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Placental Dysfunction and Fetal Programming: The Importance of Placental Size, Shape, Histopathology, and Molecular Composition

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Abstract

Normal function of the placenta is pivotal for optimal fetal growth and development. Fetal programming commonly is associated with placental dysfunction that predisposes to obstetric complications and suboptimal fetal outcomes. We consider several clinical phenotypes for placental dysfunction that likely predispose to fetal programming. Some of these reflect abnormal development of the chorioallantoic placenta in size, shape, or histopathology. Others result when exogenous stressors in the maternal environment combine with maladaptation of the placental response to yield small placentas with limited reserve, as typical of early-onset intrauterine growth restriction and preeclampsia. Still others reflect epigenetic changes, including altered expression of imprinted genes, altered enzymatic activity, or altered efficiencies in nutrient transport. Although the human placenta is a transient organ that persists only 9 months, the effects of this organ on the offspring remain for a lifetime.

Keywords

Placenta; trophoblast; developmental origins of human adult disease; epigenetics; fetal programming

The phenomenon of changing the pattern or content of developmental signals in utero to result in cardiovascular or metabolic disease of the adult is termed *fetal programming*. The developmental origins of health and disease, abbreviated as the mnemonic DOHaD, are based on the concept of fetal programming. Much attention is focused on the molecular mechanisms for the programming effects, with hopes of targeted therapy in the population at risk. Several observations regarding placental function and outcomes of pregnancy suggests this organ is pivotal, either directly or indirectly, in DOHaD.^{1,2} First, placental dysfunction is a common feature of pregnancies that yields programming effects on the fetus, most commonly recognized in offspring with intrauterine growth restriction (IUGR). Second, fetal programming occurs in both small for gestational age and large for gestational age offspring and, because placental weight correlates with fetal weight, programming occurs when placentas are maladapted, either too small or excessively large.^{3,4} Third, programming effects are not unique to a single clinical phenotype, but instead they can be detected after a variety of clinical maladies, including pregnancies complicated by IUGR, preterm birth,

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preeclampsia, or uncontrolled gestational diabetes, among others. Finally, the etiology of the placental dysfunction that predisposes to fetal programming is not singular but instead is multifactorial with abundant gene and environment interactions. Etiologies include maldevelopment of the placenta in the first trimester, injury to villous tissues from underperfusion, mechanical damage, or reoxygenation in the third trimester, or from maladaptive changes that evolve in the placenta throughout pregnancy in response to the dynamic maternal environment. Imprinting disorders and epigenetic modulations provide the background for interaction with these placental phenotypes to yield fetal programming.

Intuitively, the placenta interfaces the fetus and mother and thus creates, or at least transmits, the environment in which fetal programming occurs in the offspring. The fetal environment is the result of multiple placental functions, including directional transport of nutrients and oxygen, secretion of cytokines, hormones, and growth factors, and adaptive responses to environmental cues (Fig. 1). We first describe some aspects of early human placental development that previously were infrequently considered in the context of fetal programming. We then highlight how modifications in the gross structure of the placenta and exposure to exogenous insults relate to placental dysfunction and placental effects on fetal programming. We next overview the roles of epigenetic changes, imprinted genes, activity of placental 11 (β hydroxysteroid dehydrogenase (11 (β HSD), and nutrient sensors. Finally, we consider therapeutic interventions that might influence the processes we discuss. We hope that further research will provide clinicians with more options to improve placental function in pregnancies predisposed to fetal programming, thereby improving both short-term and long-term outcomes.

COULD EMBRYONIC PROGRAMMING OCCUR IN TANDEM WITH EARLY PLACENTAL DEVELOPMENT?

All would accept the premise that placental development is pivotal for survival of *Homo sapiens*. However, we posit that fetal programming or, more specifically, embryonic programming may occur as a result of exogenous stress created in the intrauterine environment even before the definitive placenta evolves. We briefly outline the premise on which this hypothesis is based as an introduction to placental development.

Zygote-associated changes in a gene expression profile, determined by the nucleotide sequences, are modulated by epigenetic effects. These combine to orchestrate a highly regulated sequence of developmental events that produce the embryo and chorioallantoic placenta. For example, the progression from zygote to morula to blastocyst culminates in differentiation of cells into the trophoctoderm, which will form the placenta, and inner cell mass, which will form the fetus. Trophoctoderm of human blastocysts are highly invasive and penetrate the uterine epithelium to establish interstitial implantation. Multiple trophoblast phenotypes along with mesenchymal angiogenesis and vasculogenesis then contribute to the development of chorioallantoic placenta with trees of highly branched villi that are involved in all aspects of the maternal–fetal exchange. Importantly, two recent discoveries have changed our perception of the early environment in which both the conceptus and placenta develop. First, the villous structures only passively contribute to conceptus nutrition in the first 2 months of gestation, with organogenesis occurring in an environment where nutrition is not directly supplied by maternal blood but instead by uterine secretions called histiotroph.^{4–7} Second, there is an absence of perfusion of the intervillous space with maternal blood in normal early pregnancy. Invasive endovascular trophoblasts from the placenta migrate into the maternal basal plate where they penetrate and plug the openings in maternal spiral arterioles. This restricts the flow of oxygenated blood into the intervillous space until the end of the first trimester. Thus embryogenesis and early placental development occur in an environment with an oxygen tension < 20 mm Hg,

perhaps as a mechanism to limit oxidative stress. Removal of the blockage of the spiral arteries and perfusion of the intervillous space ensues at 10 to 12 weeks of gestation, with the placental villi directly bathed with oxygen- and nutrient-rich maternal blood until delivery. Notably, premature flow of maternal blood into the intervillous lacunae in the first 2 months of gestation, as demonstrated by ultrasound assessment, associates with a higher rate of spontaneous pregnancy loss.^{8,10} The pregnancy loss is attributed to damaging reactive oxygen species and inadequate placental antioxidant defenses, which normally do not appear until 10 to 12 weeks of gestation.

The findings just outlined suggest opportunities for the occurrence of fetal programming earlier in gestation than commonly described. For example, through an altered content of the maternal supply of histiotroph, the conceptus may modulate gene expression and epigenetic profiles in the embryo to predispose to permanent programming changes in the fetus and, ultimately, to the adult. Moreover, exposure of the conceptus to excessive reactive oxygen species, as would occur with premature perfusion of placental villi with oxygenated blood, could affect the developmental potential of the chorioallantoic placenta, the developing embryo, or both, to affect permanent programming that manifests as a predisposition to disease later in life. Experimental exploration of these hypotheses clearly will require study in animal models because such studies are ethically unlikely in humans.

CHORIOALLANTOIC PLACENTAL DEVELOPMENT

Although the events just described evolve during early embryogenesis, the chorioallantoic placenta is forming trees of villi, some free floating and others anchored to the maternal basal plate decidua. In the presence of the invasive endovascular extravillous trophoblasts, the decidual spiral arterioles lose their smooth muscle coat and their vessel walls are replaced by fibrinoid. This anatomical change in these maternal vessels allows adequate, nonvasoreactive perfusion of the placental intervillous space and associates with oxygen delivery to the rapidly developing conceptus. Free-floating villi are exposed to an oxygen tension of 40 to 80 mm Hg from the end of the first trimester through term.¹¹ Importantly, oxygen and nutrient delivery to the fetus from this point forward is primarily the responsibility of the villous trophoblast bilayer.

Injury to the villous trophoblast bilayer offers a possible mechanism for fetal programming that normally does not influence early fetal embryogenesis. The outer syncytiotrophoblast component of the trophoblast bilayer is a terminally differentiated, nonmitotic epithelium derived through differentiation and fusion of the subjacent mitotically active cytotrophoblast stem cells, to form a unique multinucleated, and apparently continuous, syncytium on the villous surface. Homeostasis of the trophoblast bilayer in normal development and in response to injury requires modulation of the proliferation, differentiation, and fusion of villous cytotrophoblasts to replenish the syncytiotrophoblast layer. Turnover of syncytiotrophoblast occurs, in part, through shedding of fragments from the syncytium into the intervillous space, yielding denudations on the villous surface. Deposits of fibrin on the basement membrane of the trophoblast identify these denudations, and the fibrin provides a matrix for reepithelialization by trophoblast at the site of the injury.¹² Clusters of nuclei with condensed chromatin typical of apoptosis, so-called syncytial knots, are characteristic of the histopathology in the syncytiotrophoblast of the villous tree of complicated pregnancies and are especially apparent when preeclampsia and IUGR occur together.¹³ Whether the syncytial knots are released into the maternal circulation during normal trophoblast turnover is a debated point,¹⁴⁻¹⁶ but the presence of increased knots in complicated pregnancies likely reflects a response to villous injury because knots also form in vitro when term villi are cultured in low oxygen tensions.¹⁷

Discontinuities in the syncytiotrophoblast affect the normal regulation of the passage of molecules through the syncytium. At sites of epithelial denudation, the barrier to passage of molecules from the maternal circulation to the fetal circulation becomes only the basement membrane that delimits the villous core connective tissue and the vessels within the core that merge into the fetal umbilical circulation. In vitro perfusion studies suggest that breaks in the trophoblast layer provide an unregulated paracellular route for molecules to cross the placenta based on their coefficient of diffusion in water.^{4,18} There is evidence of increased villous injury reflected by an increased number of fibrin deposits at breaks in the trophoblast layer in preeclampsia and in placentas from pregnancies with IUGR.¹⁹ It is possible, although not shown, that the fetus can be programmed, in part, by exposure to abnormal concentrations of ions, glucose, or other small molecules that pass from the maternal to fetal circulations through these unregulated regions of denuded villi.

Programming changes in the fetus are especially associated with placental histopathology where inadequate modification of the maternal spiral arterioles is present and so-called placental insufficiency ensues. There is a complex relationship between gene interactions and the environment to establish the spiral arteriole modifications, and dysregulation of this process commonly leads to a suboptimal pregnancy outcome and offspring with long-term health issues.²⁰ Placental dysfunction is especially prominent when suboptimal pregnancy outcomes manifest as early onset IUGR, preeclampsia, or both, but basal plate histopathology may also manifest as other clinical phenotypes, such as preterm birth or premature preterm rupture of membranes.²¹ Interestingly, fetal growth in the latter phenotypes is commonly suboptimal even though not classified as IUGR.²² All of these suboptimal clinical outcomes associate with increased risks for fetal programming with long-term effects on the afflicted offspring.

Inadequate remodeling of the maternal spiral arterioles by placental trophoblasts results in no, or only limited, widening of the lumen and retention of the muscle in the vessel walls, so that the arterioles remain responsive to endogenous vasoactive agents. These maladaptive changes result in an increase in exposure of the placental villi to injury from reactive oxygen and nitrate species, to underperfusion induced hypoxia-reoxygenation, or to a combination of these stressors.²³ Maladaptation of the spiral arterioles also increases the pressure of blood entering the intervillous space, likely inducing mechanical damage to the exposed villi.²⁴ These injuries may yield a range of downstream responses manifested as placental insufficiency. Key signaling pathways may be differentially affected by these injuries, including dysregulation of the nuclear factor κ B-mediated inflammatory pathways to yield preterm birth in some cases, and nitrate induced reductions of p38 mitogen-activated protein kinase (MAPK) activity to yield diminished placental growth and development of the villous trophoblast in cases of preeclampsia.^{23,25} Notably, the p38 MAPK pathway has been shown to regulate trophoblast differentiation.^{26,27}

The histopathology of placentas from infants delivered with the diagnosis of IUGR with absent-end diastolic flow includes elongated terminal villi, with reduced capillary branching angiogenesis.²⁸ Histopathological changes also occur in pregnancies at high altitude or with severe maternal anemia, with increased capillary branching, likely reflecting placental hypoxia.²⁹ In all these situations, the alterations in placental villous structure provide opportunities for placental dysfunction and fetal programming.

Placental Size, Shape, and Weight Matter

We know that reduced placental growth, reflected by weight and volume, generally precedes diminished fetal growth.^{30,31} As importantly, placental weight can be modified by maternal cues because placental weight at delivery is increased when mothers receive high carbohydrate loads in the first trimester and high protein loads in later pregnancy.³² How

might the gross appearances of shape and placental weight influence the outcomes of pregnancy and fetal programming?

A simple observation indicates that on a population basis the weight of the placenta at birth correlates with the weight of the infant.^{22,33} The placenta is typically described as either round or oval, but other shapes such as irregular, bilobate, or circumvallate, among others, are not infrequent.^{34,35} Irregular placental shapes have been associated with lower birthweight,^{36,37} suggesting they are associated with altered placental function. The relationship between placental weight and birthweight is sometimes expressed as the fetoplacental ratio, a proportion with fetal weight in the numerator and placental weight in the denominator. This ratio is influenced by exogenous signals in the fetus, the mother, or both. For example, maternal anemia, high body mass index, and maternal smoking all increase the placental ratio, even though smoking during pregnancy diminishes the absolute weight of the placenta compared with nonsmoking mothers.³⁸ Women with preeclampsia have placentas with reduced surface area, with a shape that is more likely oval than round, and with offspring that have an increased risk for hypertension as adults.³⁹ Indeed, several animal models and data on birthweight and placental weights in humans have correlated offspring vulnerability to cardiovascular disease and placental insufficiency, as recently reviewed.⁴⁰

Salafia and Yampolsky conducted mathematical modeling studies to show that placental proportions, such as deviations in placental shape from round and the relative thickness, modify placental functional efficiency above and beyond shape and weight relationships alone. The effects of these factors explain some of the range of birthweights possible in a normal population delivered from placental weights in the same range and account for some of the variance in birthweight that otherwise is attributed to effects of maternal factors, such as age, parity, race, ethnicity, and socioeconomic status.^{22,42}

Insertions of the umbilical cord into the placenta margin or into the fetal membranes (velamentous insertion) rather than into the main placental mass are well known to pathologists to associate with small placentas and small infants.³⁴ Concomitant alterations of the umbilical blood supply to the fetus, perhaps by torsion of the umbilical cord, is a risk factor for fetal programming that has not been studied. However, Salafia and colleagues hypothesized that the association of cord insertions to suboptimal outcomes is not limited only to these extreme insertions. They recently applied mathematical analyses to the gross parameters of the placenta and showed that nonmarginal, but markedly eccentric, cord insertion associates with a sparser chorionic vascular distribution, a reduced transport efficiency of the placental vasculature, and a reduced birthweight for a given placental weight.^{35,43} The more eccentric the umbilical cord insertion, independent of the placental shape, the less efficient the placenta is in terms of the birthweight per gram of placental weight. Indeed, placentas with a noncentrally inserted umbilical cord and with finite diameters on the surface tended to be heavier because of increased thickness, a response that reflects the developmental plasticity of the placenta to supply fetal demands for nutrients. These data suggest that infants with eccentric insertions of the umbilical cord may be predisposed to effects of fetal programming that are not directly related to maternal nutrient deficiency or reductions in the maternal supply line to the placenta. They also indicate that the development of the gross appearance of the placenta can influence fetal outcomes and, in the process, predispose the fetus to programming.

Epigenetic Modulation of Placental Function

Epigenetics likely plays a prominent role in fetal programming, either by modulating placental gene expression and placental function or by directly affecting gene expression in the fetus during its orchestrated development and growth. Simply stated, epigenetics is

changes in phenotype or gene expression caused by mechanisms other than alteration in DNA sequence. Five-methyl-cytosine methylation occurs by specific DNA methylases, typically in C/G-rich regions of the genome. The DNA methyltransferase I pathway involves folic acid, offering a potential clinical approach to modification of the methylation status of cellular DNA, as described later. Moreover, acetylation and methylation modification of histones regulates the transcriptional activity of associated genes. Epigenetic modifications can result in a change of information content even for future cell and organismal generations. Epigenetic phenomena offer a mechanism of developmental plasticity of the fetus and the placenta that allows each to respond to environmental stressors, perhaps promoting offspring survival, albeit at a potential long-term cost. A case in point is the small fetus associated with placental dysfunction that is consequently programmed through epigenetic effects to later develop postnatal diabetes and impaired insulin action.³

The presence of epigenetic modulations of human placental development remains to be identified, but animal models have provided evidence for proof of principle that epigenetic changes occur in response to environmental factors, as reviewed.⁴⁴ For example, the Agouti mouse is yellow as a result of a single gene locus that is normally hypomethylated. Supplementation of mothers with methyl donors, including folic acid and vitamin B₁₂, increases methylation of the coat gene and yields more offspring with a brown coat color compared with offspring of unsupplemented mothers.⁴⁵ A recent functional analysis of gene expression in placentas of mice exposed to stress found increased expression of genes involved in DNA methylation and histone modification compared with placentas of unstressed mice.⁴⁶ Similar studies in human placentas exposed to in utero stress are likely to identify key pathways that are susceptible to epigenetic regulation during placental development.

Imprinting and the Placenta

Over 100 protein-coding genes in humans are differentially expressed depending on parent-of-origin, a process called imprinting.⁴⁷ Most imprinted genes are present in clusters of two or more genes that contain a differentially methylated region of relatively high CpG content. A surprising number of imprinted protein encoded genes are expressed in the placenta, indicating the importance of epigenetic gene expression in this organ.^{48–50} Interestingly, the paternal genome is normally demethylated within hours after fertilization of the zygote, whereas the maternal genome is demethylated during the initial cleavages that yield the morula and precede implantation, a phenomenon that varies among species. Imprinted genes are spared this phenomenon of demethylation, or erasure, because they are critical to ongoing development.^{51,52} Genomic imprinting is conserved among primates, rodents, and mammals, highlighting the importance of this phenomenon to placental development.^{53,54} In addition to protein coding genes, mammals express > 700 microRNAs (miRNAs), which are short RNAs that regulate gene expression at the post-transcriptional level. Many miRNAs are subject to epigenetic regulation and can themselves affect epigenetic pathways, providing feedback control.^{55–57}

Studies on protein encoding imprinted RNAs provide the general insight that maternally imprinted genes tend to result in reduced placental growth whereas paternally expressed genes tend to enhance placental and fetal growth,⁴⁹ supporting the conflict hypothesis⁵⁸ that proposes paternally expressed genes enhance fetal growth and maternally expressed genes suppress fetal growth. An example is the insulinlike growth factor 2 system. The insulinlike growth factor 2 (*Igf2*) gene is maternally imprinted (paternally expressed), whereas the insulinlike growth factor 2 receptor (*Igf2r*) gene is paternally imprinted (maternally expressed). These genes have opposite effects on fetal and placental growth: Mice null for *igf2* show reduced growth of the placenta and fetus;^{59,60} mice null for *igf2r* show increased placental and fetal growth.^{61,62} Alterations of epigenetic expression of these and other

imprinted genes provide a mechanism by which nutrient and other stress in placental growth and development can ultimately alter the programming of the fetus.

Several miRNAs are expressed in the placenta and cultured human trophoblasts.^{63,66} Two groups found differential up- and downregulation of miRNAs in preeclamptic placentas compared with normal placentas,^{67,68} with, interestingly, several miRNA clusters identified, including one on 14q32.31, a chromosomal region subject to imprinting. Notably, miRNAs are present extracellularly in the maternal circulation in 50- to 100-nm diameter secreted vesicles termed *exo-somes*, and at least some of these miRNAs appear to be produced by the placenta.^{64,69} Hypoxia regulates miRNA expression in cultured human trophoblasts,⁶⁵ although expression of this miRNA subset was not significantly altered in women with growth-restricted fetuses.⁶⁹ Together, these data suggest the strong possibility that changes in miRNA expression, perhaps through epigenetic mechanisms, could alter the fetal environment and lead to fetal programming.

Placental 11 β Hydroxysteroid Dehydrogenase

The placenta produces and metabolizes steroids, as reviewed.⁴⁴ A key step in steroid metabolism is the action of 11 β HSD type 2 to convert glucocorticoids to inactive metabolites.⁷⁰ The placenta in this capacity protects the fetus from excess active glucocorticoids because the maternal concentration of active glucocorticoids is 1000-fold higher than the concentration in the fetal circulation. Notably, glucocorticoids impair the expression and function of Glut glucose transporters,⁷¹ providing a direct connection between fetal nutrient supply and the activity of 11 β HSD2. Expression of this enzyme normally increases with gestational age,⁷² and 11 β HSD2 activity changes in response to hypoxia.⁷³ Importantly, there is a reduction in 11 β HSD2 enzyme expression and activity in placentas from preeclamptic women,⁷⁴ and the reduced activity may contribute to the abnormally high steroid levels in the fetus of preeclamptic women. Such higher than normal steroid levels could result in in utero programming changes of the hypothalamic-pituitary-adrenal (HPA) axis that last a lifetime because the HPA axis in the fetus normally develops independently of the effects of maternal stress steroid hormones.

The fetal HPA axis is especially influenced by alcohol exposure during pregnancy, with a higher HPA tone apparent in offspring exposed in utero to maternal alcohol abuse.⁷⁵ Alcohol crosses the placenta with impunity, as the lipophilic nature of this small molecule is amenable to rapid transit. Notably, alcohol dehydrogenase is present at low concentrations in the placenta but may be inducible in some patients.⁷⁶ The passage of alcohol to the fetus can modulate methyl group supply in cells⁷⁷ and can alter methionine metabolism to alter protein synthesis.⁷⁵ Alcohol thereby may yield long-lasting epigenetic changes in the fetus that manifest in adult life, through modulation of the HPA axis.

Glucocorticoids enhance differentiation in a variety of tissues, and the presence of higher than normal levels of these potent inducers of organ maturation may contribute to the long-term effects of in utero stress, even into the offspring's adult life. Suboptimal maternal dietary intake reduces placental 11 β HSD2 activity. This result can also lead not only to abnormally high fetal levels of glucocorticoids, which modulate the fetal HPA axis long term, but also to effects on differentiation of other fetal organs, if exposed at critical stages of development. A case in point is kidney development in a sheep animal model,⁷⁸ where transient exposure to exogenous steroids reduces nephron numbers in the fetus and predisposes to kidney disorders and hypertension as adults.

The short- and long-term effects of reduced placental 11 β HSD2 activity, excess maternal stress hormones, or a combination of these clearly contributes to fetal programming and subsequent adult disease, and placental dysfunction is often central to the effects induced.

NUTRIENT SUPPLY EFFECTS ON FETAL PROGRAMMING

The fetus depends on nutrients for growth, and the placenta mediates the transfer of nutrients from ~10 weeks of gestation until delivery, as previously discussed and reviewed in Jansson and Powell.⁷⁹ Placental supplied nutrient availability for fetal growth relates to multiple parameters, including the metabolism of the placenta itself, the mass and surface area of placental villi, blood flow into and out of the placenta, the concentration gradient between maternal and fetal circulations, and the expression and activity of rate-limiting transporters and binding proteins in the syncytiotrophoblast layer.⁴ Function of the syncytiotrophoblasts in hormone production and substrate metabolism is also crucial. Placental metabolism of substrates otherwise destined for the fetus may be regulated in response to demands.⁸⁰ Importantly, villous trophoblasts in placentas exposed to environmental insults express altered hormone production⁸¹ and mal-adaptive expression of nutrient transporters.⁸² Saudi Arabian babies who were in their second or third trimesters of gestation during Ramadan, a month-long period of daytime fasting for Muslims, had decreased placental weight and reduced ratio of placental to birthweight, although with unchanged birthweight, suggesting compensatory changes in placental efficiency.⁸³ Although not yet investigated, it will be important to see if there are any long-term consequences of this in utero nutritional stress.

Doppler studies of the maternal arcuate arteries and the fetal umbilical arteries show that blood flow into and out of the placenta is reduced in IUGR, compared with pregnancies with average for gestational age (AGA) growth. Whether this reduced flow, and thus nutrient delivery, accounts for the reduced growth of the fetus is debated, but ultimately it is unlikely because most substrates are not flow limited. However, it is noteworthy that glucose is a primary energy source, and glucose transport in villous explants from 6 to 8 weeks of gestation, but not in term villi, is regulated by insulin.⁸⁴ Thus the hyperinsulinemic state that characterizes the second half of pregnancy is unable to compensate and enhance glucose transport to the fetus if the placental or villous surface area(s) or Glut transporter function is inadequate for optimal fetal growth.

There is a concentration gradient for most amino acids between the maternal and fetal circulations that generally provides abundant substrates for protein synthesis in the fetus. However, the fetal circulation in IUGR has a reduced concentration of some amino acids compared with AGA fetuses.^{85,86} Concordantly, there is reduced activity in IUGR, compared with AGA, fetuses for system A, taurine, leucine, and cationic amino acid transporters.⁷⁹

Jansson and Powell⁸⁷ have proposed the intriguing model that the mammalian target of rapamycin (mTOR) signaling pathway is a nutrient sensor within the placenta. mTOR signaling influences the use of substrates for cell growth in a variety of systems, and this kinase integrates signals from growth factors, extracellular matrix, and nutritional substrates to optimize fetal growth. Importantly, extreme nutrient deficiency signals autophagy in cells through the mTOR pathway. mTOR also regulates system L amino acid transport in placental villi,⁸⁸ and we recently found that mTOR is involved with the response to hypoxia-induced autophagy in cultures of human trophoblast.⁸⁹ Localized trophoblast autophagy in vivo in response to exogenous stressors such as hypoxia, nutrient deprivation, or reactive oxygen species would temporarily benefit the fetus by providing critical substrates for ongoing growth in the presence of insufficient nutrient supply. However, this adaptive placental response may concurrently set the stage for fetal programming effects, as excessive autophagy would eventually yield placental dysfunction that would impact fetal development. Clearly, the roles of the mTOR pathway in sensing and responding to nutrient levels and stress, and in fetal programming, deserve further study.

FUTURE THERAPEUTIC POSSIBILITIES

The preceding review underscores the observation that fetal programming commonly associates with placental dysfunction. We have considered several clinical pheno-types for placental dysfunction that likely predispose to fetal programming. Some of these reflect abnormal development of the chorioallantoic placenta in size, shape, or histopathology. Others result when exogenous stressors in the maternal environment combine with maladaptation of the placental response to yield small placentas with limited reserve, as typical of early-onset IUGR and preeclampsia. Still others reflect epigenetic changes, imprinted gene expression, altered enzymatic activity, or nutrient transport deficiencies.

Although targeted modification of the placental development program is unlikely to be a clinical option in the foreseeable future, there may be some interventions that prove of benefit to reduce the effects of placental dysfunction and thus the predisposition to in utero programming of the fetus. A case in point is the fact that epigenetic changes are, by definition, reversible. Future therapeutic options for modulation of placental development may take the form of targeting individuals at high risk for IUGR or preeclampsia by increasing the administration of folate, B₁₂, or choline to influence methylation of DNA, histone proteins, or both. Further studies of animal models may also direct us to more targeted therapies that involve the insulinlike growth factors administered to enhance both placental and fetal growth. We clearly need more research into normal placental development and function, and into placental dysfunction that predisposes to in utero programming of adult diseases, before any therapy will become a clinical reality.³

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Figure 1.

Opportunities for fetal programming mediated by the placenta. Emerging possibilities, discussed in the text, indicate the placenta is an important mediator of the in utero environment predisposing to adult disease. Placental structure and function are affected by developmental plasticity, epigenetic effects, as well as by exogenous or endogenous stressors, nutrient limitation, or metabolic imbalances. The resulting placental dysfunction can affect fetal development in utero and predispose the adult to a variety of diseases. The placenta may be a possible target for clinical interventions in the future. 11 β HSD, 11 β hydroxysteroid dehydrogenase; mTOR, mammalian target of rapamycin.