Chapter 2
"Foetal–Maternal Conflicts" and Adverse Outcomes in Human Pregnancies

Jimmy Espinoza, M.D., M.Sc., FACOG

Lay Summary
In most pregnancies, there is a delicate balance between foetal demands and the maternal supply of nutrients; however, in some instances, abnormal foetal–maternal interactions can lead to pregnancy complications. These abnormal interactions can occur at the uteroplacental interface, in the placental vascular system and at the level of foetal–maternal signalling. Some of the consequences of abnormal foetal–maternal interactions include pregnancy complications such as foetal growth restriction, pre-eclampsia, gestational diabetes, preterm parturition and in extreme cases foetal death. We propose that an absolute reduction in the blood flow to the uteroplacental unit may participate in the mechanisms of disease in foetal growth restriction, early-onset pre-eclampsia and maternal thrombophilias, whereas a relative reduction in the supply line due to an excessive foetal demands for nutrients may be more relevant in the mechanism of injury in late-onset pre-eclampsia and gestational diabetes. It is possible that some of these pregnancy complications may have evolved as survival strategies for the foetus or the mother. In this context, interventions aimed at modulating the maternal blood pressure during pregnancy or delaying preterm parturition should be tailored to maximize both maternal and perinatal outcomes.

J. Espinoza (✉)
Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Baylor College of Medicine, Houston, TX, USA
e-mail: Jimmy.Espinoza@bcm.edu

J. Espinoza
Texas Children's Hospital Pavilion for Women, Houston, TX, USA

A. Alvergne et al. (eds.), *Evolutionary Thinking in Medicine*,
Advances in the Evolutionary Analysis of Human Behaviour,
DOI 10.1007/978-3-319-29716-3_2

2.1 Introduction

> The placenta appears to be a ruthless parasitic organ existing solely for the maintenance and protection of the fetus, perhaps too often to the disregard of the maternal organism. Ernest W. Page AJOG 1939.

Successful pregnancies depend on a balance between increasing foetal demand for nutrients and a measured maternal investment to safeguard her reproductive future [1]. Failure of the well-orchestrated maternal foetal interaction may lead to a conflict of interests between the mother and her foetus and subsequent pregnancy complications [2]. The term "foetal–maternal conflict" refers to a conceptual framework whereby foetal growth and development can happen sometimes at the expense of the maternal well-being [1–5]. This term has being used to describe clinical situations in which evolutionary adaptations of the mother appear to be in conflict with those of her foetus [1, 2, 4, 5]. At the histological level, foetal–maternal conflicts have been implicated in the mechanisms by which abnormal trophoblast invasion leads to the failure of physiologic transformation of the spiral arteries [2, 6–9], chronic uteroplacental ischaemia [10] and pregnancy complications including pre-eclampsia [1–13], preterm parturition [14, 15], foetal growth restriction [11, 13, 16, 17] and foetal death [18]. The conventional obstetrical view is to compartmentalize and treat pregnancy complications as if problems arising during pregnancy have either foetal or maternal origin. In contrast, the evolutionary approach to pregnancy complications is to consider them as a result of abnormal foetal–maternal interactions. This chapter reviews the evidence supporting the notion that foetal growth restriction, early- and late-onset pre-eclampsia, preterm parturition and gestational diabetes may result from inadequate foetal–maternal interactions.

2.2 Research Findings

2.2.1 Foetal Growth Restriction and Abnormal Foetal–Maternal Interactions

One of the most common expressions of the "foetal–maternal conflict" is manifested in abnormalities of foetal growth. Paternally derived imprinted genes tend to maximize foetal growth; in contrast, maternally derived imprinted genes tend to do the opposite [5] presumably as an evolutionary strategy to protect the maternal well-being. A remarkable example of this view is the observation that human triploidic foetuses, for which the extra set of chromosomes (a total of 69 rather than the normal 46 chromosomes) is derived from the mother (dyginic triploidy), are associated with early-onset foetal growth restriction even in the first trimester of pregnancy (Fig. 2.1). These foetuses not only have very small bodies and disproportionably large heads but also very thin and small placentas. Moreover, there is

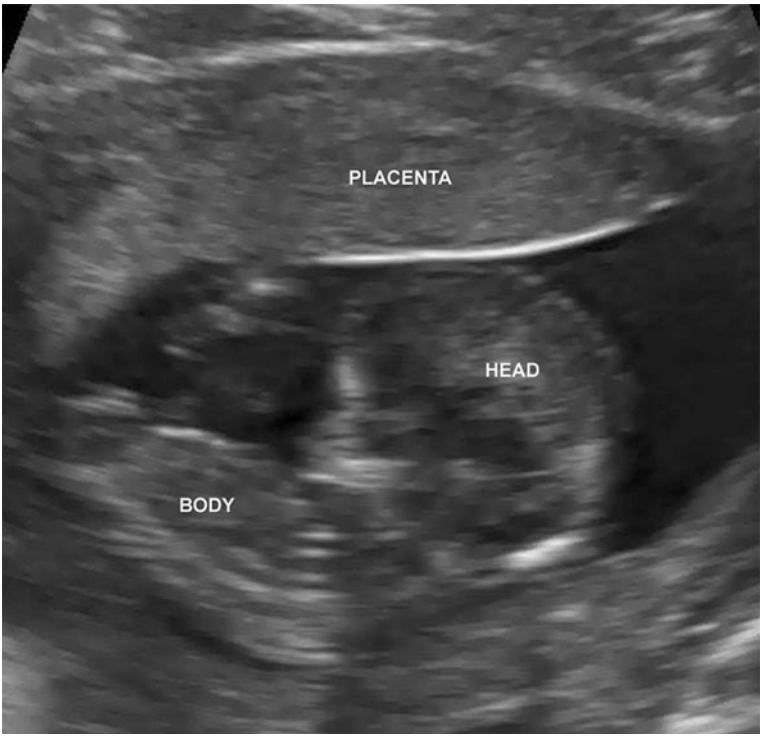

Fig. 2.1 Ultrasonographic findings in a foetus with dyginic triploidy in the first trimester of pregnancy note the significant disproportion between the foetal head and the body

sonographic evidence that dyginic triploidic foetuses show blood redistribution to the foetal brain in the first and early second trimester of pregnancy [19]. Asymmetric early-onset foetal growth restriction in triploidic foetuses may be due to the chromosomal anomaly, but it is possible that blood redistribution starting very early in pregnancy may contribute to the phenotype seen in dyginic triploidy. In contrast, triploidic foetuses for which the extra set of chromosomes is derived from the father (dyandric triploidy) are associated with partial mole pregnancies. These foetuses tend to be of normal size but have large molar placentas and are often associated with early-onset pre-eclampsia before 20 weeks of gestation. It is noteworthy that pregnancy complications that are normally seen in the second or third trimester, including foetal growth restriction and pre-eclampsia, can be seen as early as the first or early second trimester in dyginic or dyandric triploidic pregnancies, respectively.

Genomic imprinting is the process by which one copy of a gene is silenced due to its parental origin. New high-throughput molecular techniques indicate that several hundred genes are imprinted. Experimental studies provide additional evidence that foetal growth is regulated by paternally or maternally derived imprinted

genes. The insulin-like growth factor II gene is paternally expressed in the foetus and the placenta; deletion of a transcript of this gene in mice leads to reduced placental growth and foetal growth restriction [4]. Grb10 is an adapter signalling protein that appears to control foetal growth independently from insulin-like growth factor 2 [20]. Grb10 is a potent growth inhibitor, and the majority of its gene expression arises from the maternally derived allele which is located on chromosome 7 [20]. In mice, disruption of this allele results in overgrowth of both the embryo and placenta, such that the mutant mice at birth are 30 % larger than normal [20]. In humans, about 10 % of individuals affected by Silver–Russell syndrome, characterized by severe foetal growth restrictions, inherit both copies of chromosomes 7 from their mother, and it has been proposed that an overexpression of the GRB10 gene accounts for these restrictions in growth [20].

2.2.2 *Chronic Ischaemia of the Uteroplacental Unit: Early-Onset Pre-eclampsia and Foetal Growth Restriction*

During pregnancy, the uterus and placenta form an anatomic and functional uteroplacental unit. An absolute uteroplacental ischaemia may result from (i) placental bed disorders; (ii) vascular insults to the placenta; or (iii) abnormal foetal placental circulation. Abnormalities in the placental bed and subsequent failure of physiologic transformation of the spiral arteries in the first or early second trimester [6, 7] limit the blood flow to the uteroplacental unit. Indeed, high impedance to blood flow in both uterine arteries, a surrogate marker of chronic reduction of the blood flow to the uteroplacental unit [21, 22], is associated with the failure of the normal physiologic transformation of the spiral arteries in placental bed biopsies from patients with pre-eclampsia [11, 13, 16, 23] and those with foetal growth restriction [11, 13, 16, 17]. However, not all patients with these pregnancy complications have evidence of failure of physiologic transformation of the spiral arteries [11–13, 16, 17, 23]. Moreover, this pathological finding is not limited to patients with pre-eclampsia or foetal growth restriction because it has also been described in a subset of patients with preterm parturition [14, 15] and foetal death [18].

Additional mechanisms leading to absolute uteroplacental ischaemia include insults to the placental vasculature during pregnancy. Recent reports indicate not only that pre-eclampsia is associated with placental vascular lesions consistent with “underperfusion”, but also that the earlier the gestational age at which pre-eclampsia develops, the higher the prevalence of lesions consistent with placental ischaemia [24, 25]. Indeed, the frequency of placental histological lesions consistent with “maternal underperfusion” is as high as 75 % in pre-eclampsia that develop between 25 and 27 weeks and as low as 13 % in pre-eclampsia that develop at more than 41 weeks [25]. These observations suggest that there may be a dose response between the magnitude of uteroplacental ischaemia and the timing of onset of pre-eclampsia.

A remarkable example of the latter is the development of pre-eclampsia before 20 weeks of gestation in patients with mole or partial mole. These pregnancy complications are characterized by the presence of "avascular placental villi" or placental villi with capillary remnants [26]. Thus, by definition, mole and partial mole may represent an extreme in the spectrum of ischaemic disease of the trophoblast [27]. The dose response between the magnitude of uteroplacental ischaemia and the timing of the development of pre-eclampsia suggests that there is an absolute or relative "trophoblast ischaemic threshold" beyond which pre-eclampsia develops as a foetal adaptive strategy in an attempt to improve the blood perfusion to the foetal and placental tissues. It is possible that the response to this threshold may be modified by gene–environment interaction [28], the magnitude of angiogenic imbalances [27, 29] and foetal signalling in response to absolute or relative uteroplacental ischaemia [30, 31].

Accumulating evidence indicates that chronic reduction of blood flow to the uterus and placenta is associated with imbalances between circulating angiogenic and anti-angiogenic factors characterized by an excess of the soluble form of vascular endothelial growth factor (VEGF) receptor 1 (sFlt-1) and the soluble endoglin (s-Eng) as well as low circulating maternal concentrations of both VEGF and placental growth factor (PlGF) [27]. Clinical and experimental evidence indicates that angiogenic imbalances are associated with the maternal manifestations of pre-eclampsia, eclampsia and HELLP syndrome [27]. Teleologically, it is difficult to believe that natural selection did not select against pre-eclampsia, which can endanger the survival of both the mother and the foetus. From the evolutionary point of view, it is possible that in preeclamptic patients, the foetus may stimulate the placental release of anti-angiogenic factors to increase the maternal blood pressure in an attempt to increase the blood flow to the placental and foetal tissues. The magnitude of the angiogenic imbalances, gene–environment interaction (Subtle differences in genetic factors that cause some people to possess a low risk for developing a disease through an environmental insult, while others are much more vulnerable) and other factors may determine whether a patient with chronic trophoblast ischaemia will develop pre-eclampsia, foetal growth restriction, both or any of the other intermediate phenotypes including gestational hypertension and gestational proteinuria [27].

Recent reports suggest that among patients with pre-eclampsia, the foetus may use adenosine among other signalling mechanisms in order to increase the maternal blood pressure in an attempt to compensate for limited blood flow to the foetal and placental tissues [27, 30, 32]. In one study [32], the authors compared the foetal plasma concentrations of adenosine from normal pregnancies with those from pre-eclampsia; patients with pre-eclampsia were sub-classified into patients with and without abnormal uterine artery Doppler velocimetry. The results of the study indicated that foetal plasma concentrations of adenosine were significantly higher in patients with pre-eclampsia with abnormal uterine artery Doppler velocimetry than in normal pregnancies. The authors concluded that patients with pre-eclampsia and sonographic evidence of chronic uteroplacental ischaemia have high foetal plasma

concentrations of adenosine and proposed that in these patients the foetus may use the adenosine system and/or other signalling mechanisms to increase the maternal blood pressure in an attempt to increase uteroplacental blood flow. An elegant in vitro study provided additional evidence in support of this view [33]. In this study, the authors determined the adenosine concentrations in foetal venous perfusates using isolated dual-perfused human placental cotyledons. In the latter experimental setting, both the foetal and maternal compartments of the placenta are perfused under controlled conditions. The authors reported that a substantial reduction in the perfusion of the maternal compartment of the placenta was associated with a significant increase in foetal venous perfusate concentrations of adenosine and a concomitant increase in foetoplacental perfusion pressure. Furthermore, perfusate pressure and the concentration of adenosine in the foetal compartment returned to baseline levels on reperfusion of the "maternal" circuit [33]. A more recent study using cultures of placental cells indicates that the administration of adenosine to the cultures significantly increases the concentration of the anti-angiogenic factor sFlt-1 in the cell culture media under normoxic conditions and that the addition of dipyridamole (an adenosine transporter antagonist which increases extracellular adenosine concentration) to cell cultures leads to a significant increase in the concentrations of sFlt-1 in the culture media [34]. Moreover, although hypoxia was associated with a twofold increase in the concentrations of sFlt-1 in the cell culture media, blockade of adenosine signalling (using a non-specific adenosine receptor antagonist) blunted the hypoxic effect on the concentrations of sFlt-1 and VEGF to a level similar to normoxic conditions [34]. These results indicate that adenosine signalling is important for placental overexpression and release of sFlt-1 under both normoxic and hypoxic conditions. An excess of sFlt-1 is associated with endothelial dysfunction, maternal hypertension and the liver and renal injury described in pre-eclampsia. Collectively, this evidence suggests that foetal signalling may play an important role in the development of pre-eclampsia in the context of chronic reduction of blood flow to the uteroplacental unit.

2.2.3 Maternal Thrombophilias

Histological vascular lesions have been described in the foetal and/or maternal side of the placenta in mothers with inherited and acquired maternal thrombophilias [35–38], but not in foetal thrombophilias [39]. Thus, chronic placental ischaemia may contribute to the increased rate of adverse pregnancy outcomes observed in patients with thrombophilias [38, 40–42]. In the context of the foetal–maternal conflict, it is possible that the evolutionary advantage of preserving thrombophilic genes in a particular population is to favour the maternal well-being over that of her foetus, in addition to reducing the risk of peripartum haemorrhage [43, 44].

2.2.4 Late-Onset Pre-eclampsia

Absolute uteroplacental ischaemia appears to be less relevant in the pathophysiology of late-onset pre-eclampsia, defined as the onset of pre-eclampsia beyond 34 weeks of gestation [45, 46]. Evidence in support of this view includes the recent observation that more than half of patients with late-onset pre-eclampsia do not have placental histological lesions consistent with "maternal underperfusion" [47]. Furthermore, late-onset pre-eclampsia is frequently associated with foetuses that are adequate or large-for-gestational age [45, 48–53]. We proposed that in these cases, an increased foetal demand for substrates that surpass the placental ability to sustain foetal growth may induce foetal signalling for placental overproduction of anti-angiogenic factors and subsequent "compensatory" maternal hypertension [27]. Thus, it is possible that a relative uteroplacental ischaemia due to a mismatch between a limited uteroplacental blood flow and increased foetal demand for nutrients may be central to the development of late-onset pre-eclampsia. It is possible that in both early and late-onset pre-eclampsia, the foetus may signal for the onset of pre-eclampsia. In early-onset pre-eclampsia, real reduction in blood flow appears to be central to the disease; in contrast, in late-onset pre-eclampsia, foetal over-demand may create a state of relative scarcity of nutrients, which in turn would prompt foetal signalling to elevate the maternal blood pressure.

A large metanalysis demonstrated that overzealous attempts to control blood pressure during pregnancy are associated with foetal growth restriction [54]. These observations suggest that pre-eclampsia may have evolved as one of the foetal strategies to compensate for a relative or absolute uteroplacental ischaemia.

2.2.5 Abnormal Foetal–Maternal Interactions and Preterm Parturition

Foetal strategies to cope with chronic uteroplacental ischaemia may include growth restriction, foetal signalling to increase the maternal systemic blood pressure leading into pre-eclampsia [30, 31] or preterm parturition to exit an inadequate intrauterine environment. The observation that the absence of physiological transformation of spiral arteries is also present in a subset of patients with spontaneous preterm delivery [14, 15] suggests that the clinical manifestations of "foetal–maternal conflict" may also include preterm parturition. Smallness at birth may be the result of different insults during pregnancy including chronic reduction of blood flow to the uteroplacental unit. In some growth-restricted foetuses, spontaneous preterm parturition (Delivery before 37 weeks of gestation) may represent a survival strategy to exit an inadequate intrauterine environment [55]; failure of this adaptive strategy may result in foetal or neonatal death. Evidence in support of this view includes the observations that spontaneous preterm parturition is associated with foetal growth abnormalities [56–66]. Of note, the association of smallness at birth (less than 10th percentile for

gestational age) and prematurity confers a higher risk of foetal [67] or neonatal death [68] among other adverse perinatal outcomes [68–73]. To the extent that preterm parturition is a survival strategy to exit an inadequate intrauterine environment, the safety of tocolysis (interventions to stop uterine contractions) in the growth-restricted premature foetus should be re-evaluated.

2.2.6 Gestational Diabetes

David Haig in a very insightful article proposed that gestational diabetes mellitus (GDM), among other pregnancy complications, may also be the result of a foetal–maternal conflict [1]. Dr. Haig proposed that a mother and her foetus compete after every meal over the glucose share that each one receives in a way that

> The longer the mother takes to reduce her blood sugar, the greater the share taken by her fetus. [1]

In the last half of pregnancy, there is an increased tissue resistance to the action of insulin; to compensate for this, the mother increases insulin production. According to the foetal–maternal conflict hypothesis, this is caused by foetal signalling using placental allocrine hormones including human placental lactogen (hPL) and human placental growth hormone among others, to guaranty its adequate glucose supply, whereas the increased production of insulin would be a maternal countermeasure [1]. Thus, the nutrient content in the maternal blood may be determined by the balance between foetal signalling using placental-derived hormones and maternal countermeasures. Human experimentation done in the late 1960s provides evidence supporting the notion of the diabetogenic effect of hPL [74, 75]. Indeed, intravenous infusion of physiological amounts of hPL to non-pregnant subjects is associated with glucose intolerance despite increased insulin responses [74]. It is possible that failure of a well-orchestrated maternal–foetal interaction, between foetal signalling increasing the placental production of diabetogenic hormones and maternal countermeasures increasing insulin production, may lead to GDM. Thus, gestational diabetes would develop if a woman were unable to increase her insulin production sufficiently to match the increased peripheral insulin resistance.

A large population-based study indicated that GDM is an independent factor for the development of pre-eclampsia after controlling for confounding factors including maternal age, parity, BMI, smoking and chronic hypertension or renal disease (Adjusted Odds-Ratio: 1.61, 95 % CI: 1.39–1.86) [76]. Moreover, a large retrospective study in the USA involving 1813 women with GDM demonstrated that the rates of pre-eclampsia among those with poor glycaemic control were about twice as high as those with better glycaemic control (18 % vs. 9.8 %; OR: 2.56, 95 % CI: 1.5–4.3) [77]. However, there is limited literature in regard to the timing of onset of pre-eclampsia among women with GDM.

In a study involving 45 patients with GDM demonstrated normal placental histology in 80 % of them [76], thus, placental vascular lesions are not common in

the foetal or maternal side of the placenta in women with GDM. Since this pregnancy complication is associated with large-for-gestational age neonates, it is possible that in women with GDM who develop pre-eclampsia, an increased foetal demand for substrates that surpass the placental ability to sustain foetal growth may induce foetal signalling for placental overproduction of anti-angiogenic factors and subsequent "compensatory" maternal hypertension. Additional studies are needed to explore the role of angiogenic imbalances in these patients.

2.3 Implications for Policy and Practice

The recognition that some pregnancy complications may be due to abnormal foetal–maternal interactions is important for the clinical management of these pregnancy complications. In the context of a long-lasting reduction of blood flow to the foetal and placental tissues, the foetus may signal the placental release of "pressor substances", which could elevate the maternal blood pressure in an attempt to increase the delivery of nutrients to the foetus. Any medical attempt to "normalize" the blood pressure in the mother could be deleterious to the foetus by preventing the beneficial effect of a compensatory mechanism. The use of medications to lower the blood pressure should be aimed at reducing the blood pressure to a level that will prevent cardiovascular accidents in the mother, but not at "normalizing" the blood pressure. Similarly, the use of medications to stop the uterine contractions in women with preterm labour should be judiciously used in foetuses that are growth-restricted because it is possible that the foetus may have initiated the process of premature labour in order to exit a hostile intrauterine environment.

Glossary

Pre-eclampsia	Hypertensive disorder of pregnancy that typically starts after the 20th week of pregnancy.
Genomic imprinting	The process by which one copy of a gene is silenced due to its parental origin.
Mole pregnancy	Results from a genetic error during the fertilization process that leads to growth of abnormal placenta within the uterus.
Grb10	Growth factor receptor-bound protein 10 also known as insulin receptor-binding protein.
Spiral arteries	Small arteries that are remodelled into highly dilated vessels during pregnancy to increase the blood supply to foetal and placental tissues.

Placental bed disorders	Refers to defective placentation in the human which is associated with pregnancy complications such pre-eclampsia, foetal growth restriction, and foetal death.
Uteroplacental ischaemia	During pregnancy, the uterus and placenta form a functional unit. This term refers to reduced blood flow to this unit.
Angiogenic factors	Promote the viability and growth of endothelial cells. Foetal signalling: proposed pathways used by the foetus to alter the maternal of placental physiology.
HELLP syndrome	A severe form of pre-eclampsia characterized by abnormal liver enzymes, low platelets and destruction of red blood cells.
Adenosine	Compound that plays an important role in energy transfer signal transduction and regulation of blood flow to various organs.
Uterine artery Doppler velocimetry	Ultrasonographic technique to evaluate the characteristics of blood flow in vessels.
VEGF	Vascular endothelial growth factor is a signalling protein involved in the formation and growth of blood vessels.
sFlt-1	Splice variant of VEGF receptor 1an excess of this soluble form in the circulation can reduce the bioavailability of VEGF (anti-angiogenic).
Thrombophilia	Abnormality of blood coagulation that increases the risk of thrombosis.
Tocolysis	Medical interventions to reduce or stop uterine contractions.
Allocrine hormones	Foreign hormones being taken up and eliciting a response in an organism.

References

1. Haig D (1993) Genetic conflicts in human pregnancy. Q Rev Biol 68:495–532
2. Pijnenborg R, Vercruysse L, Hanssens M (2008) Fetal-maternal conflict, trophoblast invasion, preeclampsia, and the red queen. Hypertens Pregnancy 27:183–196
3. Page EW (1939) The relation between hydatid moles, relative ischemia of the gravid uterus, and the placental origin of eclampsia. Am J Obstet Gynecol 37:291–293

4. Constancia M, Hemberger M, Hughes J, Dean W, Ferguson-Smith A, Fundele R (2002) Placental-specific IGF-II is a major modulator of placental and fetal growth. Nature 417:945–948
5. Fowden AL, Coan PM, Angiolini E, Burton GJ, Constancia M (2011) Imprinted genes and the epigenetic regulation of placental phenotype. Prog Biophys Mol Biol 106:281–288
6. Espinoza J, Romero R, Mee KY, Kusanovic JP, Hassan S, Erez O (2006) Normal and abnormal transformation of the spiral arteries during pregnancy. J Perinat Med 34:447–458
7. Pijnenborg R, Vercruysse L, Hanssens M (2006) The uterine spiral arteries in human pregnancy: Facts and controversies. Placenta 27:939–958
8. Burton GJ, Woods AW, Jauniaux E, Kingdom JC (2009) Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta 30:473–482
9. Burton GJ, Yung HW (2011) Endoplasmic reticulum stress in the pathogenesis of early-onset pre-eclampsia. Pregnancy Hypertens 1:72–78
10. Burton GJ, Jauniaux E (2004) Placental oxidative stress: From miscarriage to preeclampsia. J Soc Gynecol Investig 11:342–352
11. Olofsson P, Laurini RN, Marsal KA (1993) High uterine artery pulsatility index reflects a defective development of placental bed spiral arteries in pregnancies complicated by hypertension and fetal growth retardation. Eur J Obstet Gynecol Reprod Biol 49:161–168
12. Sagol S, Ozkinay E, Oztekin K, Ozdemir N (1999) The comparison of uterine artery doppler velocimetry with the histopathology of the placental bed. Aust N Z J Obstet Gynaecol 39:324–329
13. Aardema MW, Oosterhof H, Timmer A, van RI, Aarnoudse JG (2001) Uterine artery doppler flow and uteroplacental vascular pathology in normal pregnancies and pregnancies complicated by pre-eclampsia and small for gestational age fetuses. Placenta 22:405–411
14. Kim YM, Chaiworapongsa T, Gomez R, Bujold E, Yoon BH, Rotmensch S (2002) Failure of physiologic transformation of the spiral arteries in the placental bed in preterm premature rupture of membranes. Am J Obstet Gynecol 187:1137–1142
15. Kim YM, Bujold E, Chaiworapongsa T, Gomez R, Yoon BH, Thaler HT (2003) Failure of physiologic transformation of the spiral arteries in patients with preterm labor and intact membranes. Am J Obstet Gynecol 189:1063–1069
16. Lin S, Shimizu I, Suehara N, Nakayama M, Aono T (1995) Uterine artery doppler velocimetry in relation to trophoblast migration into the myometrium of the placental bed. Obstet Gynecol 85:760–765
17. Madazli R, Somunkiran A, Calay Z, Ilvan S, Aksu MF (2003) 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 24:510–516
18. Avagliano L, Bulfamante GP, Morabito A, Marconi AM (2011) Abnormal spiral artery remodelling in the decidual segment during pregnancy: From histology to clinical correlation. J Clin Pathol 64:1064–1068
19. Wu RT, Shyu MK, Lee CN, Wu CC, Hwa HL, Lin CJ (1995) Sonographic manifestation and doppler blood flow study in fetal triploidy syndrome: Report of two cases. J Ultrasound Med 14:555–558
20. Charalambous M, Smith FM, Bennett WR, Crew TE, Mackenzie F, Ward A (2003) Disruption of the imprinted Grb10 gene leads to disproportionate overgrowth by an Igf2-independent mechanism. Proc Natl Acad Sci USA 100:8292–8297
21. Kuzmina IY, Hubina-Vakulik GI, Burton GJ (2005) Placental morphometry and doppler flow velocimetry in cases of chronic human fetal hypoxia. Eur J Obstet Gynecol Reprod Biol 120:139–145
22. Prefumo F, Sebire NJ, Thilaganathan B (2004) Decreased endovascular trophoblast invasion in first trimester pregnancies with high-resistance uterine artery doppler indices. Hum Reprod 19:206–209
23. Voigt HJ, Becker V (1992) Doppler flow measurements and histomorphology of the placental bed in uteroplacental insufficiency. J Perinat Med 20:139–147

24. Moldenhauer JS, Stanek J, Warshak C, Khoury J, Sibai B (2003) The frequency and severity of placental findings in women with preeclampsia are gestational age dependent. Am J Obstet Gynecol 189:1173–1177
25. Ogge G, Chaiworapongsa T, Romero R, Hussein Y, Kusanovic JP, Yeo L (2011) Placental lesions associated with maternal underperfusion are more frequent in early-onset than in late-onset preeclampsia. J Perinat Med
26. Benirschke K, Kaufmann P, Baergen R (2006) Pathology of the human placenta. Springer, New York
27. Espinoza J, Uckele JE, Starr RA, Seubert DE, Espinoza AF, Berry SM (2010) Angiogenic imbalances: The obstetric perspective. Am J Obstet Gynecol 203:17–18
28. Sandrim VC, Palei AC, Cavalli RC, Araujo FM, Ramos ES, Duarte G (2009) Vascular endothelial growth factor genotypes and haplotypes are associated with pre-eclampsia but not with gestational hypertension. Mol Hum Reprod 15:115–120
29. Burton GJ, Charnock-Jones DS, Jauniaux E (2009) Regulation of vascular growth and function in the human placenta. Reproduction 138:895–902
30. Espinoza J, Espinoza AF (2011) Pre-eclampsia: A maternal manifestation of a fetal adaptive response? Ultrasound Obstet Gynecol 38:367–370
31. Espinoza J, Espinoza AF, Power GG (2011) High fetal plasma adenosine concentration: A role for the fetus in preeclampsia? Am J Obstet Gynecol
32. Espinoza J, Espinoza AF, Power GG (2011) High fetal plasma adenosine: A role for the fetus in preeclampsia? Am J Obstet Gynecol. doi:10.1016/j.ajog.2011.06.034
33. Slegel P, Kitagawa H, Maguire MH (1988) Determination of adenosine in fetal perfusates of human placental cotyledons using fluorescence derivatization and reversed-phase high-performance liquid chromatography. Anal Biochem 171:124–134
34. George EM, Cockrell K, Adair TH, Granger JP (2010) Regulation of sFlt-1 and VEGF secretion by adenosine under hypoxic conditions in rat placental villous explants. Am J Physiol Regul Integr Comp Physiol 299:R1629–R1633
35. Gogia N, Machin GA (2008) Maternal thrombophilias are associated with specific placental lesions. Pediatr Dev Pathol 11:424–429
36. Sebire NJ, Backos M, Goldin RD, Regan L (2002) Placental massive perivillous fibrin deposition associated with antiphospholipid antibody syndrome. BJOG 109:570–573
37. Redline RW (2006) Thrombophilia and placental pathology. Clin Obstet Gynecol 49:885–894
38. Arias F, Romero R, Joist H, Kraus FT (1998) Thrombophilia: A mechanism of disease in women with adverse pregnancy outcome and thrombotic lesions in the placenta. J Matern Fetal Med 7:277–286
39. Ariel I, Anteby E, Hamani Y, Redline RW (2004) Placental pathology in fetal thrombophilia. Hum Pathol 35:729–733
40. Kupferminc MJ, Many A, Bar-Am A, Lessing JB, Ascher-Landsberg J (2002) Mid-trimester severe intrauterine growth restriction is associated with a high prevalence of thrombophilia. BJOG 109:1373–1376
41. Paidas MJ, Ku DH, Arkel YS (2004) Screening and management of inherited thrombophilias in the setting of adverse pregnancy outcome. Clin Perinatol 31:783–805
42. Kupferminc MJ, Rimon E, Ascher-Landsberg J, Lessing JB, Many A (2004) Perinatal outcome in women with severe pregnancy complications and multiple thrombophilias. J Perinat Med 32:225–227
43. Lindqvist PG, Dahlback B (2008) Carriership of Factor V Leiden and evolutionary selection advantage. Curr Med Chem 15:1541–1544
44. Lindqvist PG, Svensson PJ, Dahlback B, Marsal K (1998) Factor V Q506 mutation (activated protein C resistance) associated with reduced intrapartum blood loss–a possible evolutionary selection mechanism. Thromb Haemost 79:69–73
45. Rasmussen S, Irgens LM (2003) Fetal growth and body proportion in preeclampsia. Obstet Gynecol 101:575–583

46. Aardema MW, Saro MC, Lander M, De Wolf BT, Oosterhof H, Aarnoudse JG (2004) Second trimester doppler ultrasound screening of the uterine arteries differentiates between subsequent normal and poor outcomes of hypertensive pregnancy: Two different pathophysiological entities? Clin Sci (Lond) 106:377–382
47. Soto E, Romero R, Kusanovic JP, Ogge G, Hussein Y, Yeo L (2011) Late-onset preeclampsia is associated with an imbalance of angiogenic and anti-angiogenic factors in patients with and without placental lesions consistent with maternal underperfusion. J Matern Fetal Neonatal Med
48. Odegard RA, Vatten LJ, Nilsen ST, Salvesen KA, Austgulen R (2000) Preeclampsia and fetal growth. Obstet Gynecol 96:950–955
49. Xiong X, Demianczuk NN, Buekens P, Saunders LD (2000) Association of preeclampsia with high birth weight for age. Am J Obstet Gynecol 183:148–155
50. Xiong X, Fraser WD (2004) Impact of pregnancy-induced hypertension on birthweight by gestational age. Paediatr Perinat Epidemiol 18:186–191
51. Rasmussen S, Irgens LM, Espinoza J (2014) Maternal obesity and excess of fetal growth in pre-eclampsia. BJOG 121:1351–1358
52. Rasmussen S, Espinoza J, Lee W, Martin SR, Belfort MA (2014) Re: Customized growth curves for identification of large-for-gestational age neonates in pre-eclamptic women. Ultrasound Obstet Gynecol 43:165–169
53. Espinoza J, Lee W, Martin SR, Belfort MA (2014) Customized growth curves for identification of large-for-gestational age neonates in pre-eclamptic women. Ultrasound Obstet Gynecol 43:165–169
54. von Dadelszen P, Ornstein MP, Bull SB, Logan AG, Koren G, Magee LA (2000) Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: A meta-analysis. Lancet 355:87–92
55. Romero R (1996) Prenatal medicine: The child is the father of the man. Prenat Neonatal Med 1:8–11
56. Ott WJ (1988) The diagnosis of altered fetal growth. Obstet Gynecol Clin North Am 15:237–263
57. Deter RL, Rossavik IK, Harrist RB (1988) Development of individual growth curve standards for estimated fetal weight: I Weight estimation procedure. J Clin Ultrasound 16:215–225
58. Ott WJ (1993) Intrauterine growth retardation and preterm delivery. Am J Obstet Gynecol 168:1710–1717
59. Zeitlin J, Ancel PY, Saurel-Cubizolles MJ, Papiernik E (2000) The relationship between intrauterine growth restriction and preterm delivery: An empirical approach using data from a European case-control study. BJOG 107:750–758
60. Goldenberg RL, Nelson KG, Koski JF, Cutter GR (1985) Low birth weight, intrauterine growth retardation, and preterm delivery. Am J Obstet Gynecol 152:980–984
61. Bukowski R, Gahn D, Denning J, Saade G (2001) Impairment of growth in fetuses destined to deliver preterm. Am J Obstet Gynecol 185:463–467
62. Secher NJ, Kern HP, Thomsen BL, Keiding N (1987) Growth retardation in preterm infants. Br J Obstet Gynaecol 94:115–120
63. Morken NH, Kallen K, Jacobsson B (2006) Fetal growth and onset of delivery: A nationwide population-based study of preterm infants. Am J Obstet Gynecol 195:154–161
64. Mercer BM, Merlino AA, Milluzzi CJ, Moore JJ (2008) Small fetal size before 20 weeks' gestation: Associations with maternal tobacco use, early preterm birth, and low birthweight. Am J Obstet Gynecol 198:673–677
65. Hediger ML, Scholl TO, Schall JI, Miller LW, Fischer RL (1995) Fetal growth and the etiology of preterm delivery. Obstet Gynecol 85:175–182
66. MacGregor SN, Sabbagha RE, Tamura RK, Pielet BW, Feigenbaum SL (1988) Differing fetal growth patterns in pregnancies complicated by preterm labor. Obstet Gynecol 72:834–837
67. Odibo AO, Cahill AG, Odibo L, Roehl K, Macones GA (2011) Prediction of intrauterine fetal death in small-forgestational-age fetuses: Impact of including ultrasound biometry in customized models. Ultrasound Obstet Gynecol

68. Garite TJ, Clark R, Thorp JA (2004) Intrauterine growth restriction increases morbidity and mortality among premature neonates. Am J Obstet Gynecol 191:481–487
69. Aucott SW, Donohue PK, Northington FJ (2004) Increased morbidity in severe early intrauterine growth restriction. J Perinatol 24:435–440
70. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A (2000) The vermont oxford network. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. Am J Obstet Gynecol 182:198–206
71. Hemming K, Hutton JL, Bonellie S (2009) A comparison of customized and population-based birth-weight standards: The influence of gestational age. Eur J Obstet Gynecol Reprod.Biol 146:41–45
72. Zhang X, Platt RW, Cnattingius S, Joseph KS, Kramer MS (2007) The use of customised versus population-based birthweight standards in predicting perinatal mortality. BJOG 114:474–477
73. Engineer N, Kumar S (2010) Perinatal variables and neonatal outcomes in severely growth restricted preterm fetuses. Acta Obstet Gynecol Scand 89:1174–1181
74. Beck P, Daughaday WH (1967) Human placental lactogen: Studies of its acute metabolic effects and disposition in normal man. J Clin Invest 46:103
75. Samaan N, Yen SC, Gonzalez D, Pearson OH (1968) Metabolic effects of placental lactogen (HPL) in man. J Clin Endocrinol Metab 28:485–491
76. Ostlund I, Haglund B, Hanson U (2004) Gestational diabetes and preeclampsia. Eur J Obstet Gynecol Reprod Biol 113:12–16
77. Yogev Y, Xenakis EM, Langer O (2004) The association between preeclampsia and the severity of gestational diabetes: The impact of glycemic control. Am J Obstet Gynecol 191:1655–1660

http://www.springer.com/978-3-319-29714-9

Evolutionary Thinking in Medicine
From Research to Policy and Practice
Alvergne, A.; Jenkinson, C.; Faurie, C. (Eds.)
2016, XIV, 382 p. 37 illus., 17 illus. in color., Hardcover
ISBN: 978-3-319-29714-9