Placenta and Reproductive Medicine

REVIEW ARTICLE

Placental biomarkers of fetal-originated diseases

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ABSTRACT

Fetal-originated diseases refer to birth defects of offspring and multiple chronic diseases in adulthood caused by abnormal embryonic development. However, due to the vulnerability of fetuses and newborns, as well as technical limitations, it is very difficult to carry out effective development assessment and early warning of long-term diseases in the early stages of life. It is known that the placenta is the unique link between the mother and the fetus, and its role in the occurrence and progression of fetal-originated diseases cannot be ignored. Studies have found that a variety of adverse environmental factors (such as nanoparticle exposure) cannot pass through the placental barrier, but can lead to fetal dysplasia and multi-organ development programming changes by affecting placental development, and ultimately mediate the occurrence of fetal-originated diseases. Meanwhile, some environmental factors that can pass through the placental barrier can cause placenta-fetal co-exposure, resulting in similar signaling pathways and epigenetic changes. The placenta originates from the fetus and the mother, and its development is accompanied by changes in indicators that can be objectively and quantitatively detected. These factors can be used as a biomarker to assess maternal exposure, and placental function, and to predict the developmental status and long-term disease susceptibility of offspring. To date, researchers have discovered a variety of potential placental biomarkers, and show promising application prospects. This paper reviews the recent research on placenta-related mechanisms leading to fetal-originated diseases and placental biomarkers, to provide the theoretical and experimental basis for early warning, prevention, and treatment of fetal-originated diseases.

Key words: placenta, adverse environment, fetal growth restriction, fetal-originated diseases, biomarkers

INTRODUCTION

The "Developmental Origins of Health and Disease (DOHaD)" theory proposes that experiencing adverse environments early in life increases the incidence of chronic diseases such as obesity, diabetes, and cardiovascular disease in adulthood.[1] Despite the developmental plasticity of fetal organs and systems, a variety of adverse environments can lead to irreversible changes in fetal development programming, laying the groundwork for adverse pregnancy outcomes and long-term disease susceptibility.[2] The placenta is the unique interface connecting the mother and the fetus. Functionally, the placenta sustains the growth of the fetus as it facilitates the delivery of oxygen and nutrients and the removal of waste products. Meanwhile, the placenta is an active endocrine organ, secreting a plethora of factors, such as steroids, glycoproteins, peptide hormones, cytokines, and neuroactive factors, that prevent immune rejection of the fetus and regulate the maternal pregnancy process and fetal development. In addition, the placenta is also a physical and biological barrier between the mother and the fetal circulatory system, which can protect the fetus from adverse

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environmental interference. When the placenta has abnormal morphology and functional damage, it is often accompanied by objectively and quantitatively detectable biochemical molecules, signal transducers, functional proteins, and epigenetic modification changes. These indicators can be used as placental biomarkers to evaluate placental function and fetal development, and even have the potential to predict the occurrence and progression of fetal diseases after birth. At present, the combination of magnetic resonance examination of placenta structure, placental biomarkers, and ultrasonic fetal bioassay has shown a strong ability to predict the occurrence of fetal growth restriction (FGR) and related complications. Meanwhile, the development of "multi-omics" technology offers great possibilities for the identification of novel biomarkers related to fetal growth. This review will discuss the placental origin of fetal-originated diseases and summarize the latest research on placental biomarkers to provide the theoretical basis for early warning and comprehensive prevention and treatment of fetal-originated diseases.

THE ADVERSE ENVIRONMENT DURING PREGNANCY LEADS TO THE OCCURRENCE OF FETAL-ORIGINATED DISEASES

The fetal-originated diseases refer to birth defects caused by abnormal embryonic development and a variety of chronic diseases in adulthood, such as diabetes, fatty liver, and osteoporosis.[3] In addition to genetic factors, the occurrence of fetal-originated diseases is largely affected by adverse environments and is closely related to altered programming of fetal development. The adverse environment during pregnancy can be divided into exogenous factors and maternal factors. It has been found that most of the adverse environmental factors can cross the placental barrier and directly affect embryonic or fetal development, such as polycyclic aromatic hydrocarbons,[4] particulate matter 2.5 (PM2.5),[5,6] dexamethasone,[7,8] heavy metals,[9,10] nicotine,[11,12] ethanol,[13] caffeine,[14,15] cocaine,[16,17] and opioids,[17–19] *etc.* Besides, some environmental factors that cannot cross the placental barrier can indirectly affect fetal development by disrupting the structure and function of the placenta, such as exposure to cobalt and chromium nanoparticles causing placental autophagic flow impairment and interleukin (IL)-6 release, which disrupts fetal astrocytes and neurons development.[20] This review lists some common adverse environmental factors and their effects on the early development and long-term health of offspring (Table 1). In summary, the adverse environment during pregnancy can lead to adverse pregnancy outcomes such as FGR and increased susceptibility to a variety of chronic diseases after birth by interfering with the developmental programming of multiple organs.

PLACENTAL ORIGIN OF FETAL-ORIGINATED DISEASES

At present, an increasing number of clinical and animal experimental studies have led to a deeper understanding of the biological mechanism of the developmental origin of diseases. The placenta plays an important role in the occurrence and progression of fetal-originated diseases, which means that there is a placental origin for fetal-originated diseases. In this review, we focus on the important role of the placenta in fetal-originated diseases.

Placenta and fetal growth

Slowed fetal growth occurs in about 10% of pregnancies, but only a few have a pathological background known as FGR or intrauterine growth retardation (IUGR). Studies have found that approximately 75% of FGR is due to abnormal placental development.[69] Changes in the shape and size of the placenta lead to a decrease in the volume, efficiency, and function of the placenta. The Helsinki Cohort Study showed that placental size is associated with fetal FGR,[70] possibly due to vascular dysplasia in the low-weight placenta, which impairs the exchange of oxygen and nutrients between mother and fetus.[71] The placenta has a variety of functions, such as transport, endocrine, barrier, and so on, and acts as the lungs, intestines, liver, and kidneys of the fetus during pregnancy. The proper development of the placenta is essential to ensure fetal growth, and the occurrence of FGR is closely related to placental dysfunction. This review summarizes the abnormalities of placental function associated with fetal-originated diseases (Table 2).

Placenta-fetal organ axis

The placenta originates from the trophectoderm of the blastocyst and shares the same genetic information and a similar developmental trajectory as the fetus. Some adverse factors that can cross the placental barrier, such as environmental pollution, endocrine disruptors, heavy metals, *etc.*, can cause synchronous destruction of the common development pathways of the placental and fetus, resulting in abnormal placenta-fetal development and susceptibility to long-term diseases. As research progressed, a close link between the placenta and the development of certain fetal organs (e. g., the brain and heart) was demonstrated, giving rise to terms such as the "placenta-brain axis" and the "placenta-heart axis".

Placenta-brain axis

It has been reported that the placenta protects and shapes the fetal brain through the "placenta-brain axis", mainly through its gas exchange, nutrient transport, and endocrine functions.[101] A study analyzed the differentially regulated receptor-ligand gene expression patterns

Table 1: Adverse environment during pregnancy and effects on early development and long-term health of offspring

Adverse environment type	Designation	Cross placental barrier	Effects on offspring development	Species	References
Environmental toxic substance	PAH	Yes	FGR; Behavior disorder, allergies, or asthma	Human	[21,22]
	1-NP	Yes	Interference with placental blood vessels and proliferation results in fetal growth restriction	Mice	[23]
	PBDE	Yes	FGR, Changes in placental methylation	Human	[24,25]
	DEHP	Yes	Interference with placental thyroid hormone receptor signaling results in FGR; Impaired male reproductive development and neurodevelopment	Mice	[26]
	Fenvalerate	Yes	Oxidative stress damage to the placenta; FGR	Mice	[27,28]
	Cadmium	Yes	Inhibits placental progesterone synthesis. Mitochondrial autophagy in placental trophoblast cells; FGR; Fetal liver and lung weight reduced	Mice	[9,10]
	Mercury	Yes	FGR; Anxiety-like behavior; Altered glucose metabolism; Insulin resistance	Human; Mice	[29,30]
	PM2.5	Yes	Low birth weight; cardiovascular disease in adults	Mice; Human	[5,6]
	Bisphenol A	Yes	FGR; Spiral artery remodeling; Testicular tumor	Mice	[31,32]
	Pesticide	Yes	Placental maturity and FGR	Human	[33]
	Phthalate	Yes	FGR	Human	[34]
	Tobacco smoke	Yes	FGR	Human	[35]
	Nicotine	Yes	FGR; The programmed changes of neuroendocrine metabolism in offspring rats; Fetal metabolomics changes	Rat	[11,12]
	Nanoparticles (cobalt and chromium)	No	Abnormal fetal neurodevelopment	Human; Mice	[20,36]
Drugs	Benzedrine	Yes	Preeclampsia, placental abruption	Human	[37]
	Dexamethasone	Yes	FGR; Multiple organ dysplasia	Mice; Human	[7,8]
	Acetaminophen	Yes	Childhood asthma	Human	[38]
	Cocaine	Yes	Spontaneous abortion; Stillbirth; Birth weight, head circumference, length, and Apgar score all decreased; Vascular dysfunction in adult offspring; Increased susceptibility to depressive and anxiety-like behavior, memory impairments, and epilepsy	Human; Rat	[39–41]
	Opiates	Yes	Neonatal abstinence syndrome; Low birth weight; Increased risk of spina bifida	Human;	[42–44]
	Marijuana	Yes	Low birth weight; Attention scores are worse in early childhood; Mid-childhood psychopathological symptoms Glucose metabolism dysfunction; cardiovascular disease	Human	[45–47]
	Methylamphetamine	Yes	Low birth weight; cardiovascular disease; Neurocognitive and behavioral deficits	Mice; Rat; Human	[48–50]
	Azithromycin	No	Low birth weight; Abnormal development of long bones, cartilage, liver, and gonads; Increased risk of spontaneous abortion	Mice; Human	[51,52]
	Insulin	No	neonatal hypoglycemia;	Human	[53]
Food and beverage	Alcohol	Yes	Fetal alcohol spectrum disorder	Human	[13]
	Caffeine	Yes	FGR; Dysfunction of adrenal steroid synthesis	Rat; Human	[14,15]
maternal health factors	Gestational hypertension/ Preeclampsia	-	FGR; Abnormal development of the fetal corpus callosum; Cardiovascular risk in children and young adults	Human	[54,55]
	Depression	-	Attention deficit/hyperactivity disorder symptoms in childhood	Human	[56]
	Gestational diabetes	-	Fetal overgrowth; Obesity; Lower insulin sensitivity; Cardiovascular risk from childhood to early adulthood; Neurocognitive and behavioral deficits	Human	[57,58] [57,59–62]
	Malnutrition	-	FGR; Hepatic metabolic changes; Cardiac development changes; Cognitive and neurodevelopmental impairments	Human; Rat	[63–66]
	Obesity	-	Non-alcoholic fatty liver disease; Neurodevelopmental disorders;	Human	[67,68]

PAH, polycyclic aromatic hydrocarbons; FGR, fetal growth restriction; 1-NP, 1-nitropyrene; PBDE, polybrominated diphenyl ethers; DEHP, diesters of phthalate; PM2.5, particulate matter 2.5.

Table 2: Fetal-originated diseases caused by placental dysfunction

Function	Mechanism	Pregnancy outcome and long-term disease	Species	References
Transport	mTOR inhibition reduces glutamine transport	FGR	Mice	[72]
	GLUT3 upregulated	FGR	Human; Mice	[73,74]
	Inhibition of amino acid transport expression	FGR	Human	[75–77]
	Down-regulation of Na^+/K^+-ATPase	FGR	Human	[78]
	Abnormal expression of fatty acid transporters	FGR	Human	[79,80]
	Abnormal expression of thyroid hormone transporters	FGR	Human	[81–83]
	Decreased lactate transport capacity	FGR	Human	[84]
Endocrine	Placental endocrine insufficiency	FGR; Anxiety-like behaviors, cognitive deficits, and atypical social behaviors increased	Mice	[85]
	Abnormal secretion of IGF-1	FGR	Human	[86,87]
	Lack of allopregnanolone	Autism spectrum disorder-like behaviors in male offspring	Mice	[88]
	Dysregulation of serotonin synthesis, metabolism, and transport in the placenta	FGR; Autism spectrum disorder and anxiety- and depression-like behaviors	Mice; Human	[89–92]
	The short leptin receptor and leptin expression were decreased	FGR	Rat; Human	[93,94]
Barrier	fibrin deposits and diffuse calcification	FGR	Human	[95]
	The expression of P-gp decreased	FGR	Rat	[96,97]
	Increased methylation and decreased expression of 11β-HSD2 in the placenta	FGR; Neonatal neurobehavioral changes; HPA axis changes, anxiety-like behavior, glucose intolerance in adult offspring	Human; Rat	[98–100]

mTOR, mammalian target of rapamycin; FGR, fetal growth restriction; GLUT3, glucose transporter 3; IGF-1, insulin-like growth factor-1; P-gp, p-glycoprotein; 11β-HSD2, 11β-hydroxysteroid dehydrogenase 2; HPA, hypothalamic-pituitary-adrenal.

between the fetal brain and placenta in *Foxa2* knockout mice and found that it is mainly associated with biological functions such as brain development, fetal response to oxygen, and regulation of synaptic transmission.[102] The placental vascular bed is the interface between the maternal and fetal and receives 25% to 32% of the total fetal cardiac output. Therefore, placental vascular abnormalities can have a significant impact on the overall circulatory function of the fetus, especially the blood flow to the central nervous system. Reports have shown that the occurrence, duration, and anatomical location of four types of severe placental fetal vasculopathy (including fetal thrombotic vasculopathy, chronic chorioamnionitis with occlusion fetal vasculopathy, chorioamnionitis with severe fetal vasculopathy, and meconium-associated fetal vascular necrosis) are highly correlated with neurological impairment and cerebral palsy.[103] It may be caused by poor perfusion of placental blood vessels, chronic inflammation, and hypoplasia of villi, which lead to impaired functional brain development by decreasing the oxygen delivery to the fetal brain.[103,104] In addition, Whitehead *et al.* reported a significant association between bleeding at the decidual-placental interface due to placental abruption and childhood epilepsy in a large population-based cohort study.[105] Fatty acids are important components of fetal brain adipose tissue, and n-3 and n-6 fatty acids can only be obtained from the maternal diet and transported to the fetal side through the placenta. Studies have found that long-chain fatty acid transport between mother and fetus is impaired in pregnancies associated with placental dysplasia (e. g., gestational diabetes mellitus, cadmium exposure) and affects fetal brain development and long-term health.[106,107] In addition to transferring nutrients and gases, the placenta produces a variety of neurotransmitters and hormones that can enter the fetal circulation and affect brain development, such as 5-hydroxy tryptamine (5-HT), dopamine, adrenaline/norepinephrine, and tetrahydroprogesterone, thereby affecting fetal neurogenesis and neuronal migration. It has been reported that maternal inflammation in the second trimester can lead to upregulation of 5-HT transformation in the mice placenta, inhibit the growth of endogenous 5-HT axons in the fetal forebrain, disrupt the fetal neurodevelopment process, which in turn affects adult brain functions, such as memory deficits.[108] This remarkable correlation between the placenta and the brain is known as the "placenta-brain axis" and has spurred the development of the field of placenta-neuro development.

Placenta-heart axis

The placenta is the "gatekeeper" of fetal heart development.[109] Cohort studies have shown a link between placental phenotypic characteristics and an increased risk of cardiovascular disease in adulthood.[70,110,111] Martyn *et al.* found that stroke and

coronary heart disease mortality tended to be highest in British men with low birth weight,[112] which was one of the first studies to link placenta to cardiovascular disease. Subsequently, the intricate relationship between the placenta and the fetal heart was highlighted in clinical cases of placental pathology. In placental dysplasia associated with FGR, inadequate remodeling of the uterine spiral arteries leads to poor placental perfusion and increased vascular resistance, which can impair placental endocrine and transport function.[113] Approximately 45% of the ventricular output of the fetal heart flows directly to the placenta, and a higher placental vascular resistance will result in an increased fetal cardiac load on the fetus. Therefore, placental abnormalities may disrupt the development of the heart by altering the hemodynamics and leading to fetal death.[114] The development of the placenta and the fetal heart are parallel, and the two organs share several developmental pathways and also have the same susceptibility to genetic defects, known as the "placenta-heart axis".[115–117] In early pregnancy, gene expression changes associated with angiogenesis and angiogenesis can lead to both placental and cardiac defects.[118] Currently, 329 genes have been identified through the mouse genome informatics database that can simultaneously cause placental morphology abnormalities and cardiovascular defects.[109] A single-cell sequencing analysis showed that cardiomyocytes, endothelial cells, and placental trophoblast cells share common expression genes and signaling pathways in early pregnancy. These genes and signaling pathways are essential for normal cell and organ function and have been implicated in coronary heart disease and placenta-related diseases.[119] For instance, the classical Wnt/β-catenin pathways are critical for placental development, implantation, and cardiac development in early pregnancy, and alterations in these pathways may lead to perturbations in the development of both organs simultaneously.[116]

Others

In addition to the placenta-brain axis and placenta-heart axis, there are also significant associations between the placenta and other tissues or organs, but due to the paucity of research, it is not widely recognized at present. For example, several population-based mother-child cohort studies have found that placental size is associated with skeletal development in the offspring,[120] and this association persists into childhood and even adolescence.[121,122] Transient receptor potential cation channel subfamily V member 5 (TRPV5) and TRPV6 are involved in calcium transport in the placenta and bone and can affect calcium homeostasis during both placental and fetal bone development.[123] In short, there may be interactions or similar changes and injuries between the placenta and various organs of the fetus in the intrauterine co-exposure environment, suggesting the existence of a "placenta-fetus organ axis".

PLACENTAL BIOMARKER TYPES

Biomarkers are objective measurements that allow the assessment of physiological activity, pathological progression, and pharmacological response.[124] Biomarkers are extremely valuable in both *in vivo* and *in vitro* experiments, as well as in the early efficacy and safety evaluation of clinical trials. The placenta produces a variety of important substances that enter the maternal circulation to maintain a normal pregnancy. In response to adverse environmental, significant molecular changes in the placenta may indicate specific fetal pathological features. Although there are still no placental biomarkers for predicting fetal-originated diseases for clinical use, detection of placenta-derived substances in maternal blood (such as bioactive peptides and subcellular fragments), or detection of placental gene expression patterns after delivery (such as epigenetic modifications) can be useful for indicating fetal multiple organ development abnormalities or predicting future susceptibility to fetal-originated diseases. Here we list some types of placental biomarkers that can be used to monitor placenta-fetal development in real time or to predict future disease occurrence in offspring.

Bioactive peptides

The placenta produces a variety of bioactive peptides that contribute to maternal adaptation to pregnancy. It has long been suggested that the detection of placenta-derived bioactive peptides in maternal blood may provide diagnostic or prognostic value for pregnancy complications. For example, the detection of placenta-secreted human chorionic gonadotropin (hCG) in maternal blood is used to confirm pregnancy, detection of placenta-derived angiogenesis regulator soluble fms-like tyrosine kinase 1 (sFLT1) and placental growth factor (PlGF) in maternal blood can be used to predict preeclampsia (PE). Some researchers have also combined molecular tracking techniques and bioinformatics analysis to integrate the secreted protein maps of human and mouse placentas, validating in clinical cases that detection of the relative abundance of secreted placenta proteins at 12 weeks of gestation can be used for the early diagnosis of pregnancy complications, and identified a variety of factors that may affect placental hormone expression and pregnancy outcome.[125] With the deepening of research, a variety of bioactive factors secreted by the placenta (Pregnancy-associated plasma protein A [PAPP-A], sEng, insulin-like growth factor [IGF], A disintegrin and metalloproteinase [ADAM12], Placental protein 13 [PP-13], *etc.*) are useful for monitoring fetal development and are expected to be early predictive biomarkers of FGR, although their applicability as clinical markers needs

more verification.[126–128]

Subcellular fractions

Several emerging technologies are being used to monitor or assess fetal development. For example, subcellular fractions derived from the placenta or fetus in the maternal circulation can be detected, including cell-free DNA (cfDNA), RNA, and miRNA. Studies as early as 1997 and 2000 have found the presence of fetal DNA and RNA in maternal blood.[129,130] Maternal blood cfDNA, derived primarily from placental trophoblasts and maternal hematopoietic cells, contains a nucleosome footprint that carries information about its origin tissue and gene expression, which allows for non-invasive monitoring of pregnancy-related complications and has the potential to predict adverse pregnancy outcomes. Placental mRNA in maternal plasma is a stable and easily detectable subcellular fraction. In 2004, Tsui *et al.* systematically evaluated the expression profiles of placental tissues by microarray analysis and demonstrated that placental gene expression levels exceeding a specific threshold can usually be detected in maternal plasm.[131] Some of these placental-specific mRNAs, including chorionic growth hormone 1, placental growth hormone 2 (PGH_2), kisspeptin-1 (KISS1), and A disintegrin and metalloprotease (ADAM-12) are functionally associated with fetal or placental development. Non-invasive aneuploidy detection techniques based on cfDNA in maternal plasma and placental mRNA have made great progress over the past decade.[132] Placental miRNAs are released by exosomes and exported from the syncytiotrophoblast into the maternal circulation. A study found that 17 miRNAs were present in the placenta at concentrations at least 10-fold higher than those in maternal blood and were undetectable in maternal plasma after delivery, with miR-141, miR-149, miR-299–5p, and miR-135b being the four most abundant placental miRNAs present in maternal plasma.[133] In a case-control study, miRNAs in the plasma of PE and healthy pregnant women were examined using droplet digital PCR, and elevated levels of placenta-specific miR518b were found and could be used as a potential biomarker for PE.[134] Given that miRNAs are stable in plasma, detection of placental-derived miRNA expression can be used to assess placental and fetal development and is expected to be a biomarker. In summary, by directly targeting the analysis of fetal/placental DNA and RNA in maternal plasma (rather than the indirect analysis of placental proteins), a more definitive diagnosis can be produced, and this non-invasive assay offers the possibility to assess the occurrence of fetal-originated diseases.

Epigenetic modification changes

The placenta is a more accessible tissue than the fetus and has unique global and site-specific DNA methylation patterns. Unlike embryonic cells (inner cell mass), cells of the trophectoderm (cells that develop into the placenta) do not undergo extensive remethylation after demethylation, thus maintaining a genome-wide hypomethylated state.[135] Since placental DNA methylation may result from the hypomethylation of the early embryo, the disturbance of the specific DNA methylation pattern may reflect the abnormal programming of early embryonic development. A growing number of studies have found that detecting the DNA methylation characteristics of the placenta can serve as a biomarker to predict long-term diseases.[136–139] Histone modification is involved in gene transcriptional regulation, and abnormal histone modification status is commonly implicated with pregnancy-related diseases and placental dysplasia. A genome-wide analysis of healthy human placentas and FGR placentas showed that changes in placental histone 3 lysine 27 acetylation are associated with placental function and early fetal development.[140] Therefore, epigenetic results of gene-environment interactions in the placenta may serve as biomarkers for abnormal fetal development and susceptibility to long-term diseases.

Combined screening of maternal characteristics, serum biomarkers, and fetal biometric parameters

At present, the sensitivity and specificity of clinical detection methods for FGR are not ideal. It is estimated that close to 50% of FGR cases are missed prenatally.[141] Fetal biometric parameters (ultrasound measurements) could not distinguish healthy but small fetuses from FGR fetuses. There are also no serum biomarkers that are accurate enough to be used clinically as a single predictive marker. Therefore, many researchers have proposed combined models to obtain better predictive values. The combined screening approach can reflect a variety of pregnancy conditions: maternal characteristics (such as gestational age and disease) can help identify high-risk individuals and be closely monitored, Doppler ultrasound of the uterine artery can indicate the adequacy of spiral arterial infiltration, and biomarker levels reflect impaired placental secretory function. Several studies have found that using a combination of maternal characteristics, serum biomarkers, and fetal biometrics may improve predictive correlations.[142–144]

PLACENTAL BIOMARKERS OF FETAL-ORIGINATED DISEASES

Current clinical detection techniques are still suboptimal in identifying the risk of FGR and predicting long-term diseases, so there is an urgent need to explore more potential biomarkers and detection techniques for early identification of fetal dysplasia, timely improvement of pregnancy outcomes, and intervention of long-term

disease susceptibility.

Placental biomarkers of fetal growth restriction

FGR is a leading cause of stillbirth and is strongly associated with increased perinatal morbidity. There is no effective intrauterine treatment, so it relies on early detection and timely delivery. Some specific factors reflecting placental and fetal development can be secreted into the maternal circulation, and these specific factors have the potential to be biomarkers for early diagnosis of FGR (Table 3).

Pregnancy-associated plasma protein-A

Pregnancy-associated plasma protein-A (PAPP-A) is a protein hydrolase produced by the placenta, and its plasma level depends on placental volume and function. In 2005, A study of 4, 390 women with single pregnancies showed that low levels of maternal PAPP-A during 11–13 weeks of gestation were significantly associated with adverse pregnancy outcomes.[163] Cohort studies have shown that low levels of PAPP-A in maternal blood are associated with neonatal birth weight, gestational age, and preterm birth and that β-hCG is an independent predictor of gestational hypertension and PE.[164,165] Notably, although PAPP-A has a certain detection sensitivity for the occurrence of FGR, its predictive power is not sufficient for screening for FGR alone. Since then, a prospective cohort study was established to evaluate a multiparametric screening model in which maternal blood PAPP-A, β-hCG, maternal mean arterial pressure, and uterine artery Doppler parameters increased the sensitivity of the detection of early-onset small for gestational age (SGA) infants to 73%. However, the detection sensitivity of late-onset SGA was low (Table 4).[166]

Pro-angiogenic and anti-angiogenic factors

The placenta is one of the most vascularized organs. The imbalance between pro-angiogenic and anti-angiogenic factors is thought to be an important trigger for placental dysfunction and FGR. Soluble endoglin (sEng) is a placental-derived anti-angiogenic factor. A prospective case-control study showed that maternal plasma biochemical parameters (sFlt-1, sEng, and PAPP-A) combined with uterine artery Doppler parameters provide a better prediction of the degree of placental vascular injury and assess the risk of fetal FGR.[126] Longitudinal case-control studies have also demonstrated that imbalances in maternal PlGF and anti-angiogenic factors (sEng and sVEGFR-1) increase the risk of delivering SGA newborns and/or the occurrence of PE. Continuous determination of PlGF, sEng, and soluble vascular endothelial growth factor receptor 1 (sVEGFR-1) in early and second trimesters is valuable for the risk assessment of PE and SGA.[167] Vascular endothelial growth factor (VEGF) plays a vital role in placental vasculogenesis and angiogenesis. Clinical studies have shown that VEGF levels in maternal blood and placenta are positively correlated with neonatal birth weight and may have the potential to predict the occurrence of FGR.[153,168] Another study also showed that maternal peripheral blood VEGF levels exhibited the highest predictive value for increased risk of FGR in the third trimester.[152] In addition, serum soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1), which reflects vascular endothelial function, also have the potential to predict pregnancy comorbidities and adverse pregnancy outcomes. In a prospective longitudinal study, sICAM-1 and sVCAM-1 in maternal circulation during mid-gestation were highly predictive of PE or other pregnancy comorbidities in late-gestation, with predictive sensitivities of 50% and 46% for FGR and preterm labor, respectively.[161]

Insulin-like growth factor and its receptor and binding protein

IGF and its receptors and binding proteins can be expressed in the placenta and released into the maternal circulation. There is growing evidence that abnormal expression of IGF-related genes is involved in the occurrence of FGR. A prospective cohort study that collected consecutive maternal samples from a low-risk population at 28 weeks gestation and followed fetal growth until delivery found that the mRNA expression of six growth factors (including IGF1, IGF2, PGH, IGFBP2, IGF1R, ADAM12) was dysregulated in the blood of mothers carrying severely preterm fetuses with FGR. Notably, as early as 28 weeks of gestation, the mRNA that codes for growth genes in the maternal circulation was dysregulated.[87] It suggests that measurement of IGF-related genes at 28 weeks of gestation, even when an ultrasound shows normal fetal size at that time, can identify pregnancies at risk for full-term FGR and may be a novel biomarker for predicting and diagnosing FGR. IGF binding protein-4 (IGFBP-4) is involved in the regulation of IGF bioavailability. Maternal serum IGFBP-4 levels may be implicated in abnormal placental growth and fetal development and have the potential to be an early biomarker of FGR.[155] Placental growth hormone (PGH) and a disintegrin and metalloprotease 12 (ADAM12) are placental-derived growth factors that are also involved in the regulation of IGF-related signaling pathways. It was found that PGH_2 mRNA levels in the maternal circulation may be related to fetal growth and are significantly correlated with fetal biometrics and birth weight.[156] However, another study suggested that maternal serum PGH at 11–13 weeks of gestation is unlikely to be a useful biochemical marker

Table 3: Potential placental biomarkers of fetal growth restriction in humans

Placental biomarkers	Detection sample	References
PlGF/sFlt1	Maternal plasma	[145–147]
PAPP-A	Maternal plasma	[127,148]
sEng	Maternal plasma	[149–151]
VEGF	Placenta/ Maternal plasma	[152,153]
IGF2	Maternal plasma /Placenta	[87,154]
IGFBP-4	Placenta	[155]
ADAM12	Maternal plasma	[127,148]
PGH	Maternal plasma	[87,156]
SPINT1	Maternal plasma	[157–159]
DLK1	Maternal plasma	[160]
sICAM-1, sVCAM-1	Maternal plasma	[161]
PP-13	Maternal plasma	[128,162]

PlGF, placental growth factor; sFlt1, soluble fms-like tyrosine kinase 1; PAPP-A, pregnancy-associated plasma protein-A; sEng, soluble endoglin; VEGF, vascular endothelial growth factor; IGF2, insulin-like growth factor 2; IGFBP-4, IGF binding protein-4; ADAM12, a disintegrin and metalloprotease 12; PGH, placental growth hormone; SPINT1, serine peptidase inhibitor Kunitz type 1; DLK1, delta-like noncanonical Notch ligand 1; sICAM-1, serum soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; PP-13, placental protein.

Table 4: Potential human placental biomarkers of fetal-originated diseases in humans

Long-term disease		Placental biomarkers	Detection object	References
Cardiovascular system	Heart development	DNA methylation of HEY2, ISL1, SRF, ACTC1, HEYL	Placenta	[139]
	Ventricular septal defect	miR-191, miR-548F1, miR-148A, miR-423, miR-92B, miR-611, miR-2110, miR-548H4	Placenta	[139]
	Tetralogy of Fallot	DNA cytosine methylation of ARHGAP22, CDK5, TRIM27, IER3	Placenta	[175]
	Congenital heart disease	DNA methylation of TLL1, CRABP1, FDFT1, PCK2	Placenta	[176]
	Conical heart defect	DNA methylation of HOXD9, CNN1, NOTCH1, ECE1	Placenta	[177]
Neurological behavior	Autism spectrum disorder	DNA methylation of CYP2E1 and IRS2	Placenta	[138]
	Autism spectrum disorder	Expression of NHIP gene	Placenta	[178]
	Autism spectrum disorder	DNA methylation changes of NOS1AP, MOSPD1, AFAP1L2, GRIPAP1	Placenta	[179]
	Adverse neurobehavioral outcomes	DNA methylation of HSD11B2	Placenta	[98, 180]
	Schizophrenia	ZNF664, KLC1, MAN2A2, CTDSPL, MSI2	Placenta/ Maternal plasma	[181]
	Neurobehavioral changes at birth	miR-509–3p and miR-193b-5p	Placenta	[182]
	Neurodevelopmental disorders	OGT	Placenta	[183, 184]
Others	Pulmonary development	DNA methylation changes of JAK2	Placenta	[185, 186]
	Cryptorchidism and hypospadias in neonates	Antiandrogen activity or exogenous estrogen levels	Placenta	

HEY2, hairy and enhancer of split-related with YRPW motif 2; ISL1, LIM-homeodomain transcription factor Islet-1; SRF, serum response factor; ACTC1, cardiac alpha-actin; HEYL, hairy and enhancer of split-related with YRPW motif-Like; ARHGAP22, RhoGAP protein; CDK5, cyclin-dependent kinase 5; TRIM27, tripartite motif-containing 27; IER3, immediate early response 3; TLL1, tolloid-like 1; CRABP1, cellular retinoid-binding protein 1; FDFT1, farnesyl-diphosphate farnesyltransferase 1; PCK2, phosphoenolpyruvate carboxykinase; HOXD9, homeobox D9; CNN1, calponin 1; NOTCH1, Notch receptor 1; ECE1, endothelin converting enzyme-1; CYP2E1, cytochrome P450 2E1; IRS2, insulin receptor substrate 2; NHIP, LOC105373085; NOS1AP, nitric oxide synthase-1 adaptor protein; MOSPD1, major sperm protein domain□ containing proteins 1; AFAP1L2, actin filament associated protein 1 like 2; GRIPAP1, GRIP1 associated protein 1; HSD11B2, 11beta-hydroxysteroid dehydrogenase type 2; ZNF664, zinc finger protein 664; KLC1, kinesin light chain 1; MAN2A2, mannosidase alpha class 2A member 2; CTDSPL, CTD small phosphatase like; MSI2, musashi RNA binding protein 2; OGT, O-GlcNAc transferase; JAK2, Janus kinase 2.

for early prediction of SGA.[169] Maternal ADAM12 and PAPP-A concentrations were reduced in SGA and all neonates weighing less than 2.5 kg, with a linear relationship between the severity of FGR and reductions in ADAM12 and PAPP-A.[148] In early pregnancy screening, the detection rate of FGR using a

combination of maternal blood PAPP-A, ADAM12 levels, and uterine artery Doppler analysis was 68%.[127]

Others

There are also several bioactive factors derived from the placenta that can predict FGR, but fewer studies have been published and their application in the diagnosis of FGR remains to be explored. For example, delta-like noncanonical Notch ligand 1 (DLK1) is a cell growth regulator. Clinical and rodent studies have shown that placental and fetal-derived DLK1 in the maternal circulation may serve as a potential marker of FGR and SGA.[160,170] However, other studies have concluded to the contrary, that although circulating DLK1 levels are reduced in mid-gestation in pregnant women delivering newborns with SGA, DLK1 alone does not predict the occurrence of SGA.[171]

Serine peptidase inhibitor Kunitz type 1 (SPINT1) is a highly expressed placental protein. Prospective cohort studies have identified low-circulating SPINT1 as a marker of placental insufficiency and a novel biomarker for predicting fetal dysplasia. SPINT1 has a positive predictive value ranging from 10% to 38% for newborns below the 3rd, 5th, and 10th percentiles of birth weight.[157,158] In addition, it has been noted that SPINT2 can also be used as a biomarker to identify pregnancies with an elevated risk of stillbirth, such as PE combined with FGR, but its predictive potential for FGR is lower than that of its homolog, SPINT1.[159]

PE is a pregnancy complication involving placental impairment and/or placental dysfunction that can lead to an increased risk of FGR.[172] Placenta-derived PlGF and sFlt-1 in maternal blood have been recommended by several countries and organizations as diagnostic and/or predictive biomarkers for PE.[173] Some studies have also found that the sFlt-1 / PlGF ratio can be used both for the diagnosis of PE and to predict the occurrence of PE-induced FGR, but its predictive potential is controversial.[145–147]

Placental protein 13 (PP-13) is highly expressed in the placenta and is involved in placental implantation, vascular invasion, and remodeling. Chaftez *et al.* found that low levels of PP-13 in early pregnancy had a detection sensitivity of 79% for PE, 33% for IUGR, and 28% for preterm birth, respectively.[128] In another study, based on a 5% fixed false positive rate, the sensitivity of maternal circulating PP-13 in early pregnancy to PE, early-onset PE, and SGA was 24%, 45%, and 26%, respectively.[162]

In addition, a large-scale retrospective study in 2020 sequenced the whole genome of maternal plasma cfDNA from 2, 199 pregnancies and found different cfDNA promoter coverage patterns between healthy and pregnancies with comorbidities (macrosomia, FGR, gestational diabetes mellitus, and PE).[174] In the construction and validation of classifiers based on a literature search, it was found that the prediction accuracy of multi-gene combinations for FGR could reach 70.0% to 79.5%.

In summary, the in-depth study of placental biomarkers is highly likely to develop early warning and prevention measures for FGR, which will help to improve adverse pregnancy outcomes and ensure normal fetal development.

Placental biomarkers for long-term diseases

Given the existence of the placenta-fetal organ axis and the synchronous disruption of placental and fetal development in response to adverse environmental exposures, placental biomarkers may have the potential to predict the occurrence of long-term diseases. Given the existence of the placenta-fetal organ axis and the synchronous disruption of placental and fetal development in response to adverse environmentalexposures, placental biomarkers may have the potential to predict the occurrence of long-term diseases (Table 4).

Cardiovascular system diseases

Currently, there are no biomarkers available in clinical practice for the prenatal or postnatal detection of congenital heart defects. Studies of the Helsinki birth cohort have found that placental phenotypic characteristics such as size, shape, and efficiency are strong predictors of cardiovascular disease in offspring.[70,110,111] It is reported that in the placenta of the fetal ventricular septal defect (VSD), there was likely to be a significant minority of cytosine loci in which parallel or correlated epigenetic modifications could be identified in cardiac development genes in general and specific genes related to ventricular development in the placenta from VSD pregnancies, and ultimately the study identified 1, 488 unique loci (one per gene).[139] These loci were significantly differentially methylated in VSD placenta, with 80 highly accurate potential cytosine-guanine (CpG) sites are available for detection of VSD (AUC= 1.0 at FDR $P < 0.005$), including genes involved in ventricular development (HEY2, ISL1), cardiac circulation (SRF), cardiomyocyte differentiation (ACTC1, HEY2), and cardiac septal development (ISL1), cardiac morphogenesis (SRF, HEY2, ISL1, HEYL), Notch signaling pathway (HEY2, HEYL), cardiac ventricular development (ISL1) and myocardial tissue development (ACTC1, ISL1). In addition, methylation changes in 8 miRNAs (including miR-191, miR-548F1, miR-148A, miR-423, miR-92B, miR-611, miR-2110, and miR-548H4) were identified alter cardiac development programming at the post-transcriptional level and serve

as biomarkers for predicting fetal VSD. A retrospective study identified several novel placental CpG biomarkers with excellent predictive accuracy (AUC $\geqslant$ 0.95; 95% CI) for tetralogy of Fallot, where the four CpG loci with the best predictive performance were located on the ARHGAP22, CDK5, TRIM27, and IER3 genes.[175] In addition, abnormal DNA methylation levels of TLL1, CRABP1, FDFT1, and PCK2 in placental tissue are also closely related to fetal congenital heart disease.[176] Another clinical study also found that altered DNA methylation levels of HOXD9, CNN1, NOTCH1, and ECE1 in the placenta are associated with conotruncal heart defects and may be used as potential epigenetic biomarkers to detect conotruncal heart defects.[177]

Nervous system diseases

The brain is one of the organs most susceptible to the effects of the placenta, and the origin of multiple neurobehavioral disorders may be attributed to pathological changes in the placenta.[190,191] Placental lesions (such as increased syncytial knots, and chorioamnionic edema) as predictors of cerebral palsy and neurocognitive abnormalities in very low birth weight school-age children.[192] A prospective cohort study found that DNA methylation levels of placental cytochrome P450 2E1 (CYP2E1) and insulin receptor substrate 2 (IRS2) may serve as early warning indicators of autism in children.[138] Another study that conducted a full methylomics analysis of placentas in the prospective MARBLES cohort found that methylation levels of placental CYP2E1 and IRS2 DMR were genetic and environmental modifiers associated with a high risk of autistic spectrum disorder (ASD), which is expected to serve as a biomarker for early intervention and prevention of ASD.[138] In addition, a novel gene, LOC105373085 (renamed NHIP due to neuronal hypoxia induction), present within chromosome 22q13.33, is expressed in both the placenta and neurons in response to hypoxia and may be a new gene regulatory locus for ASD.[178] Another genome-wide methylation analysis of full-term placental tissue for ASD subtypes identified five placental markers with high accuracy for ASD: NOS1AP, MOSPD1, AFAP1L2, and GRIPAP1.[179]

A transcriptome-wide association study of healthy full-term placentas (N= 147) screened for multiple candidate placental genes associated with offspring schizophrenia: ZNF664 (preferred), KLC1, MAN2A2, CTDSPL, and MSI2, which can be detected in maternal blood (cfRNA) and can be used to predict pregnancy outcomes or offspring schizophrenia.[181] In addition, placental 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) expression was affected by the intrauterine environment, and its DNA methylation was correlated with neonatal neurobehavior. Assessing the degree of HSD11B2 (11β-hydroxysteroid dehydrogenase 2 coding gene) methylation in the placenta can prospectively predict psychological, behavioral, and cognitive problems in later childhood.[98,180] miRNAs also have the potential to predict neurological disorders in offspring. A study of full-term placentas found that increased placental miR-16 expression was negatively associated with neonatal attention scores and miR-146a and miR-182 were positively correlated with neonatal motor quality scores.[193] Another observational study also showed that altered placental miR-509–3p and miR-193b-5p abundance associated with cadmium exposure may be predictive of atypical neurobehavioral outcomes in newborns.[182]

Others

The main determinant of intrauterine bone mineralization is fetal blood calcium concentration, which is dependent on placental calcium ion transport. A cohort study suggests that IUGR placenta size and impaired mineral supply are associated with reduced bone size after birth and an increased risk of long-term fracture.[122] It has also been shown that the mRNA expression level of calcium transporter proteins in the placental basal membrane is positively correlated with the whole-body bone mineral content of offspring.[194] Although the mechanism is unknown, it can be evaluated as an independent risk factor for poor fetal bone growth, short stature in childhood, and increased susceptibility to osteoporosis in adulthood, and provides new ideas for the study of placental biomarkers.

Boys with low placental weight at birth have a higher risk of cryptorchidism and hypospadias, according to a Danish cohort study.[187] A case-control study found that antiandrogen biological activity in the placenta at delivery was significantly associated with the risk of neonatal cryptorchidism/hypospadias in males and may be a biomarker for genitourinary malformation.[188] In addition, a prospective maternal and infant cohort study also suggests that the concentration of exogenous estrogen accumulated in the placenta may play a role in assessing and predicting the risk of cryptorchidism and/or hypospadias.[189]

In summary, although the development process of the placenta is not entirely consistent with that of the fetus, the molecular characteristics of the placenta may reveal the intrauterine development and long-term health outcomes of the fetus to a certain extent. Although the specific mechanisms by which the placenta-fetal organ axis exerts its influence are unknown, numerous current studies have provided strong evidence for a link between placental response and offspring health/disease status and may serve as biomarkers to identify which children are at risk of fetal-originated diseases.

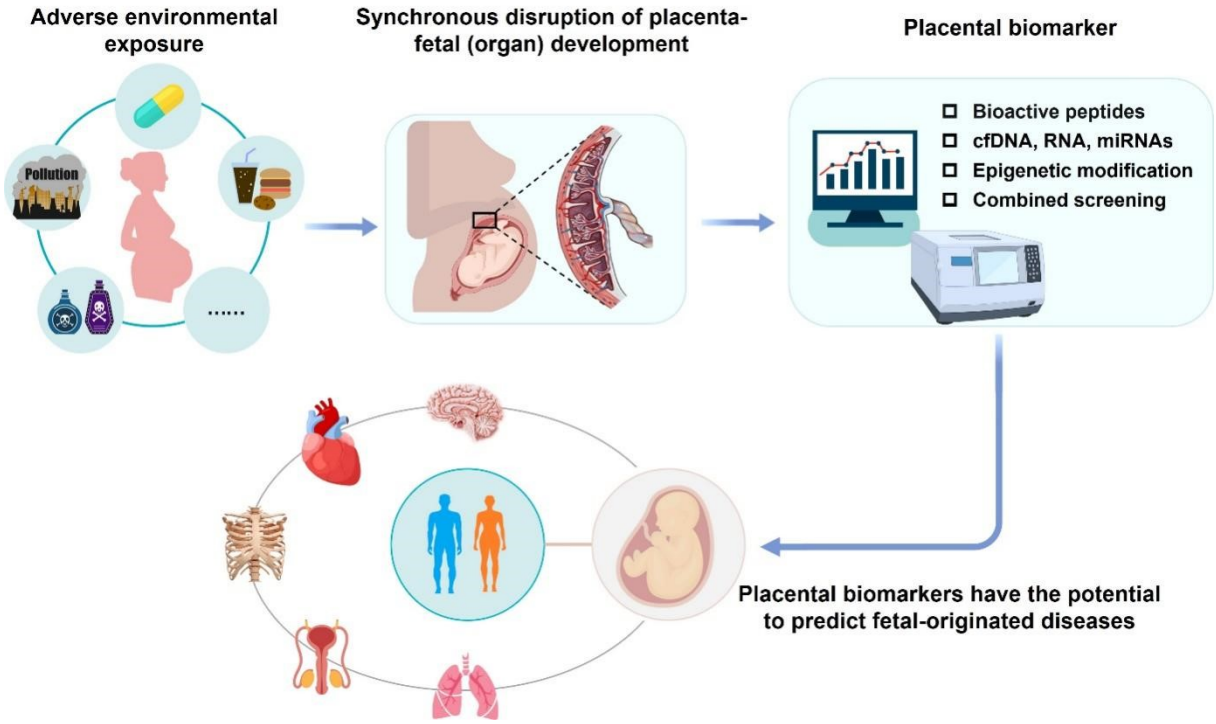

Figure 1. Placental biomarkers have the potential to predict susceptibility to fetal-originated diseases.

SUMMARY AND PROSPECT

In conclusion, adverse environments can lead to fetal dysplasia and susceptibility to a variety of fetal-originated diseases by affecting placental development or synchronously disrupting placental-fetal development. Biomarkers that can reflect placental dysfunction can be used for non-invasive detection of fetal organ development and have the potential to predict susceptibility to fetal-originated diseases (Figure 1). However, the mechanisms underlying the susceptibility to fetal-originated diseases due to abnormal placental development are not well understood, and the targets that have been established all have significant limitations. Before these new findings can be translated into clinically relevant technologies, more basic research is needed to further explore the pathogenesis and key targets. An increasing number of "candidate" biomarkers will be identified as a result of continued research into the mechanism of placenta origin of fetal-originated diseases and the ongoing development of related experimental technologies. This will pave the way for the early diagnosis, multi-organ development assessment of offspring, early warning, and comprehensive prevention and treatment of fetal-originated diseases.

DECLARATION

Author contributions

All authors were involved in preparing the manuscript with contributorship: Conception and design PY, SC, HW; Manuscript draft PY, SC; Critical revision of manuscript PY, HW.

Ethics approval

Not applicable.

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Conflict of interest

The authors in preparing this manuscript did not receive any compensation from any source and declare that they have no potential conflict of interest. None of the authors have been involved in legal or regulatory matters related to the paper's contents. All authors approved the final manuscript draft and are fully responsible for the writing and content of the manuscript.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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