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Advanced MR Imaging of the Placenta: Exploring the in utero placenta-brain connection

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Abstract

The placenta is a vital organ necessary for the healthy neurodevelopment of the fetus. Despite the known associations between placental dysfunction and neurologic impairment, there is a paucity of tools available to reliably assess in vivo placental health and function. Existing clinical tools for placental assessment remain insensitive in predicting and assessing placental well-being.

Advanced MRI techniques hold significant promise for the dynamic, non-invasive, real-time assessment of placental health and identification of early placental-based disorders. In this review, we summarize the available clinical tools for placental assessment including ultrasound, Doppler, and conventional MRI. We then explore the emerging role of advanced placental MR imaging techniques for supporting the developing fetus, appraise the strengths and limitations of quantitative MRI in identifying early markers of placental dysfunction for improved pregnancy monitoring and fetal outcomes.

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Keywords

Placenta; Magnetic Resonance Imaging; Fetal Brain

Introduction

Fetal brain development undergoes exponential growth throughout gestation, with highly prescribed developmental changes during each trimester, all of which require substantial nutrient and metabolic support (1). The placenta plays a critical role for oxygenation of the fetus. However, the relationship between oxygen availability and placental development and function is highly complex, and incompletely understood. In the healthy pregnancy, the placenta not only provides maternal-fetal transit of essential metabolites and clearance of toxic substances, but also serves important immune and neuroendocrine functions that are necessary to support normal fetal brain development (2–7). Acute and chronic disruptions of normal placental development and function are associated with adverse neurologic outcomes in the term and preterm infant. Placental abruption, complete umbilical cord occlusion, or fetal hemorrhage are acute processes that can result in severe hypoxic-ischemic brain injury in the term or preterm infant prior to delivery, increasing the risk of cerebral palsy and permanent neurologic injury. Placental vascular lesions, such as fetal thrombotic vasculopathy, chronic villitis with obliterative fetal vasculopathy, chorioamnionitis with severe fetal vasculitis and meconium-associated fetal vascular necrosis, are highly correlated with neurologic impairment and cerebral palsy (8). In the term population, infants presenting with neonatal encephalopathy and later diagnosed with cerebral palsy are four times more likely to demonstrate placental infarcts on pathology than infants with normal placentas (9). Similarly, 87% of term infants with neonatal encephalopathy and evidence of injury on brain MRI show evidence of placental anomalies on histopathology (10). Multiple studies also have described increased seizure risk in term infants born with chorioamnionitis (11–13). Furthermore, placental anomalies have also been implicated in the development of perinatal stroke of term and near-term infants (14–16).

Placental dysfunction has also been related to neurodevelopmental injury in the preterm and low birth weight infant. Premature birth alone is a major independent risk factor for brain injury including cognitive, motor and behavior deficits (17). Intra-amniotic infection and chorioamnionitis account for up to one fourth of preterm deliveries (18, 19). The resulting fetal inflammatory response, particularly fetal vasculitis on placental pathology, is an independent risk factor for brain injury, including cerebral palsy (19–21). Infants born small for gestational age (SGA) or with fetal growth restriction (FGR) are also at significantly increased risk for neurodevelopmental disorders when compared to infants with appropriate for gestational age (AGA) birth weights (22–27). While there are numerous causes for impaired growth during pregnancy, the most common identifiable cause of SGA or FGR remains placental insufficiency with or without maternal vascular disease (28–31).

Despite significant evidence linking placental health with normal fetal brain development and satisfactory perinatal transitions, much of the available literature comes from epidemiologic, retrospective and histopathologic data. In this review we will briefly

summarize the role and current limitations of ultrasound/Doppler in the evaluation of the placenta. We will then provide a critical appraisal of conventional magnetic resonance imaging (MRI) in assessing placental structure and explore the emerging role of advanced MRI techniques for measuring placental growth, development, perfusion and diffusion.

The Role of Ultrasound in Placental Evaluation

Although a comprehensive appraisal of the role of ultrasound in evaluating placental health and wellness is beyond the scope of this review, a brief overview is warranted.

Current Clinical Standard of Placental Imaging

Ultrasound (US) has been the mainstay of in vivo placental evaluation for over thirty years, primarily given its safety profile, ease of accessibility and relative cost (32, 33). US features of the placenta and cord have been well described; while the placenta may be visualized as early 10 weeks gestation, it is most consistently visualized after 15 weeks (34). As the healthy placenta matures throughout gestation, there are accompanying changes detectable by US. These changes include progressive increases in thickness and length, as well as qualitative changes in echogenicity and shape (34). Using such US techniques, anomalies of placental length or thickness have been associated with increased risk of stillbirth (35).

Ultrasound can also detect a number of pathologic lesions, including infarcts, calcifications and placental lakes. Such lesions have been shown to increase the risk of FGR, premature delivery and subsequent anomalies on neonatal cranial US (36, 37). On US, placental infarcts appear as echogenic cystic lesions with irregular borders, and their clinical significance is highly dependent on the size and location. Extensive, central infarcts are associated with pregnancy induced hypertension, FGR, preterm delivery and intrauterine demise (34). Placental calcification is a normal developmental phenomenon as the placenta approaches term (38) and appears as hyperechoic areas on US. Abnormally early or late calcifications of the placenta is associated with pregnancy-induced hypertension, diabetes, Rh incompatibility, FGR and intrapartum fetal distress (34). Placental lakes are villous vascular spaces filled with maternal blood flowing at a low velocity and are identified on US as anechoic areas surrounded by placental tissues of normal echogenicity (39). They are thought to result from vascular thrombosis or trauma, and despite being the most common anomaly seen on US, the clinical significance remains unknown (34).

The use of Doppler velocimetry of the maternal-fetal circulation in conjunction with standard US has become an important adjuvant tool to assess placental function (39). When the fetal villous vasculature of the placenta is damaged, there is increased resistance throughout the placental bed, which eventually translates into increased resistance through the umbilical artery circulation (40). Further disruptions in the fetoplacental circulation and chronic fetal hypoxia can manifest as alterations in the umbilical venous circulation (41). Fetal Doppler studies of the middle cerebral artery can also inform us about placental function, and serve as one of the earliest markers of uteroplacental insufficiency (42). The next section summarizes the role of advanced ultrasound techniques for placental imaging.

Advanced Ultrasound Techniques in Placental Imaging

Color/Power Doppler US—More recently, color or power Doppler US has been used in the evaluation of the placenta. Power Doppler utilizes the amplitude component of Doppler to detect low-flow velocities previously undetected by standard color Doppler and has been used to estimate perfusion changes over time (39). With the addition of color/power Doppler, intervillous blood flow can be detected as early as 12 weeks, intraplacental arteries can be detected by 16 weeks, and retro- and intra-placental arteries can be well visualized by 28 weeks (34). The clinical application of this technology, however, remains limited. While power Doppler may reflect placental blood flow volume, early studies have not been able to demonstrate an association between power Doppler signals and placental vascular resistance. Future applications may include the use power Doppler to improve the detection of placental infarction by US, which with power Doppler appear as areas of diminished blood flow (43).

Three-Dimensional Ultrasound—Three dimensional US (3D-US) offers volumetric assessment of the placenta, which provides increased accuracy of placental growth compared to standard two-dimensional measures of length or thickness, while also minimizing errors of measurement (44). Early studies of placental volume using 3D-US in the first trimester have been shown to predict preeclampsia and fetal growth restriction. The added value of this technique is most pertinent when combining 3D US to power Doppler US. The addition of 3D-power Doppler US improves the accuracy of blood flow measures compared to standard 2D power Doppler measures. 3D-power Doppler US has been used to calculate a vascularization index to estimate overall placental perfusion, a flow index to measure the intensity of placental blood and a vascularization flow index to estimate vascularization and blood flow (45, 46). To date, studies using 3D-power Doppler have not demonstrated significant changes in uteroplacental blood flow throughout gestation, but that intervillous flow may be abnormally increased prior to miscarriage, and decreased in FGR pregnancies (45, 47, 48). The added sensitivity of 3D-US to current Doppler studies remains controversial and warrants further study (34).

Limitations of Ultrasound—Given the extensive use of US in the evaluation of the placenta, easy accessibility and real-time results, it is likely to remain a primary screening tool for placental health. Nonetheless, there are significant limitations with this technique. First, US techniques are limited by maternal body habitus and placental implantation site, particularly in evaluating the posterior placenta. Similarly, standard US provides limited field of view, so that only a limited portion of the placenta can be visualized at any given time and can also be limited in the presence of oligohydramnios. While accelerated placental maturation has been associated with adverse pregnancy outcomes, multiple studies have demonstrated poor inter-observer agreement of placental grading (49–51). Similarly, the detection of placental infarcts by US and subsequently confirmed by histology revealed only a 37% sensitivity and 63% positive predictive value for US (34). Furthermore, standard US techniques provide structural and anatomic information of the placenta, but limited functional information. Advanced US techniques, such as 3D-power Doppler US offer more in-depth physiologic assessment of the developing placenta, these techniques are more complex and time consuming, and their added value requires further investigation.

Role of Magnetic Resonance Imaging in Assessing Placental Health

Clinical Applications of Placental MRI

The successful application of in vivo fetal MRI has resulted in important advances in our understanding of the maturational processes of the healthy fetal brain and placenta, and how in utero development can be derailed following developmental lesions and acquired injury. Advances in MRI technology, including faster acquisition times, and documented safety and tolerance for both the fetus and the mother, has resulted in MRI becoming an increasingly common clinical tool in obstetrics over the last 20 years and has many advantages over US imaging (52). Specifically, MR imaging can provide better tissue resolution and a larger field of view, while at the same time, has less inter user-dependence and is less affected by maternal body habitus or placental implantation.

MR imaging of the healthy placenta reveals a relatively homogenous organ, with low signal intensity on T1-weighted images, and high signal intensity on T2-weighted images (53, 54) (Figure 1). From 24 weeks, the normal placenta becomes slightly lobulated and shows increasing heterogeneity with advancing gestational age (55). Alterations in signal intensity and significant increases in heterogeneity have been shown to correlate with areas of infarction, necrosis or fibrosis (53) (Figure 2). T1 and T2 relaxation times normally decrease throughout gestation, reflecting the increase in villous surface area as the placenta matures (53).

Conventional MR imaging has been used to evaluate placental position, attachment, and depth invasion of the placenta into the myometrium, without the need for contrast (55). Likewise, abnormal placental morphology, such as accessory lobes, can be well visualized by MRI. These accessory lobes increase the risk of postpartum hemorrhage or fetal exsanguination (55). MRI of the placenta also provides better resolution of implantation margins, which is particularly useful in the identification of placenta previa (Allen, 2013). Placenta previa can be associated with additional implantation anomalies, such as placenta accreta which can also be detected by MRI. In current practice, the most common indication for placental MRI is for the evaluation of implantation anomalies (56). Specifically, MR can distinguish between placenta accrete from increta, and increta from percreta, particularly if the placenta is invading adjacent organs (55). The accurate detection of such implantation anomalies have immediate clinical significance in the delivery and surgical planning for the obstetrician, given the significant risk of post-partum hemorrhage and maternal morbidity and mortality (55). Several studies comparing US with MR in the diagnosis of implantation anomalies revealed conflicting results regarding sensitivity and specificity between modalities, although MRI was found to be superior in predicting depth of placental invasion (39, 55). Thus, while US remains the primary screening modality, MR imaging is a useful adjuvant, particularly when US is inconclusive, and for guiding the obstetrician with surgical planning in complex cases.

Quantitative MRI of the Placenta

The increased availability of a larger repertoire of in vivo placental MRI acquisitions, alongside the recent advent of dedicated image processing motion correction and image

registration pipelines is beginning to offer unparalleled access to in utero placental micro- and macro-structure, metabolism, perfusion and function. The next section will provide an overview of these emerging quantitative MRI methods for placental structural and functional assessment.

Quantitative Measures of Placental Growth and Development

Recent studies have explored the feasibility of acquiring three-dimensional (3-D) volumetric placenta MRI data in vivo, enabling 3-D reconstruction and volume rendering of the placenta across gestation (Figure 3). These quantitative MRI studies are providing important insights into the rate and progression of placental growth in the healthy and high-risk pregnancy in utero. As discussed earlier, 3D volumetric imaging has demonstrated more accurate measurement of fetal biometry (44) and shown that biometric measures such as placental length alone, are insufficient clinical markers of fetal growth (57, 58). Moreover, 3D-MR imaging of the placenta provides more reliable measures of growth compared to 3D US (59, 60). Using quantitative 3-D volumetric MRI in healthy fetuses, our studies have demonstrated that placental volumetric growth increased exponentially between 17–38 weeks (Figure 4). The relationship between placental volume and outcome has been explored in a small number of high-risk pregnancies. Volumetric measures of the placenta in the second trimester have revealed smaller placentas in pregnancies that ultimately delivered SGA infants, regardless of whether estimated fetal weight at the time of MRI was suggestive of FGR (61). In our experience, we also found that placental volume is significantly decreased in FGR pregnancies compared to controls throughout the second and third trimesters (62). In addition, placental volume was associated with both birthweight and gestational age at birth in pregnancies complicated by complex congenital heart disease of the fetus (62).

Measures of Placental Diffusion and Perfusion

The recent application and ongoing refinement of multimodal placental MRI sequences is providing novel, previously unavailable in vivo information regarding placental function. These novel placental MR techniques include diffusion weighted imaging, diffusion tensor imaging, susceptibility weighted imaging, and arterial spin labeling. In addition, tissue oxygenation can also be assessed using MRI, and several hyperoxia studies of placental perfusion have also been reported that provide complimentary in vivo information regarding placental function. These studies are summarized below.

Diffusion Weighted Imaging of the Placenta

Diffusion Weighted Magnetic Resonance Imaging (DW MRI or DWI) capitalizes on the differences of water molecule diffusion between different human tissue compartments. In the pregnant patient, this technique has the potential to provide valuable information on the diffusion and perfusion properties of the human placenta (Figure 5). Additional benefits of placental DWI include the increased contrast between placental tissue and adjacent myometrial tissue. Distinguishing these two tissue compartments has immediate impact on the diagnosis of placental invasion, improving the accurate diagnosis of placenta accrete, increta and percreta than with conventional MR sequences alone without having to expose the fetus to gadolinium or other contrast agents (63).

Apparent diffusion coefficient (ADC) mapping using DWI

Diffusion weighted sequences can be used to create an apparent diffusion coefficient (ADC) map that identify and quantify areas of accelerated and restricted diffusion. Important maturational changes in the normal placenta that result in increased villous surface area resulting from microstructural changes that may influence diffusion can be detectable by DWI. In the failing placenta, areas of necrosis, infarction or fibrosis result in altered diffusion, and therefore also may be detectable by DWI. Therefore, in the pathologic placenta, DWI and ADC mapping has the potential to quantify early changes in diffusion even in the absence of gross structural anomalies detected on US or conventional MRI.

In a feasibility study by Manganaro et al, the authors reported conflicting trends for changes in ADC values with increasing GA and concluded that these differences indicate perfusional and circulatory motion influences on the DWI acquisition and therefore could not provide reliable ADC maps to study placental maturation (64). A subsequent study of placental DWI used a correction factor for calculating ADC maps to account for maturational density changes that occur with MR acquisition of the developing placenta (65). The relative ADC (rADC) measurements were applied to regions of the placenta that were manually selected to avoid areas of calcification, hemorrhage, necrosis or cysts. Using these methods, the placental rADC value did not differ between gestational age groups, despite using a similar MR acquisition protocol as the previous study (65). In this report, the authors concluded that the stable rADC values reflect stable extracellular water diffusion despite calcification changes and extravascular tissue fibrosis in the maturing placenta (65). Animal studies have also explored the correlation between ADC values and placental aging throughout gestation, which did not demonstrate any statistically significant difference between early and late gestation (66). Collectively, these studies are line with the results of T1 and T2 relaxation time changes seen throughout pregnancy. Both animal and human models have demonstrated decreased T2 relaxation times with advancing gestational age (67–69). Available evidence suggests that the microstructural changes that occur in the placenta throughout gestation reflect increases in local deoxyhemoglobin concentration, increase in blood volume fraction or variations in blood flow that may not be detected by diffusion measures alone.

ADC techniques have also been applied to pregnancies at high risk for uteroplacental dysfunction. A retrospective study of DWI imaging of the placenta in growth-restricted and non-growth restricted fetuses showed decreased regional ADC measurements in the growth restricted fetuses (70). In this study, the addition of DWI to standard US measures increased the sensitivity of placental insufficiency from 73–100%, increased the accuracy of diagnosis from 91 to 99% and maintained specificity of 99% (70).

Intravoxel incoherent motion (IVIM) studies DWI

The intravoxel incoherent motion (IVIM) technique using diffusion weighted MR sequences to measure perfusion has also been explored in the placenta by calculating perfusion fraction to estimate the volume fraction of perfused tissue. Using IVIM to assess placental perfusion, a decrease in perfusion fraction with advancing gestational age has been described in healthy pregnancies (71, 72). This technique has also been explored in the high-risk pregnancy,

including those complicated by preeclampsia, diabetes mellitus and FGR (summarized below).

In a small case series of women with early preeclampsia (< 34 weeks GA), the perfusion fraction of the placenta was found to be significantly reduced compared to healthy pregnancies (19% compared to 36%) (71). Two of the five fetuses were considered growth restricted and demonstrated the lowest perfusion fraction of the entire cohort (11% and 16%). In the same study, late preeclampsia (≥ 34 weeks GA) did not demonstrate the normal decrease in perfusion fraction, but rather had elevated values (35%) compared to controls (28%). All infants were born at term with appropriate for gestational age birth weights (71). This data supports previous literature that suggests different pathophysiologic mechanisms and pregnancy implications for early versus late preeclampsia (73, 74). A similar trend of decreased perfusion fraction in the placenta was also seen in a small series of pregnancies complicated by maternal diabetes mellitus, although these differences did not reach statistical significance (75).

FGR pregnancies also have demonstrated low perfusion rates compared to controls using echoplanar imaging (76). In pregnancies affected by FGR, IVIM was used to create placental perfusion maps, by comparing perfusion between inner and outer regions of the placenta (77). These maps showed that placental perfusion was significantly decreased compared to controls. Interestingly, the difference in perfusion between placental zones was reversed in FGR cases compared to controls (77).

A recent prospective study comparing women with healthy pregnancies and normal uterine artery Doppler studies, to women at risk for preeclampsia with and without FGR were followed through delivery after fetal MR imaging (78). In all pregnancies that delivered SGA fetuses, the perfusion fraction of the basal plate, where the placenta implants into the uterus, as well as the central portion of the placenta was significantly decreased compared to the pregnancies that delivered AGA fetuses, regardless of the estimated fetal weight at the time of MRI examination (78). These preliminary data suggest that IVIM MRI may be a promising, early, non-invasive marker for placental function and fetal outcome. Ongoing studies are needed to validate these intriguing initial findings.

Diffusion Tensor Magnetic Resonance Imaging

Diffusion tensor imaging (DTI) measures the restricted diffusion of water in tissue to produce cellular tract images. Maximum diffusivity, mean diffusivity and fractional anisotropy are DTI measures extracted from the diffusion images that are thought to represent membrane density and cellularity (mean diffusivity) and microstructural integrity (fractional anisotropy). Most commonly applied to the brain to create neural tract images, there is a single report of this technique being applied to the placenta (79). In this study, a significant reduction in the microscopic motion of water was described in FGR compared to non-FGR cases for measures of maximum diffusivity, mean diffusivity and fractional anisotropy, suggesting diminished functional placental tissue and altered placental microstructure in these pregnancies (79). Taken together, these preliminary studies suggest that diffusion MRI may play an important role for early detection of placental based disorders.

Arterial Spin Labeling: Flow Sensitive Alternating Inversion Recovery Imaging

Flow sensitive alternating inversion recovery (FAIR) imaging is used to measure classical perfusion of a target organ, by applying a pulse sequence to a vascular network where blood is unidirectional. In the placenta, blood flow is multi-directional, challenging the classic paradigm of FAIR imaging and interpretation of classic perfusion measurements (53). To date, only two studies have explored the use of in vivo FAIR imaging in the placenta, likely due to the difficulty in reliably acquiring perfusion data in the placenta. Although FAIR imaging did not reveal differences in perfusion between healthy and compromised pregnancies in one study (80), when the authors generated perfusion maps, they reported decreased perfusion fraction in pregnancies complicated by FGR. The authors speculate that perfusion maps were more representative of overall blood movement, given the multi-directional flow and could be used to distinguish normal and pathologic pregnancies (80). In another prospective study of placental imaging, FAIR measures of perfusion also revealed diminished perfusion to the placenta in pregnancies that delivered SGA infants compared to AGA controls (78). Ongoing studies are needed to overcome the technical challenges of reliably performing and measuring non-invasively, global and regional perfusion of the placenta in order for these exciting imaging techniques to play a role in the clinical setting.

Measures of Placental Vasculature

Dynamic Contrast-Enhanced MRI of the Placenta—Dynamic contrast-enhanced MRI (DCE-MRI) utilizes an intravenous contrast agent to map the vascular component of tissues. Originally described in tumor evaluation to distinguish healthy from damaged cells, this technique has recently been applied to the placenta in animal studies to characterize the maternal from fetal vascular components of the fetus.

In a study by Solomon et al, pregnant mice were administered a contrast agent that does not cross into the fetal compartment of the placenta to delineate the maternal vascular component of the placenta (66). By distinguishing maternal from fetal blood, as well as identifying the trophoblastic layer of the placenta, the authors were then able to measure the ADCs of the maternal and fetal components. Though the maternal blood compartment was larger than the fetal blood (66% compared to 24%), the fetal ADC was significantly larger compared to the maternal ADC (240 mm²/s compared to 3 mm²/s) and the DW MRI-derived data showed good agreement with subsequent ex vivo analysis (66). These data suggest that the placenta is structured in such a way to allow for large volume of maternal blood but active and rapid diffusion so that a large degree of exchange of nutrients and metabolites can occur between maternal and fetal compartments. While this technique cannot currently be translated to the human placenta, it does provide a useful model to study placental, maternal and fetal vascular disease in the mouse, which in turn, could inform pathophysiologic mechanisms in the human pregnancy. Furthermore, similar DCE-MRI techniques have been used in the primate, which may better approximate the human placenta (81). This technique's dependence on contrast, however, has restricted its application to animal models and has not been described in human pregnancies.

Susceptibility Weighted Imaging—Susceptibility weighted imaging (SWI) is an MRI sequence that is sensitive to compounds that have paramagnetic or ferromagnetic properties

that distort the magnetic field; therefore, compounds such as deoxyhemoglobin, ferritin, hemosiderin and calcifications can be readily identified on this sequence, without the need for exogenous contrast material. The ability to detect deoxyhemoglobin has been capitalized as an endogenous contrast agent to enhance visualization of venous structures (67). When applied to the murine placenta, SWI was able to distinguish three distinct placental zones – the labyrinth, junctional zone and maternal decidua. To date, SWI been not been applied to the human placenta in vivo.

Measures of Placental Oxygenation

The paramagnetic properties of oxygen have been used to study oxygenated and deoxygenated blood using Oxygen-Enhanced MRI (OE-MRI) and Blood Oxygen Level Dependent Imaging (BOLD). Studies have begun interrogating the use of maternal oxygen challenge to decipher the extent to which maternal hyperoxia can result in detectable changes in placental oxygenation using OE-MRI and BOLD techniques.

In healthy, uncomplicated pregnancies, available evidence has shown that the administration of supplemental oxygen to mothers is associated with a significant increase in the OE-MRI signal, which represents increases in blood and tissue oxygenation. Similarly, a significant, concomitant increase in BOLD signal was also detected, suggesting increases in pO₂ and sO₂ (82). Interestingly, increases in the OE-MRI signal has been reported to diminish throughout gestation, which is believed to reflect the growing oxygen demands of the fetus (82). The same authors used BOLD-MRI to study the effect of maternal hyperoxia on the placenta and the fetal brain in healthy pregnancies (83). While placental oxygenation increased, fetal brain oxygenation was unchanged (83) suggesting that oxygen extraction remains constant across variations of oxygen delivery in a normal pregnancy with healthy placentas. Similarly, Sorensen et al (84) demonstrated increased oxygenation in the placenta using BOLD MRI, however the fetal brain remained unaffected by maternal hyperoxia. The authors speculate that this may be due to a ‘reverse’ brain sparing mechanism among healthy fetuses exposed to hyperoxia, and that the lack of oxygenation changes in the fetal brain support the notion that cerebral blood flow is decreased during hyperoxia. OE-MRI and BOLD MRI may provide novel biomarkers for identifying impaired placental and fetal brain function in pregnancies complicated by placental insufficiency. However, ongoing validation of these techniques is needed.

Measures of Placental Metabolism

Magnetic Resonance Spectroscopy—Magnetic resonance spectroscopy (MRS) is a non-invasive technique that has been used to study metabolic changes in the body. Most commonly, MRS uses signals from hydrogen protons (¹H) to determine the relative concentrations of target metabolites, but phosphorus (³¹P) has also been described for human tissue analysis. ³¹P-NMS has been used to detect adenosine triphosphate (ATP) among other inorganic phosphates and phosphodiesteres in the human placenta (85). Phosphodiesteres and phosphomonoesters are related to cell membrane degradation and formation. When applied to the placenta, they may inform cell proliferation and tissue growth throughout gestation. To date, very few studies have explored the application of ³¹P-NMS in the in vivo placenta. In one study of healthy pregnancies, the ratio of these

phosphodiester signals increased with advancing gestational age, suggesting increasing cell membrane formation over time (86). Furthermore, this study also demonstrated an increase in cell degradation and decreased cell membrane proliferation in early onset preeclampsia compared to healthy pregnancies (86). Noteworthy, an abnormal phosphodiester signal has been reported from the in vivo placenta in a case of fetal demise (87). Ex vivo spectroscopic studies of normal and FGR placentas have also demonstrated increased phosphorus metabolites, including ATP, in the abnormal placentas, which may reflect the increased metabolic demand of a hypoxic placenta (88). While ^{31}P -NMS has the potential to inform in vivo data regarding placental metabolism, this technique is not commonly available for clinical application. Unlike ^{31}P -NMS, ^1H -NMS has a much more widespread clinical availability. However, only one study has explored the use of ^1H -NMS on the human placenta, in which the spectra revealed a dominant lipid ratio that limited the description of alternate metabolites (89). (Figure 6). While the authors suggest that the choline lipid ratio can distinguish between healthy and growth-restricted pregnancies, it has been our experience that the significant lipid peak from the placenta limits meaningful interpretation of the spectra. Ongoing research is needed to address the role of ^1H -NMS in understanding placental metabolism.

Current Challenges

At present, there are limited tools available for the clinician to assess placental health and disease *prior* to the onset of fetal or neonatal distress. Advanced MRI techniques hold much potential in providing important, real-time, in-vivo, structural and functional information of the developing placenta and its relation to the developing brain. To date, available studies propose novel applications of MRI to the study of the placenta, but have been limited by small sample sizes, and the need to validate the results with histopathology. Motion is an ongoing challenge with fetal MRI, and while the placenta is relatively immobile, maternal respirations and fetal motion at the surface of the placenta can corrupt MR imaging sequences. In some of the studies reported, up to 50% of DWI-acquired data have been excluded due to resulting image corruption or artifact (78). For BOLD acquisition series, additional data corruption occurs with maternal cardiac pulsations and multi-directional blood flow throughout the placenta. Technical advances in both MR image acquisition, and dedicated pre- and post-processing pipelines are needed and currently under development (90) to mitigate the effects of fetal/maternal motion on image quality allowing for meaningful and reliable MR image interpretation.

Across studies, there are significant variations in methodology, including MRI field strength (from 0.5 to 3T Tesla in human studies and up to 4.7 Tesla in animal studies). Within the same MRI modalities, there are differences in acquisition protocol parameters; for example in DWI acquisitions, important variations in the number of sequences acquired and the diffusion sensitivity parameters applied likely account for difficulties in reproducing and interpreting measures of IVIM. The more widespread clinical application of these tools will necessitate the development of local experience and expertise in MR application and interpretation.

Future Directions

Placental health undoubtedly involves a complex interplay between macro and microstructural tissue integrity as well as, intact, functional perfusion, oxygenation, and metabolite extraction that take place throughout gestation. It is unlikely that a single MRI modality or measure will independently distinguish the healthy from the diseased placenta. However, advanced fetal MRI offers a promising non-invasive method to interrogate multiple facets of placental development and function, and is becoming a powerful obstetrical tool to assess placental health and wellness in the living fetus. Faster, more robust and dedicated MRI pulse sequences are needed to capture and quantify intricate developmental changes that unfold within the placenta during pregnancy. Likewise, ongoing developments in MRI postprocessing pipelines are needed to enable the quantification of these critical maturational processes in the healthy placenta in order to understand how, when, and why these processes are derailed in the high-risk pregnancy. The availability of normative placental MRI values will be critical to reliably capture very early alterations in placenta structure, microstructure, metabolic and function in the compromised fetus. Finally, the successful uptake and adoption of these emerging fetal imaging placental biomarkers in the clinic will require continued validation and a substantial reduction in computational burden that is associated with these quantitative MRI techniques at the present time. Collectively, this will result in advanced fetal diagnostic capabilities for placental failure, so that future therapeutics can augment and preserve placental function, and in turn support the developing fetus.

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Figure 1.

T2-weighted image of the placenta from a healthy 21 week fetus. Note the large field of view that captures the length of the placenta and the smooth contours. The placenta has relatively high-signal intensity and the implantation site can be distinguished from the maternal myometrium (white arrow).

Figure 2.

2A: T2-weighted image of a 26 week healthy placenta. Note the homogeneous high-signal intensity throughout the organ. 2B: T2-weighted image of a 26 week placenta from a growth-restricted fetus. Note the heterogeneity in signal intensity, thought to correlate with areas of infarction, necrosis or fibrosis.

Figure 3.

3A: T2-weighted image of 36 week fetus, with the placenta outlined in red. 3B: Final 3D reconstruction of the placenta, which can be used for quantitative analysis, such as placental volume.

Figure 4.
Relationship between placental volume and gestational age in healthy fetuses.

Figure 5.
Diffusion weighted Image of a healthy fetus and placenta (5A) with the placenta highlighted in red (5B).

Figure 6.
 ^1H -NMR placental spectra in a 35 week fetus depicting choline and lipid peaks.