlight the fact that the placental lesions associated with increased resistance to flow in the umbilical arterial circulation in FGR are complex and involve the entire anatomy of the villous structure, not only its terminal vasculature.

Atherosis of the spiral arteries is characterized by fibrinoid necrosis of the arterial wall, subendothelial lipid-filled foam cells and perivascular lymphocytic infiltration (Figure 4). It is histologically similar to early-stage atherosclerosis and is a common microscopic feature of pre-eclampsia, FGR, fetal death, and spontaneous preterm labour with intact or ruptured membranes. [46, 58] Failure of spiral artery remodelling in the placental basal plate is associated with increased frequency of decidual artery atherosis, interstitial extravillous trophoblast and arterial endothelial activation. [46] Decidual atherosis is the main cause of maternal underperfusion of the intervillous space leading to fibrin deposition, thrombosis and villous infarcts. Small lesions appear to occur at points of localised stasis at the basal plate and are probably pathological markers of more generalised disturbances in placental circulation or of hypercoagulability in the intervillous space, [155] leading progressively to the macroscopic vascular lesions described previously. Obstructive lesions in the myometrial segment of spiral bed arteries have been found in 70% of the cases FGR associated with pre-eclampsia. [46]

Non-infectious villitis, also called villitis of unknown etiology (VUE), has been described as a pattern of placental injury occurring predominantly in term placentas [156]. High-grade lesions, affecting more than 10 villi per focus, have been found in fetuses presenting with FGR. [156, 157] Their histologic characteristics are distinct from infectious villitis and thought to be caused by maternal T lymphocytes, predominantly CD8-positive, that inappropriately gain access to the villous stroma. [156] VUE is found in 5-15% of placenta in uncomplicated pregnancies, [156, 157] 15-100% of placenta from pregnancies complicated by FGR [158-160] and 20% of placenta in pregnancies presenting with FGR and pre-eclampsia. [161] A systematic review including 12 studies focussing on placental pathologies associated with IUGR found significant heterogeneity in study design which can explain the wide range in incidence of VUE in FGR placentas. [157] It is not known if these lesions are the primary cause of FGR or secondary to mechanical damage to the villous surface caused by the aberrant hemodynamics (ischemia-reperfusion) of the maternal circulation in the intervillous space ,[24] or oxidative stress and the corresponding metabolic and morphological alteration of the villous trophoblastic layer.

Umbilical cord anomalies

FGR has been associated with abnormalities of the umbilical cord insertion ie, eccentric, marginal, or velamentous. [119, 162] These anomalies are rare and often associated with abnormalities of the placental shape and thus there are no data supporting a direct link between the location of the umbilical cord insertion and poor fetal growth.

The absence of one of the two normal umbilical arteries or single umbilical artery (SUA) cord is one of the most common congenital fetal malformations with an

incidence of approximately one per cent of all deliveries. [163, 164] SUA occurs three to four times more frequently in twins, and almost invariably accompanies the acardia malformation and sirenomelia or caudal regression syndrome. [163-165] Most SUA are part of fetal syndromes with major anatomical defects which are largely responsible for the poor perinatal outcomes. The incidence of FGR is significantly elevated among fetuses with a SUA and may develop without any other congenital anomalies in around 15 of the cases. [163, 164, 166-169] A population-based, retrospective cohort study of 37,500 singleton pregnancies including 223 SUA diagnosed at birth has found a higher incidence of birth weight <10th percentile (OR 2.1; CI 1.44-2.93) in isolated SUA [166]. A retrospective case-control series of 136 SUA diagnosed at second-trimester ultrasound has reported isolated SUA to be independent risk factor for FGR (adjusted OR = 11.3, 95% CI 4.8-25.6) compared normal three-vessel cord [167]. Two recent systematic reviews have reported OR ranging between 1.6 (95% CI, 0.97-2.6) [170] and 2.75 (95% CI, 1.97 to 3.83) [171] for SGA in isolated SUA compared to normal cord. The use of colour Doppler imaging (CDI) has made the diagnosis of SUA accurate in early pregnancy [172] but its detection at the first trimester (Figure 4) or routine mid-pregnancy ultrasound has been mainly as part of the fetal aneuploidy screening. There is a need for prospective case-control study on the impact on fetal growth of isolated SUA diagnosed in the first half of pregnancy.

Conclusion

The placental changes seen in cases of FGR of non-infective and non-genetic origin form part of a spectrum of pathology associated with different degrees of deficient remodelling of the uterine spiral arteries. [46, 173] Deficient remodelling results in maternal blood entering the placental intervillous space in jet-like streams that carve

large channels and lakes within the villous trees. The high velocity, uneven and, most likely, intermittent perfusion of the placenta causes oxidative stress and activation of the Unfolded Protein Response pathways, supressing placental growth and compromising its endocrine and transport functions. We speculate that the pathophysiology starts towards the end of the first trimester, at the time of onset of the maternal circulation. Remodelling of the arteries and onset are linked through the endovascular trophoblast that initially plug the vessels; a deficiency in one is likely to be associated with abnormalities in the other. [15] When endovascular trophoblast is particularly poorly developed, onset of the maternal circulation is premature and disorganised spatially, not following the periphery to centre progression seen in normal pregnancies. [35, 174] There is overwhelming oxidative stress throughout the placental tissues, leading to widespread degeneration of the trophoblast and to miscarriage (Figure 11). [175] We speculate that less severe deficiencies in arterial remodelling result in ongoing pregnancies with differing degrees of compromise as discussed earlier. At one extreme will be early-onset FGR with pre-eclampsia where there is excessive villous regression and extensive infarction due to secondary atherotic changes, through FGR alone to late-onset pre-eclampsia at the opposite extreme where there appears to be minimal placental involvement. [173, 176]

Considering these complications of pregnancy, and others such as pre-term delivery and premature rupture of the membranes, [15, 46] as a spectrum caused by poor placentation highlights two main conclusions. Firstly, there is an urgent need for more research into maternal-fetal interactions during the earliest phases of pregnancy, not just to understand the pathophysiology of FGR but this array of disorders. Secondly, clinical care should be focussed just as much on the pre- and

peri-conceptional periods as in later pregnancy in order to ensure that when the conceptus implants it does so into an endometrium that is in the healthiest state possible.

Figure legends

Figure1. Photomicrographs of an archival placenta-in-situ specimen (H710) at 6 weeks gestational age demonstrating histotrophic nutrition. A) The gestational sac with the developing placenta (P) is implanted in the superficial endometrium, and had been opened during processing to remove the embryo. The glands in the endometrium (E) beneath the sac are highly active, although haemorrhage has occurred in some (asterisk). M; myometrium. Scale bar = 2 mm, B) Higher power view of the interface between the placenta and endometrium showing the opening of an endometrial gland (EG) into the intervillous space (IVS) through the cutotrophoblastic shell (CS) and developing basal plate. Scale bar = 250 μm. Modified from [16] and [177].

Figure 2. Photomicrograph of a placenta-in-situ specimen (H673) at 8 weeks gestational age showing endovascular trophoblast 'plugging' of a spiral artery. A) The endovascular trophoblast arise from anchoring villi (AV) that attach to the basal plate and can be seen virtually occluding the lumen in three cross-sectional profiles of the artery (arrowed). Note the deposition of fibrinoid material surrounding the artery, a characteristic feature of remodelling. EG, endometrial gland. Scale bar = 0.5 mm. B) Higher power view of the mouth of the spiral artery showing the endovascular trophoblast cells (ET) streaming into the lumen from the anchoring villi (AV). Flow into the intervillous space will be restricted to seepage through the network of intercellular channels. Scale bar = 0.1 mm.

Figure 3. Placenta-in situ specimen (H916) at 8.5 weeks gestational age showing formation of the chorion laeve. A) Regression of the villi can be seen beginning over the superficial pole of the gestational sac (asterisk). Scale bar = 1 cm. B) Diagrammatic representation of how onset of the maternal arterial circulation in the periphery of the placenta (arrows), where plugging of the spiral arteries by extravillous trophoblast is least extensive, causes localised oxidative stress (asterisk). The stress induces apoptosis and regression of the villi, giving rise to the chorion laeve. C) Higher power view of the area marked by the box (solid lines) over

the superficial pole of the sac illustrating avascular villi with hypocellular stromal cores. DC, decidua capsularis. D) Higher power view of the area marked by the box (dashed lines) over the central region display blood vessels, a denser stromal core and thick layer of trophoblast. Scale bars C) and D) = 0.5 mm. A) reproduced from [35] and B) modified from [178].

Figure 4. Photomicrograph of a spiral artery within the decidua from a case of pre-eclampsia displaying acute atherosis. Foam cells (FC) accumulate in the wall of the arteries, severely restricting the calibre of the lumen. Scale bar = 50 μm.

Figure 5. Schematic representation of the cellular detoxification of reactive oxygen species. The superoxide anion ($O_2^{\bullet -}$) is generated as a by-product of aerobic respiration and various oxido-reductase enzymes, and acts at physiological levels as a signalling intermediate to regulate gene expression. It can be scavenged by naturally occurring antioxidants, such as vitamins C and E, but also converted to hydrogen peroxide by the superoxide dismutase (SOD) enzymes. Hydrogen peroxide is then detoxified by the enzymes glutathione peroxidase and catalase. Excess levels of ROS can cause widespread damage to biomolecules, impairing cell function and leading to cell death.

Figure 6. Interactions between mitochondria and the endoplasmic reticulum. The mitochondrial and ER membranes are closely approximated at punctate sites rich in calcium transporters and ion channels. Calcium signalling integrates the functional activity of these two organelles, so that both contribute to increased production of ROS during malperfusion. Elevated ROS and a high level of activation of UPR pathways lead to an increase in pro-inflammatory pathways, which may distinguish FGR alone from FGR compounded by pre-eclampsia. Reproduced from [179].

Figure 7. Schematic representation of the possible pathways leading to placental-related FGR alone or FGR complicated by pre-eclampsia. See text for details.

Figure 8. Transabdominal colour Doppler mapping of a placental (P) in a pregnancy at 36 weeks complicated by FGR and presenting with multiple cystic lesions (*) corresponding to intervillous thrombosis on histopathology. A) Note the increased echogenicity in the periphery of the lesions due to degenerative villous tissue embedded in fibrin deposits. B) The utero-placental blood arterial supply to the lesion from the basal plate (BP). Video clips of the same lesions (C & D) showing the pulsatile flow from a utero-placental artery. E) and F) further examples of pulsatile flow.

Figure 9: Transabdominal ultrasound longitudinal view of a “Jelly like” placenta (P) at 18 (A) and 19 (B) weeks in a pregnancy complicated by very early-onset FGR. The placental base is very narrow and most of the placental mass contains areas of patchy decrease in echogenicity (*). Video clip of the same placenta at 23 weeks showing increased thickness and patchy decrease in echogenicity secondary to the fetal plate being pushed up by jet-like blood streams from the spiral arteries. A massive subchorial thrombosis involving more than 70% of the chorionic plate, extended fibrin deposition, intervillous thrombosis and villous infarcts were found at birth at 34 weeks.

Figure 10. Color flow mapping of a fetal abdomen and its placenta (P) at 12 weeks of gestation showing a two-vessel umbilical cord.

Figure 11. Diagrammatic representation of the proposed relationship between the degree of oxidative stress and placental development in normal pregnancies, late-onset preeclampsia, early-onset preeclampsia and miscarriage. In normal

pregnancies onset of the maternal circulation in the periphery causes local oxidative stress, villous regression and formation of the chorion laeve. In miscarriage endovascular trophoblast is severely deficient, leading to incomplete plugging of the spiral arteries, premature and disorganised onset of blood flow, and overwhelming oxidative stress. The situation is intermediate in pre-eclampsia, being more severe in the early-onset form of the syndrome associated with FGR (IUGR). Reproduced from [173].

References

1. Jaddoe VW, De Jonge LL, Hofman A, Franco OH, Steegers EA, Gaillard R. First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study. BMJ. 2014;348:g14.
2. Burton GJ, Fowden AL, Thornburg KL. Placental Origins of Chronic Disease. Physiol Rev. 2016;96:1509-65.
3. Burkhardt T, Schaffer L, Schneider C, Zimmermann R, Kurmanavicius J. Reference values for the weight of freshly delivered term placentas and for placental weight-birth weight ratios. Eur J Obstet Gynecol Reprod Biol. 2006;128:248-52.
4. Resnik R. Intrauterine growth restriction. Obstet Gynecol. 2002;99:490-6.
5. Gruenwald P. Abnormalities of placental vascularity in relation to intrauterine deprivation and retardation of fetal growth. Significance of avascular chorionic villi. N Y State J Med. 1961;61:1508-13.
6. Jauniaux E, Jurkovic D, Campbell S, Kurjak A, Hustin J. Investigation of placental circulations by colour Doppler ultrasound. Am J Obstet Gynecol. 1991;164:486-88.
7. Jauniaux E, Jurkovic D, Campbell S, Hustin J. Doppler ultrasound features of the developing placental circulations: correlation with anatomic findings. American Journal of Obstetrics and Gynecology. 1992;166:585-87.
8. Fleischer A, Schulman H, Farmakides G, et al. Uterine artery Doppler velocimetry in pregnant women with hypertension. Am J Obstet Gynecol. 1986;154:806-13.
9. Velauthar L, Plana MN, Kalidindi M, et al. First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55,974 women. Ultrasound Obstet Gynecol. 2014;43:500-7.
10. Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev. 2017;6:CD007529.
11. Luria O, Barnea O, Shalev J, et al. Two-dimensional and three-dimensional Doppler assessment of fetal growth restriction with different severity and onset. Prenat Diagn. 2012;32:1174-80.
12. Moran MC, Mulcahy C, Zombori G, Ryan J, Downey P, Mcauliffe FM. Placental volume, vasculature and calcification in pregnancies complicated by pre-eclampsia and intra-uterine growth restriction. Eur J Obstet Gynecol Reprod Biol. 2015;195:12-7.
13. Zhu MY, Milligan N, Keating S, et al. The hemodynamics of late-onset intrauterine growth restriction by MRI. Am J Obstet Gynecol. 2016;214:367 e1-67 e17.
14. Jauniaux E, Poston L, Burton GJ. Placental-related diseases of pregnancy: involvement of oxidative stress and implications in human evolution. Hum Reprod Update. 2006;12:747-55.
15. Burton GJ, Jauniaux E. The cytotrophoblastic shell and complications of pregnancy. Placenta. 2017; Epub ahead of print.
16. Burton GJ, Watson AL, Hempstock J, Skepper JN, Jauniaux E. Uterine glands provide histiotrophic nutrition for the human fetus during the first trimester of pregnancy. J Clin Endocrinol Metab. 2002;87:2954-59.
17. Burton GJ, Jauniaux E, Charnock-Jones DS. Human early placental development: potential roles of the endometrial glands. Placenta. 2007;28 Suppl A:S64-9.
18. Maruo T, Matsuo H, Murata K, Mochizuki M. Gestational age-dependent dual action of epidermal growth factor on human placenta early in gestation. J Clin Endocrinol Metab. 1992;75:1362-67.
19. Burton GJ, Scioscia M, Rademacher TW. Endometrial secretions: creating a stimulatory microenvironment within the human early placenta. Implications for the

etiopathogenesis of pre-eclampsia. J Reprod Immunol. 2011;89:118-25.
20. Filant J, Spencer TE. Uterine glands: biological roles in conceptus implantation, uterine receptivity and decidualization. Int J Dev Biol. 2014;58:107-16.
21. Cindrova-Davies T, Van Patot MT, Gardner L, Jauniaux E, Burton GJ, Charnock-Jones DS. Energy status and HIF signalling in chorionic villi show no evidence of hypoxic stress during human early placental development. Mol Hum Reprod. 2015;21:296-308.
22. Burton GJ, Jauniaux E, Charnock-Jones DS. The influence of the intrauterine environment on human placental development. Int J Dev Biol. 2010;54:303-12.
23. Van Uitert EM, Exalto N, Burton GJ, et al. Human embryonic growth trajectories and associations with fetal growth and birthweight. Hum Reprod. 2013;28:1753-61.
24. Burton GJ, Woods AW, Jauniaux E, Kingdom JC. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta. 2009;30:473-82.
25. Burchell C. Arterial blood flow in the human intervillous space. American Journal of Obstetrics and Gynecology. 1969;98:303-11.
26. Pijnenborg R, Vercruysse L, Hanssens M. The Uterine Spiral Arteries In Human Pregnancy: Facts and Controversies. Placenta. 2006;27:939-58.
27. Hustin J, Schaaps JP. Echographic and anatomic studies of the maternotrophoblastic border during the first trimester of pregnancy. American Journal of Obstetrics and Gynecology. 1987;157:162-68.
28. Burton GJ, Jauniaux E, Watson AL. Maternal arterial connections to the placental intervillous space during the first trimester of human pregnancy; the Boyd Collection revisited. Am J Obstet Gynecol. 1999;181:718-24.
29. Rodesch F, Simon P, Donner C, Jauniaux E. Oxygen measurements in endometrial and trophoblastic tissues during early pregnancy. Obstetrics and Gynecology. 1992;80:283-85.
30. Jauniaux E, Watson AL, Ozturk O, Quick D, Burton G. In-vivo measurement of intrauterine gases and acid-base values in early human pregnancy. Human Reproduction. 1999;14:2901-04.
31. Harris LK. Review: Trophoblast-vascular cell interactions in early pregnancy: how to remodel a vessel. Placenta. 2010;31 Suppl:S93-8.
32. Whitley GS, Cartwright JE. Cellular and molecular regulation of spiral artery remodelling: lessons from the cardiovascular field. Placenta. 2010;31:465-74.
33. Moffett A, Hiby SE, Sharkey AM. The role of the maternal immune system in the regulation of human birthweight. Philos Trans R Soc Lond B Biol Sci. 2015;370.
34. Collins SL, Birks JS, Stevenson GN, Papageorghiou AT, Noble JA, Impey L. Measurement of spiral artery jets: general principles and differences observed in small-for-gestational-age pregnancies. Ultrasound Obstet Gynecol. 2012;40:171-8.
35. Jauniaux E, Hempstock J, Greenwold N, Burton GJ. Trophoblastic oxidative stress in relation to temporal and regional differences in maternal placental blood flow in normal and abnormal early pregnancies. American Journal of Pathology. 2003;162:115-25.
36. Pijnenborg R, Bland JM, Robertson WB, Dixon G, Brosens I. The pattern of interstitial trophoblastic invasion of the myometrium in early human pregnancy. Placenta. 1981;2:303-16.
37. Jauniaux E, Watson AL, Hempstock J, Bao Y-P, Skepper JN, Burton GJ. Onset of maternal arterial bloodflow and placental oxidative stress; a possible factor in human early pregnancy failure. American Journal of Pathology. 2000;157:2111-22.
38. Barker DJ, Thornburg KL. The obstetric origins of health for a lifetime. Clin Obstet

Gynecol. 2013;56:511-9.
39. Salafia CM, Zhang J, Miller RK, Charles AK, Shrout P, Sun W. Placental growth patterns affect birth weight for given placental weight. Birth Defects Res A Clin Mol Teratol. 2007;79:281-8.
40. Salafia CM, Yampolsky M, Misra DP, et al. Placental surface shape, function, and effects of maternal and fetal vascular pathology. Placenta. 2010;31:958-62.
41. Yampolsky M, Salafia CM, Shlakhter O, Haas D, Eucker B, Thorp J. Centrality of the umbilical cord insertion in a human placenta influences the placental efficiency. Placenta. 2009;30:1058-64.
42. Salafia CM, Yampolsky M, Shlakhter A, Mandel DH, Schwartz N. Variety in placental shape: when does it originate? Placenta. 2012;33:164-70.
43. Schwartz N, Quant HS, Sammel MD, Parry S. Macrosomia has its roots in early placental development. Placenta. 2014;35:684-90.
44. Gruenwald P. Expansion of placental site and maternal blood supply of primate placentas. Anat Rec. 1972;173:189-203.
45. Mayhew TM, Jackson MR, Boyd PA. Changes in oxygen diffusive conductances of human placental during gestation (10-41 weeks) are commensurate with the gain in fetal weight. Placenta. 1993;14:51-61.
46. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. Am J Obstet Gynecol. 2011;204:193-201.
47. Brosens I, Dixon HG, Robertson WB. Fetal growth retardation and the arteries of the placental bed. Br J Obstet Gynaecol. 1977;84:656-63.
48. Gerretsen G, Huisjes HJ, Elema JD. Morphological changes of the spiral arteries in the placental bed in relation to pre-eclampsia and fetal growth retardation. Br J Obstet Gynaecol. 1981;88:876-81.
49. Khong TY, De Wolf F, Robertson WB, Brosens I. Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. Br J Obstet Gynaecol. 1986;93:1049-59.
50. Lyall F, Robson SC, Bulmer JN. Spiral artery remodeling and trophoblast invasion in preeclampsia and fetal growth restriction: relationship to clinical outcome. Hypertension. 2013;62:1046-54.
51. Ong SS, Baker PN, Mayhew TM, Dunn WR. Remodeling of myometrial radial arteries in preeclampsia. Am J Obstet Gynecol. 2005;192:572-9.
52. Aardema MW, Oosterhof H, Timmer A, Van Rooy I, Aarnoudse JG. Uterine artery Doppler flow and uteroplacental vascular pathology in normal pregnancies and pregnancies complicated by pre-eclampsia and small for gestational age fetuses. Placenta. 2001;22:405-11.
53. Falco ML, Sivanathan J, Laoreti A, Thilaganathan B, Khalil A. Placental histopathology associated with preeclampsia: A systematic review and Meta-Analysis. Ultrasound Obstet Gynecol. 2017.
54. Sebire NJ. Implications of placental pathology for disease mechanisms; methods, issues and future approaches. Placenta. 2017;52:122-26.
55. Kadyrov M, Schmitz C, Black S, Kaufmann P, Huppertz B. Pre-eclampsia and maternal anaemia display reduced apoptosis and opposite invasive phenotypes of extravillous trophoblast. Placenta. 2003;24:540-48.
56. Hiby SE, Apps R, Sharkey AM, et al. Maternal activating KIRs protect against human reproductive failure mediated by fetal HLA-C2. J Clin Invest. 2010;120:4102-10.
57. Martin CB, Mcgaughey HS, Kaiser IH, Donner MW, Ramsey EM. Intermittent functioning of the uteroplacental arteries. American Journal of Obstetrics and

Gynecology. 1964;90:819-23.
58. Labarrere CA, Dicarlo HL, Bammerlin E, et al. Failure of physiologic transformation of spiral arteries, endothelial and trophoblast cell activation, and acute atherosis in the basal plate of the placenta. Am J Obstet Gynecol. 2017;216:287 e1-87 e16.
59. Hubel CA. Oxidative stress in the pathogenesis of preeclampsia. Proc Soc Exp Biol Med. 1999;222:222-35.
60. Myatt L. Review: Reactive oxygen and nitrogen species and functional adaptation of the placenta. Placenta. 2010;31 Suppl:S66-9.
61. Burton GJ, Jauniaux E. Oxidative stress. Best Pract Res Clin Obstet Gynaecol. 2011;25:287-99.
62. Cadenas E, Davies KJA. Mitochondrial free radical generation, oxidative stress, and aging. Free Radical Biology and Medicine. 2000;29:222-30.
63. Guzy RD, Schumacker PT. Oxygen sensing by mitochondria at complex III: the paradox of increased reactive oxygen species during hypoxia. Experimental physiology. 2006;91:807-19.
64. Hung TH, Skepper JN, Burton GJ. In vitro ischemia-reperfusion injury in term human placenta as a model for oxidative stress in pathological pregnancies. Am J Pathol. 2001;159:1031-43.
65. Hung T-H, Skepper JN, Charnock-Jones DS, Burton GJ. Hypoxia/reoxygenation: a potent inducer of apoptotic changes in the human placenta and possible etiological factor in preeclampsia. Circulation Research. 2002;90:1274-81.
66. Cindrova-Davies T, Spasic-Boskovic O, Jauniaux E, Charnock-Jones DS, Burton GJ. Nuclear factor-kappa B, p38, and stress-activated protein kinase mitogen-activated protein kinase signaling pathways regulate proinflammatory cytokines and apoptosis in human placental explants in response to oxidative stress: effects of antioxidant vitamins. Am J Pathol. 2007;170:1511-20.
67. Cindrova-Davies T, Yung HW, Johns J, et al. Oxidative Stress, Gene Expression, and Protein Changes Induced in the Human Placenta during Labor. Am J Pathol. 2007;171:1168-79.
68. Rayman MP, Bath SC, Westaway J, et al. Selenium status in UK pregnant women and its relationship with hypertensive conditions of pregnancy. Br J Nutr. 2015:1-10.
69. Poston L, Briley AL, Seed PT, Kelly FJ, Shennan AH. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. Lancet. 2006;367:1145-54.
70. Bravo R, Gutierrez T, Paredes F, et al. Endoplasmic reticulum: ER stress regulates mitochondrial bioenergetics. Int J Biochem Cell Biol. 2012;44:16-20.
71. Ron D, Walter P. Signal integration in the endoplasmic reticulum unfolded protein response. Nat Rev Mol Cell Biol. 2007;8:519-29.
72. Han J, Kaufman RJ. Physiological/pathological ramifications of transcription factors in the unfolded protein response. Genes Dev. 2017;31:1417-38.
73. Fahling M. Surviving hypoxia by modulation of mRNA translation rate. J Cell Mol Med. 2009;13:2770-9.
74. Wouters BG, Koritzinsky M. Hypoxia signalling through mTOR and the unfolded protein response in cancer. Nat Rev Cancer. 2008;8:851-64.
75. Rutkowski DT, Hegde RS. Regulation of basal cellular physiology by the homeostatic unfolded protein response. J Cell Biol. 2010;189:783-94.
76. Teasdale F. Idiopathic intrauterine growth retardation: histomorphometry of the human placenta. Placenta. 1984;5:83-92.
77. Mayhew TM, Ohadike C, Baker PN, Crocker IP, Mitchell C, Ong SS. Stereological investigation of placental morphology in pregnancies complicated by pre-eclampsia

with and without intrauterine growth restriction. Placenta. 2003;24:219-26.
78. Egbor M, Ansari T, Morris N, Green CJ, Sibbons PD. Pre-eclampsia and fetal growth restriction: how morphometrically different is the placenta? Placenta. 2006;27:727-34.
79. Hafner E, Metzenbauer M, Hofinger D, et al. Placental growth from the first to the second trimester of pregnancy in SGA-foetuses and pre-eclamptic pregnancies compared to normal foetuses. Placenta. 2003;24:336-42.
80. Sferruzzi-Perri AN, Owens JA, Pringle KG, Roberts CT. The neglected role of insulin-like growth factors in the maternal circulation regulating fetal growth. J Physiol. 2011;589:7-20.
81. Roos S, Powell TL, Jansson T. Placental mTOR links maternal nutrient availability to fetal growth. Biochem Soc Trans. 2009;37:295-8.
82. Roos S, Jansson N, Palmberg I, Saljo K, Powell TL, Jansson T. Mammalian target of rapamycin in the human placenta regulates leucine transport and is down-regulated in restricted fetal growth. J Physiol. 2007;582:449-59.
83. Yung HW, Calabrese S, Hynx D, et al. Evidence of placental translation inhibition and endoplasmic reticulum stress in the etiology of human intrauterine growth restriction. Am J Pathol. 2008;173:451-62.
84. Yung HW, Cox M, Tissot Van Patot M, Burton GJ. Evidence of endoplasmic reticulum stress and protein synthesis inhibition in the placenta of non-native women at high altitude. FASEB J. 2012;26:1970-81.
85. Sibley CP, Turner MA, Cetin I, et al. Placental phenotypes of intrauterine growth. Ped Res. 2005;58:827-32.
86. Jansson T, Powell TL. IFPA 2005 Award in Placentology Lecture. Human placental transport in altered fetal growth: does the placenta function as a nutrient sensor? -- a review. Placenta. 2006;27 Suppl A:S91-7.
87. Cetin I, Alvino G. Intrauterine growth restriction: implications for placental metabolism and transport. A review. Placenta. 2009;30 Suppl A:S77-82.
88. Gaccioli F, Lager S. Placental Nutrient Transport and Intrauterine Growth Restriction. Front Physiol. 2016;7:40.
89. Jansson N, Pettersson J, Haafiz A, et al. Down-regulation of placental transport of amino acids precedes the development of intrauterine growth restriction in rats fed a low protein diet. J Physiol. 2006;576:935-46.
90. Zhang K, Kaufman RJ. From endoplasmic-reticulum stress to the inflammatory response. Nature. 2008;454:455-62.
91. Hotamisligil GS. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. Cell. 2010;140:900-17.
92. Xu C, Bailly-Maitre B, Reed JC. Endoplasmic reticulum stress: cell life and death decisions. J Clin Invest. 2005;115:2656-64.
93. Deng J, Lu PD, Zhang Y, et al. Translational repression mediates activation of nuclear factor kappa B by phosphorylated translation initiation factor 2. Mol Cell Biol. 2004;24:10161-8.
94. Goswami D, Tannetta DS, Magee LA, et al. Excess syncytiotrophoblast microparticle shedding is a feature of early-onset pre-eclampsia, but not normotensive intrauterine growth restriction. Placenta. 2006;27:56-61.
95. Sgambati E, Biagiotti R, Marini M, Brizzi E. Lectin histochemistry in the human placenta of pregnancies complicated by intrauterine growth retardation based on absent or reversed diastolic flow. Placenta. 2002;23:503-15.
96. Nishizawa H, Ota S, Suzuki M, et al. Comparative gene expression profiling of placentas from patients with severe pre-eclampsia and unexplained fetal growth

restriction. Reprod Biol Endocrinol. 2011;9:107.
97. Whitehead CL, Walker SP, Ye L, et al. Placental specific mRNA in the maternal circulation are globally dysregulated in pregnancies complicated by fetal growth restriction. J Clin Endocrinol Metab. 2013;98:E429-36.
98. Mcminn J, Wei M, Schupf N, et al. Unbalanced placental expression of imprinted genes in human intrauterine growth restriction. Placenta. 2006;27:540-9.
99. Diplas AI, Lambertini L, Lee MJ, et al. Differential expression of imprinted genes in normal and IUGR human placentas. Epigenetics. 2009;4:235-40.
100. Deyssenroth MA, Li Q, Lacasana M, Nomura Y, Marsit C, Chen J. Expression of placental regulatory genes is associated with fetal growth. J Perinat Med. 2017.
101. Thamotharan S, Chu A, Kempf K, et al. Differential microRNA expression in human placentas of term intra-uterine growth restriction that regulates target genes mediating angiogenesis and amino acid transport. PLoS One. 2017;12:e0176493.
102. Hromadnikova I, Kotlabova K, Doucha J, Dlouha K, Krofta L. Absolute and relative quantification of placenta-specific microrna in maternal circulation with placental insufficiency-related complications. J Mol Diagn. 2012;14:160-7.
103. Lattuada D, Colleoni F, Martinelli A, et al. Higher mitochondrial DNA content in human IUGR placenta. Placenta. 2008;29:1029-33.
104. Poidatz D, Dos Santos E, Duval F, et al. Involvement of estrogen-related receptor-gamma and mitochondrial content in intrauterine growth restriction and preeclampsia. Fertil Steril. 2015;104:483-90.
105. Holland O, Dekker Nitert M, Gallo LA, Vejzovic M, Fisher JJ, Perkins AV. Review: Placental mitochondrial function and structure in gestational disorders. Placenta. 2017;54:2-9.
106. Colleoni F, Padmanabhan N, Yung HW, et al. Suppression of mitochondrial electron transport chain function in the hypoxic human placenta: a role for miR-210 and protein synthesis inhibition. PLoS One. 2013;8:e55194.
107. Akison LK, Nitert MD, Clifton VL, Moritz KM, Simmons DG. Review: Alterations in placental glycogen deposition in complicated pregnancies: Current preclinical and clinical evidence. Placenta. 2017;54:52-58.
108. Bastida-Ruiz D, Aguilar E, Ditisheim A, Yart L, Cohen M. Endoplasmic reticulum stress responses in placentation - A true balancing act. Placenta. 2017;57:163-69.
109. Hung TH, Chen SF, Lo LM, Li MJ, Yeh YL, Hsieh TT. Increased autophagy in placentas of intrauterine growth-restricted pregnancies. PLoS One. 2012;7:e40957.
110. Chang YL, Wang TH, Chang SD, Chao AS, Hsieh PC, Wang CN. Increased autophagy in the placental territory of selective intrauterine growth-restricted monochorionic twins. Prenat Diagn. 2013;33:187-90.
111. Fok RY, Pavlova Z, Benirschke K, Paul RH, Platt LD. The correlation of arterial lesions with umbilical artery Doppler velocimetry in the placentas of small-for-dates pregnancies. Obstet Gynecol. 1990;75:578-83.
112. Salafia CM, Pezzullo JC, Minior VK, Divon MY. Placental pathology of absent and reversed end-diastolic flow in growth-restricted fetuses. Obstet Gynecol. 1997;90:830-6.
113. Mitra SC, Seshan SV, Riachi LE. Placental vessel morphometry in growth retardation and increased resistance of the umbilical artery Doppler flow. J Matern Fetal Med. 2000;9:282-6.
114. Cindrova-Davies T, Herrera EA, Niu Y, Kingdom J, Giussani DA, Burton GJ. Reduced cystathionine gamma-lyase and increased miR-21 expression are associated with increased vascular resistance in growth-restricted pregnancies: hydrogen sulfide as a placental vasodilator. Am J Pathol. 2013;182:1448-58.

115. Lu L, Kingdom J, Burton GJ, Cindrova-Davies T. Placental Stem Villus Arterial Remodeling Associated with Reduced Hydrogen Sulfide Synthesis Contributes to Human Fetal Growth Restriction. Am J Pathol. 2017;187:908-20.
116. Fox H, Sebire NJ. *Pathology of the Placenta.* Amsterdam: Saunders Elsevier; Number of pages.
117. Benirschke K, Burton GJ, Baergen RN. *Pathology of the Human Placenta.* Heidelberg: Springer; Number of pages.
118. Mifsud W, Sebire NJ. Placental pathology in early-onset and late-onset fetal growth restriction. Fetal Diagn Ther. 2014;36:117-28.
119. Nordenvall M, Sandstedt B, Ulmsten U. Relationship between placental shape, cord insertion, lobes and gestational outcome. Acta Obstet Gynecol Scand. 1988;67:611-6.
120. Toal M, Chan C, Fallah S, et al. Usefulness of a placental profile in high-risk pregnancies. Am J Obstet Gynecol. 2007;196:363 e1-7.
121. Kalanithi LE, Illuzzi JL, Nossov VB, et al. Intrauterine growth restriction and placental location. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2007;26:1481-9.
122. Ananth CV, Demissie K, Smulian JC, Vintzileos AM. Relationship among placenta previa, fetal growth restriction, and preterm delivery: a population-based study. Obstet Gynecol. 2001;98:299-306.
123. Harper LM, Odibo AO, Macones GA, Crane JP, Cahill AG. Effect of placenta previa on fetal growth. Am J Obstet Gynecol. 2010;203:330 e1-5.
124. Jauniaux E, Campbell S. Ultrasonographic assessment of placental abnormalities. Am J Obstet Gynecol. 1990;163:1650-8.
125. Jauniaux E, Gibb D, Moscoso G, Campbell S. Ultrasonographic diagnosis of a large placental intervillous thrombosis associated with elevated maternal serum alpha-fetoprotein level. Am J Obstet Gynecol. 1990;163:1558-60.
126. Richards DS, Bennett BB. Prenatal ultrasound diagnosis of massive subchorionic thrombohematoma. Ultrasound Obstet Gynecol. 1998;11:364-6.
127. Fung TY, To KF, Sahota DS, Chan LW, Leung TY, Lau TK. Massive subchorionic thrombohematoma: a series of 10 cases. Acta Obstet Gynecol Scand. 2010;89:1357-61.
128. Alanjari A, Wright E, Keating S, Ryan G, Kingdom J. Prenatal diagnosis, clinical outcomes, and associated pathology in pregnancies complicated by massive subchorionic thrombohematoma (Breus' mole). Prenat Diagn. 2013;33:973-8.
129. Boulis TS, Rochelson BL, Williamson AK. Massive Subchorionic Placental Cyst and Poor Fetal Growth: A Case Report. J Reprod Med. 2015;60:458-60.
130. Kofinas A, Kofinas G, Sutija V. The role of second trimester ultrasound in the diagnosis of placental hypoechoic lesions leading to poor pregnancy outcome. J Matern Fetal Neonatal Med. 2007;20:859-66.
131. Proctor LK, Whittle WL, Keating S, Viero S, Kingdom JC. Pathologic basis of echogenic cystic lesions in the human placenta: role of ultrasound-guided wire localization. Placenta. 2010;31:1111-5.
132. Linduska N, Dekan S, Messerschmidt A, et al. Placental pathologies in fetal MRI with pathohistological correlation. Placenta. 2009;30:555-9.
133. Jauniaux E, Campbell S. Antenatal diagnosis of placental infarcts by ultrasonography. J Clin Ultrasound. 1991;19:58-61.
134. Jauniaux E, Campbell S. Fetal growth retardation with abnormal blood flows and placental sonographic lesions. J Clin Ultrasound. 1990;18:210-4.
135. Levine AB, Frieden FJ, Stein JL, Pisnanont P. Prenatal sonographic diagnosis of placental infarction in association with elevated maternal serum alpha-fetoprotein.

Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 1993;12:169-71.
136. Barclay D, Evans K, Fox R. Ultrasound-diagnosed placental infarction in a woman with recurrent fetal growth restriction. J Obstet Gynaecol. 2005;25:200-1.
137. Theophilou G, Sahashrabudhe N, Martindale EA, Heazell AE. Correlation between abnormal placental appearance at routine 2nd trimester ultrasound scan and histological examination of the placenta after birth. J Obstet Gynaecol. 2012;32:760-3.
138. Aurioles-Garibay A, Hernandez-Andrade E, Romero R, et al. Prenatal diagnosis of a placental infarction hematoma associated with fetal growth restriction, preeclampsia and fetal death: clinicopathological correlation. Fetal Diagn Ther. 2014;36:154-61.
139. Bonel HM, Stolz B, Diedrichsen L, et al. Diffusion-weighted MR imaging of the placenta in fetuses with placental insufficiency. Radiology. 2010;257:810-9.
140. Messerschmidt A, Baschat A, Linduska N, et al. Magnetic resonance imaging of the placenta identifies placental vascular abnormalities independently of Doppler ultrasound. Ultrasound Obstet Gynecol. 2011;37:717-22.
141. Mandsager NT, Bendon R, Mostello D, Rosenn B, Miodovnik M, Siddiqi TA. Maternal floor infarction of the placenta: prenatal diagnosis and clinical significance. Obstet Gynecol. 1994;83:750-4.
142. Naeye RL. Maternal floor infarction. Hum Pathol. 1985;16:823-8.
143. Devisme L, Chauviere C, Franquet-Ansart H, et al. Perinatal outcome of placental massive perivillous fibrin deposition: a case-control study. Prenat Diagn. 2017;37:323-28.
144. Alkazaleh F, Viero S, Simchen M, et al. Ultrasound diagnosis of severe thrombotic placental damage in the second trimester: an observational study. Ultrasound Obstet Gynecol. 2004;23:472-6.
145. Jauniaux E, Moscoso G, Campbell S, Gibb D, Driver M, Nicolaides KH. Correlation of ultrasound and pathologic findings of placental anomalies in pregnancies with elevated maternal serum alpha-fetoprotein. Eur J Obstet Gynecol Reprod Biol. 1990;37:219-30.
146. Jauniaux E, Ramsay B, Campbell S. Ultrasonographic investigation of placental morphologic characteristics and size during the second trimester of pregnancy. Am J Obstet Gynecol. 1994;170:130-7.
147. Alkazaleh F, Chaddha V, Viero S, et al. Second-trimester prediction of severe placental complications in women with combined elevations in alpha-fetoprotein and human chorionic gonadotrophin. Am J Obstet Gynecol. 2006;194:821-7.
148. Suri S, Muttukrishna S, Jauniaux E. 2D-Ultrasound and endocrinologic evaluation of placentation in early pregnancy and its relationship to fetal birthweight in normal pregnancies and pre-eclampsia. Placenta. 2013;34:745-50.
149. Redline RW. Classification of placental lesions. Am J Obstet Gynecol. 2015;213:S21-8.
150. Kovo M, Schreiber L, Ben-Haroush A, et al. The placental factor in early- and late-onset normotensive fetal growth restriction. Placenta. 2013;34:320-4.
151. Giles WB, Trudinger BJ, Baird PJ. Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation. Br J Obstet Gynaecol. 1985;92:31-8.
152. Madazli R, Somunkiran A, Calay Z, Ilvan S, Aksu MF. Histomorphology of the placenta and the placental bed of growth restricted foetuses and correlation with the Doppler velocimetries of the uterine and umbilical arteries. Placenta. 2003;24:510-6.
153. Vedmedovska N, Rezeberga D, Teibe U, Melderis I, Donders GG. Placental

pathology in fetal growth restriction. Eur J Obstet Gynecol Reprod Biol. 2011;155:36-40.
154. Spinillo A, Gardella B, Bariselli S, Alfei A, Silini E, Dal Bello B. Placental histopathological correlates of umbilical artery Doppler velocimetry in pregnancies complicated by fetal growth restriction. Prenat Diagn. 2012;32:1263-72.
155. Fitzgerald B, Shannon P, Kingdom J, Keating S. Basal plate plaque: a novel organising placental thrombotic process. J Clin Pathol. 2011;64:725-8.
156. Redline RW. Villitis of unknown etiology: noninfectious chronic villitis in the placenta. Hum Pathol. 2007;38:1439-46.
157. Derricott H, Jones RL, Heazell AE. Investigating the association of villitis of unknown etiology with stillbirth and fetal growth restriction - a systematic review. Placenta. 2013;34:856-62.
158. Salafia CM, Minior VK, Pezzullo JC, Popek EJ, Rosenkrantz TS, Vintzileos AM. Intrauterine growth restriction in infants of less than thirty-two weeks' gestation: associated placental pathologic features. Am J Obstet Gynecol. 1995;173:1049-57.
159. Parant O, Capdet J, Kessler S, Aziza J, Berrebi A. Chronic intervillositis of unknown etiology (CIUE): relation between placental lesions and perinatal outcome. Eur J Obstet Gynecol Reprod Biol. 2009;143:9-13.
160. Kovo M, Schreiber L, Ben-Haroush A, Wand S, Golan A, Bar J. Placental vascular lesion differences in pregnancy-induced hypertension and normotensive fetal growth restriction. Am J Obstet Gynecol. 2010;202:561 e1-5.
161. Veerbeek JH, Nikkels PG, Torrance HL, et al. Placental pathology in early intrauterine growth restriction associated with maternal hypertension. Placenta. 2014;35:696-701.
162. Biswas S, Ghosh SK. Gross morphological changes of placentas associated with intrauterine growth restriction of fetuses: a case control study. Early Hum Dev. 2008;84:357-62.
163. Heifetz SA. Single umbilical artery. A statistical analysis of 237 autopsy cases and review of the literature. Perspect Pediatr Pathol. 1984;8:345-78.
164. Jauniaux E, Demunter C, Pardou A, Elkhazen N, Rodesch F, Wilkin P. [Ultrasonic study of the single umbilical artery syndrome. A series of 80 cases]. J Gynecol Obstet Biol Reprod (Paris). 1989;18:341-7.
165. Hubinont C, Lewi L, Bernard P, Marbaix E, Debieve F, Jauniaux E. Anomalies of the placenta and umbilical cord in twin gestations. Am J Obstet Gynecol. 2015;213:S91-S102.
166. Khalil MI, Sagr ER, Elrifaei RM, Abdelbasit OB, Halouly TA. Outcomes of an isolated single umbilical artery in singleton pregnancy: a large study from the Middle East and Gulf region. Eur J Obstet Gynecol Reprod Biol. 2013;171:277-80.
167. Mailath-Pokorny M, Worda K, Schmid M, Polterauer S, Bettelheim D. Isolated single umbilical artery: evaluating the risk of adverse pregnancy outcome. Eur J Obstet Gynecol Reprod Biol. 2015;184:80-3.
168. Battarbee AN, Palatnik A, Ernst LM, Grobman WA. Association of Isolated Single Umbilical Artery With Small for Gestational Age and Preterm Birth. Obstet Gynecol. 2015;126:760-4.
169. Naveiro-Fuentes M, Carrillo-Badillo MP, Malde-Conde J, Gallo-Vallejo JL, Puertas-Prieto A. Perinatal outcomes in singleton pregnancies with a single umbilical artery. J Matern Fetal Neonatal Med. 2016;29:1562-5.
170. Voskamp BJ, Fleurke-Rozema H, Oude-Rengerink K, et al. Relationship of isolated single umbilical artery to fetal growth, aneuploidy and perinatal mortality: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2013;42:622-8.

171. Kim HJ, Kim JH, Chay DB, Park JH, Kim MA. Association of isolated single umbilical artery with perinatal outcomes: Systemic review and meta-analysis. Obstet Gynecol Sci. 2017;60:266-73.
172. Jauniaux E, Campbell S, Vyas S. The use of color Doppler imaging for prenatal diagnosis of umbilical cord anomalies: report of three cases. Am J Obstet Gynecol. 1989;161:1195-7.
173. Burton GJ, Jauniaux E. Placental oxidative stress; from miscarriage to preeclampsia. J Soc Gynecol Invest. 2004;11:342-52.
174. Jauniaux E, Hustin J. Histological examination of first trimester spontaneous abortions: the impact of materno-embryonic interface features. Histopathology. 1992;21:409-14.
175. Hempstock J, Jauniaux E, Greenwold N, Burton GJ. The contribution of placental oxidative stress to early pregnancy failure. Human Pathology. 2003;34:1265-75.
176. Yung HW, Atkinson D, Campion-Smith T, Olovsson M, Charnock-Jones DS, Burton GJ. Differential Activation of Placental Unfolded Protein Response Pathways Implies Heterogeneity in Causation of Early- and Late-onset Pre-eclampsia. J Pathol. 2014;234:262-76.
177. Hempstock J, Cindrova-Davies T, Jauniaux E, Burton GJ. Endometrial glands as a source of nutrients, growth factors and cytokines during the first trimester of human pregnancy; a morphological and immunohistochemical study. Reproductive Biology and Endocrinology. 2004;2:58.
178. Jauniaux E, Cindrova-Davies T, Johns J, et al. Distribution and transfer pathways of antioxidant molecules inside the first trimester human gestational sac. J Clin Endocrinol Metab. 2004;89:1452-59.
179. Burton GJ, Yung HW, Murray AJ. Mitochondrial - Endoplasmic reticulum interactions in the trophoblast: Stress and senescence. Placenta. 2017;52:146-55.