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Placental MRI: developing accurate quantitative measures of oxygenation

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Abstract

The Human Placenta Project has focused attention on the need for noninvasive MRI-based techniques to diagnosis and monitor placental function throughout pregnancy. The hope is that the management of placenta-related pathologies would be improved if physicians had more direct, real-time measures of placental health to guide clinical decision making. As oxygen alters signal intensity on MRI and oxygen transport is a key function of the placenta, many of the MRI methods under development are focused on quantifying oxygen transport or oxygen content of the placenta. For example, measurements from BOLD imaging of the placenta during maternal hyperoxia corresponded to outcomes in twin pregnancies, suggesting that some aspects of placental oxygen transport can be monitored by MRI. Additional methods are being developed to accurately

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quantify baseline placental oxygenation by MRI relaxometry. However, direct validation of placental MRI methods is challenging and therefore animal studies and ex vivo studies of human placentas are needed. Here we provide an overview of the current state of the art of oxygen transport and quantification with MR imaging. We suggest that as these techniques are being developed, increased focus be placed on ensuring they are robust and reliable across individuals as well as standardized to enable predictive diagnostic models to be generated from the data. The field is still several years away from establishing the clinical benefit of monitoring placental function in real time with MRI, but the promise of individual personalized diagnosis and monitoring of placental disease in real time continues to motivate this effort.

Keywords

placenta; oxygen; BOLD; quantitative; relaxometry; noninvasive

Introduction

The placenta is a unique organ that serves as a critical interface between a mother and her fetus. Placental insufficiency is associated with preeclampsia, intrauterine growth restriction (IUGR) and placental abruption.[1-3] In addition, placental dysfunction can occur with maternal diabetes, thrombophilias, smoking or drug abuse.[4-6] Recent studies have shown the potential connection between placental insufficiency and congenital heart disease (CHD),[7,8] even though little is known about the causal connections.[9] Deterioration in placental function throughout pregnancy may cause serious complications for both the mother and the fetus, is a leading cause of perinatal morbidity and mortality and can have long term consequences for the health of both the mother and the fetus.[1,3,10-12] In particular, animal and human studies indicate that placental insufficiency can lead to abnormal neurodevelopment.[3,13] Monitoring placental function throughout pregnancy is therefore a critical component of antenatal care but few tools currently exist for direct assessment of placental function.

The most common technology used for assessment of placental function is ultrasound (US) and in selected scenarios, umbilical artery (UA) Doppler. US is limited in its ability to characterize placental anatomy and to quantify placental function.[14] Umbilical artery Doppler is an indirect measure with limited ability to detect placental abnormalities especially in early pregnancy or in low risk pregnancies.[15,16] Additionally placental dysfunction may arise when pathologies affect the microscopic morphology altering blood flow within the placental microcirculations, which is hard to detect with US. Moreover, distinguishing the small, but normal fetus from the truly growth restricted fetus due to placental dysfunction remains an elusive goal. [1]

Development of quantitative measures of the spatiotemporal patterns of placental oxygen delivery and transport between the mother and the fetus may enable us to better understand the normal function of the placenta and placental reserve. Such measures would increase our ability to detect placental insufficiency and could motivate and evaluate potential therapeutic interventions.[17-19] Magnetic resonance imaging (MRI), with its unique features (i.e., high

soft tissue contrast, high resolution, quantification of tissue microstructure and flow) provides a tremendous potential for monitoring placental structural development and function.[20,21]

The ultimate goal of placental MRI is to improve individual patient care by increasing diagnostic accuracy and providing real time monitoring of individual placental function. In most other organs, MRI is used by radiologists to visually identify structural or physiological abnormalities. Quantitative MRI has aspired to aid clinical decision making, primarily in tumor assessments,[22] but has not been adopted in clinical practice likely due to technical challenges and the need for larger validation studies. However, given that visual inspection of the placental MR images has not provided useful clinical information in most disorders of placental dysfunction, the search is on for quantitative MRI-based tests that can better characterize its temporal spatial function.

Ideally, the development of any new diagnostic technology should proceed through several phases.[23] Phase 1 studies are designed to define the range of results obtained and to explore technical factors that influence those results. Phase 2 studies are those that begin to explore diagnostic accuracy. This phase is the search to define test characteristics such as sensitivity, specificity, positive and negative predictive values in normal and then abnormal populations with varying rates of the disorder that is sought. This is the phase where cut off values between normal and diseased results are explored and defined. Studies during this phase of development should ideally follow the STARD Guidelines for the reporting of new diagnostic test performance.[24] Phase 3 studies begin to define the ability of clinicians armed with this information to alter measurable clinical outcomes. Finally, Phase 4 studies are typically large observational studies that characterize the effects of more global deployment of a new test including pragmatic effects such as quality measures and cost implications on a broad scale.

The field of quantitative MRI assessment of placental oxygen transport is still in Phases 1 and 2, with no measurement yet sufficiently diagnostically accurate to move to Phase 3. Our aim here is to summarize the current status of MRI based measures of placental oxygenation as a possible new diagnostic technology in perinatal medicine.

Importance of Oxygen in Placental Function

The placenta is vital to the intrauterine development of the fetus. As the site of nutrient and oxygen exchange between mother and fetus, it is the largest area of close contact between maternal and fetal tissue. The maternal side of the placenta is called the basal plate. Circulating maternal blood enters the intervillous space through spiral arteries and drains back through endometrial veins in the basal plate. The fetal side is called the chorionic plate, partially consisting of the fetal chorionic blood vessels that branch from the umbilical vessels. Deoxygenated fetal blood passes through the chorionic arteries to the chorionic villi in villous trees, which are the main functional units of the placenta. Fetal and maternal blood are brought into close proximity in the villous trees and intervillous space to enable the exchange of nutrients, gasses and waste products between the mother and the fetus. Note that maternal and fetal blood are separated by two layers of trophoblast cells,

syncytiotrophoblasts and villous cytotrophoblasts that regulate this exchange. Oxygen and nutrition rich fetal blood in the chorionic villi returns to the fetus via the chorionic veins and the umbilical vein.[25]

Oxygen is essential to cellular respiration and also toxic in the form of reactive oxygen species. Thus, oxygen delivery to the fetus is regulated to provide a sufficient but not a deleterious supply. In fact, the fetus develops in a relatively hypoxic environment. Oxygen delivered to the placenta through maternal blood is absorbed by fetal blood as well as consumed in the placenta itself. A significant portion of the oxygen delivered to the uterus (around 40% of total uterine oxygen uptake at term)[26] is used for oxidative phosphorylation of glucose and for non-mitochondrial processes such as protein synthesis in the placenta itself.[27]

Oxygen is primarily transported in blood via binding with the hemoglobin in red blood cells. A small amount of additional oxygen is dissolved in the plasma. The carrying capacity of oxygen in blood (C) can be expressed as $C = (SO_2 \times [Hb] \times 1.34) + (PaO_2 \times 0.03)$, where SO_2 is the blood oxygen saturation, [Hb] is the hemoglobin concentration (typically 13.8g/dl in women,[28] but in the fetus it changes throughout development from about 11 g/dl at 17 weeks to 15 g/dl at term[29]), 1.34 is the oxygen carrying capacity of hemoglobin, PaO_2 is the partial pressure of oxygen, and 0.03 the oxygen carrying capacity of plasma. Thus C is the sum of oxygen carried by Hb and that dissolved in blood. SO_2 is related to pO2 through the oxygen binding affinity of hemoglobin which is different for adult and fetal hemoglobin. Oxygen transfer across the placenta can be affected by many factors including maternal blood flow in the intervillous space, oxygen carrying capacity and affinity of maternal blood, fetal blood flow in the placenta, oxygen carrying capacity and affinity of fetal blood, oxygen diffusing capacity of the membrane and fetal-placental oxygen consumption.[30,31] An estimate of placental or fetal oxygen demand can be made by applying Fick's principle. It relates oxygen consumption (VO_2), blood flow (Q) and the arteriovenous oxygen concentration difference: $VO_2 = Q \times |C_a - C_v|$. Therefore, the VO_2 of the entire pregnant uterus can be estimated by only four measurements (Q, $SO_{2,a}$, $SO_{2,v}$ and [Hb], and assuming dissolved oxygen content is negligible). However, to estimate placental VO_2 estimates of fetal VO2 are required with $VO_{2,placenta} = VO_{2,uterus} - VO_{2,fetus}$. We discuss below approaches to make these measurements non-invasively using MRI.

Adaptations to changes in placental oxygen delivery vary depending on the timescale of the change. Chronic hypoxia, as experienced by pregnant mothers who live at high altitudes (>2700 m) leads to decreased umbilical blood flow, increased Hct and [Hb], higher binding affinity of fetal hemoglobin and structural changes like chorangiosis and villous hypermaturation.[32-34] The net result is that fetal oxygen consumption is maintained. Changes in oxygen delivery achieved by obstructing the uterine blood supply in pregnant ewes shows that in the acute stage placental oxygen consumption remains constant at the expense of fetal oxygen consumption, but that chronic exposure leads to a greater decrease in placental than fetal oxygen consumption.[27] The effects of maternal oxygen administration on placental and fetal oxygen consumption are less well known given that human studies are mostly limited to intrapartum therapeutic interventions (30-80% FiO_2), but increases in maternal and umbilical vessel pO_2 have been consistently observed.[35,36] Studies have not

found average changes in blood flow to the placenta as a result of maternal oxygen breathing (70-100% FiO_2), but more investigation is needed to fully characterize the subtle and individual hemodynamic effects.[37-39]

A focus on oxygen delivery may only give a narrow picture of overall placental and fetal wellbeing, because it does not consider the supply of other essential substrates and signaling molecules.[40] However, MRI techniques permit non-invasive monitoring of oxygen saturation and blood flow which makes oxygen an appealing marker of metabolic processes.

MRI Techniques for Oxygen Assessment

Blood oxygen level dependent (BOLD) MRI[41,42] and relaxometry (i.e. T_2*,[43,44] T_2 ,[45-47] and T_1[48,49] mapping) have been employed to study placental oxygen transport and blood oxygen saturations in animal and human studies. These various approaches exploit MRI's sensitivity to the magnetic field perturbations caused by different concentrations of paramagnetic substances such as deoxyhemoglobin or oxygen, but these methods have varying sensitivities to field perturbations depending how the image is acquired.

BOLD imaging of the placenta has been based on gradient echo imaging.[41,42] This imaging approach was developed for functional brain imaging, and it is sensitive to changes in image signal intensity that can be attributed to physiological changes in blood volume, blood flow and blood oxygen saturation. As such, aspects of the signal time course during physiological changes have been linked to placental oxygen transport dynamics.[42] For brain applications considerable theoretical and empirical work has investigated the origin and possible quantitative interpretation of the BOLD signal.[50-52] There has been limited work to develop signal models for BOLD imaging of the placenta.[42,53] Thus far, T_2*-weighted imaging has been the predominant approach to placental BOLD imaging, with gradient echo echo planar imaging (GRE-EPI) as it permits fast acquisitions of single imaging slices that effectively freeze maternal and fetal motion, while whole placental volumes are obtained in less than 10 seconds. More recently, quantitative susceptibility mapping has been proposed for placenta imaging as it is more sensitive to the oxygenation change than the typical T_2* based BOLD acquisition with its unique feature combining T_2*-weighted magnitude data with the phase data.[54] However, determining susceptibility maps is notoriously difficult because the relationship between MR signal phase and susceptibility is ill-posed.[55] Partial volume (determining the blood volume in a voxel) and geometry (the geometry dependence of deoxygenated blood vessels on MRI signal observations) effects make this method challenging for placental imaging.[56]

Relaxometry of the placenta has been pursued because relaxation times of blood map to SO_2, pO_2, and hematocrit (Hct). This mapping is different for each relaxation time (T_2*, T_2 , and T_1) and also between methods for acquiring relaxometry. Considerable work has explored these relationships in *ex vivo* blood samples.[51,57-62] The basic approach is to scan samples of blood which have a predetermined hematocrit and oxygen saturation using the MRI sequence that will be used subsequently for *in vivo* imaging. This empirical data is then fit with a theoretical model of the relationship between MR relaxation and blood oxygenation in order to determine the best model parameters. The models make various

assumptions about the behavior of spins (diffusion and exchange characteristics) and about their environment (the properties of signals originating in erythrocytes, blood plasma and the extravascular space) which makes the models dependent on the proposed MRI sequence and physical properties of the blood. For example, studies show that perinatal and adult blood have different relationships between oxygenation and relaxation time,[61,63] that may be due to the fraction of fetal hemoglobin present in the blood and/or to the size and permeability of erythrocytes.[59,64] Combining T_1 with T_2 or T_2* can permit estimation of SO2 and Hct or SO2 and pO2, since each relaxation time has different sensitivities to oxygenation and Hct.[49,60,61,65]

The two main challenges related to relaxometry of the placenta are motion and partial volume effects. Relaxometry typically consists of acquiring images with different inversion times (for T_1) or TEs (for T_2* and T_2) and then fitting a signal model to the acquired data in order to estimate the relaxation time. This means that motion in between acquired images can greatly affect relaxation time estimates. Acquisitions and signal models have been developed that can perform single relaxation time estimation in tens of seconds,[49,62] and advanced methods have been proposed to make multiple relaxation time estimates in under ten seconds.[66,67] These accelerated techniques greatly mitigate, but do not yet eliminate the challenge of fetal and maternal motion. Partial volume effects (i.e. one voxel may contain maternal and fetal blood as well as tissue) mean that inferences of absolute oxygenation from placental relaxometry remain cautious.[49] One approach to improve accuracy of oxygenation estimates is to isolate blood compartments of interest.[68] Another is to acquire multi-modal data such that blood volumes and relaxation times can be combined in a model of the various blood and tissue compartments of interest.[69] We discuss below how these approaches have been used in placental assessment and current findings.

Ex vivo Placental MRI Experiments

Human Studies

Current MRI studies using the *ex vivo* human placenta have mainly focused on characterizing placental vascular structure.[70,71] There are a few MRI experiments conducted with the whole human placenta to visualize the macrovascular structure of the fetal network under MRI.[70,71] They reported that rotary-vane oil provided less extravasation effect and better cost-performance ratio as a contrast agent than the more conventional gadolinium bound albumin.[70] Although rotary vane oil provided an economic alternative to the gadolinium bound albumin, it is toxic to the harvested organ, nutrient transport studies can not be conducted and it does not provide information on the microvasculature. In a more recent work, whole human placenta dual perfusion chamber designed by Maulik et al.[72] has been modified to be MR compatible with a seven-channel surface coil array, to image the placenta during perfusion.[73] The purpose of this recent work is to keep the placenta viable during the perfusion experiments, simulate physiological conditions in a well-controlled environment and validate *in vivo* findings. Although this system has the capability of perfusing both the fetal and maternal circulation dynamically during scanning, initial experiments were performed only perfusing fetal circulation with a gadolinium bound albumin solution prior to scanning for structural imaging. Pilot results obtained using 300

micron resolution GRE sequences demonstrate that the perfusate reaches the distal capillary bed and was verified by histological examination (Figure 1). Optimization is underway in order to perfuse both the fetal and maternal circulation under biological conditions during image acquisition. *Ex vivo* MRI of animal placenta models is limited but have been used in a few placental perfusion studies to simulate physiological conditions.[74] Vascular structure has been assessed via microcomputed tomography.[75]

Challenges & limitations

Technical—To maintain biological conditions for an *ex vivo* placenta, the system is limited to matching the physiological values for either flow or pressure. Since flow and pressure are dependent values in a closed system, it is not possible to set the pump parameters to match both values seen *in vivo*.[76] In recent work, the pump settings were chosen to match the biological pressure because if the physiological flow value was matched, the pressure at the catheter would have been too great and would rupture microvascular structure of the placenta.[73] *In vivo*, the veins and arteries are more elastic than the tubing used, accommodating the higher flow rate without the higher pressure. Additionally, placental disruptions during delivery and difficulty in the catheterization process decreases the rate of successful *ex vivo* perfusion. When catheterization efficiency increases, biological conditions can be better preserved, more critical parameters such as perfusate gas concentrations can be accounted for in the *ex vivo* system, and the effects of different pressure and flow rates can be fine tuned for increased perfusion coverage and success.

Biological—One challenge the *ex vivo* placenta perfusion setup may encounter is maintaining a homeostatic amniotic pressure between the harvested organ and the water bath of the system. Due to the imbalance in pressure, perfusate would diffuse across the semi permeable membranes of the placenta.[77] Perfusate leakage is critical flaw to the imaging procedure because when the gadolinium bound perfusate mixes with the water bath, the contrast between the capillaries of the placenta and the water bath decreases during imaging.[78] Another limitation of using *ex vivo* perfusion model is that it mostly uses term placentas and is difficult to extrapolate the findings to earlier gestational ages.

In vivo Placental MRI Experiments

Animal Studies

Animal studies performed under anesthesia and with ventilator-controlled respiration are aimed at improving understanding of placental oxygen transport mechanisms and demonstrating the feasibility of novel MRI protocols to evaluate placental oxygen transport and placental perfusion in a more controlled fashion compared to human placental imaging while eliminating motion artifacts.[21,53,79-86] BOLD MRI has been proposed to image changes in tissue oxygenation and applied in animal models (i.e. rats,[79,81] sheep,[80,83] rhesus macaques)[53,84,86] following different maternal respiration challenges. Wedegartner et al.[83] worked with six anesthetized ewes carrying singleton fetuses, measured BOLD signal change in fetal organs and cotyledon during normoxia and a hypoxic phase and observed the highest BOLD signal decrease with hypoxia in fetal heart and liver. Note that in a sheep model, the placenta is formed with cotyledons scattered over the uterine wall (cotyledonary

as opposed to the human discoid placenta) and placental findings with sheep models might not be easily transferable to the humans due to the different placentation.[87] So, Sorenson et al.[80] presented only the BOLD signal change in fetal organs in ewes as a response to an oxygenation paradigm with normoxic, hypoxic and hyperoxic conditions and reported an increase in the signal in fetal liver, spleen and kidney with increasing tissue oxygenation while a signal change was not detected in fetal brain.

Due to the several advantages of rat models over the sheep model such as having discoid hemochorial placenta similar to that of humans, easier management (i.e. smaller size and shorter generation time)[87], Chalouhi et al.[81] and Aimot et al.[79] worked with a pregnant rat model where IUGR was induced by ligating the left vascular uterine pedicle at day 16 or 17 of gestation and measured the BOLD signal change in placenta and fetal organs with maternal hyperoxygenation. In both studies they observed a significant increase in the signal during maternal oxygenation and this increase was higher in control group compared to IUGR group in the placenta. Moreover in rat models, oxyhemoglobin dissociation curves and fetal-placental hemoglobin affinities were estimated via T_1 and T_2* mapping approaches.[85] Bobek et al.[88] and Krishnamurthy et al.[89] suggested to measure T_2 relaxation times to better understand placental inhomogeneities and the change with gestational age in murine placenta and reported a decrease in T_2 values with gestational age. Increase in intervillous fibrin content might be one of the causes to decrease T_2 with gestational age, however pathological correlations have not been reported to confirm the etiology.

Due to the similarities in placentation, more specifically the way of the spiral artery invasion in macaques and humans, macaque models might be closer analogues to human placental dysfunction linked to preeclampsia or IUGR.[87] In a study with pregnant rhesus macaques,[53] Schabel et al.[53] provided a metric reflecting oxygen transport to the fetus by analyzing spatial patterns of R_2* (=1/T_2*) maps within individual placental lobules. Lo et al.[84] applied approaches similar to those previously developed with R2* maps[53,82] to the macaque model to characterize placental insufficiency with specific focus on placental oxygen transport in the intervillous space, as well as to determine the consequences of placental insufficiency on fetal brain development. They reported an overall reduction in T_2* values in IUGR case compared to the control animal and confirmed this finding with placental histopathology (i.e. aberrant vascular development). Hirsch et al.[86] investigated the placental insufficiency due to the zika virus infection in pregnant macaques through characterizing placental oxygenation via T_2* mapping. Although basic research studies with animal models are needed to better understand human pregnancy complications, and for testing novel imaging approaches for studying the placental function, there are still some limitations as listed below.

Limitations

Technical: Although the subject number for small mammals (e.g. rats) can be increased as they require less space and housing cost is low, the numbers of big animals (e.g. macaques), which are better models to represent human placenta, are usually limited since they are expensive to maintain and the ethical concerns are much greater.[87] The model of oxygenation in the placenta based on T_2* maps of the macaque placenta[53,82] is difficult to

apply to the human placenta mainly due to the motion as described in section Human studies/technical limitations. A more recent study[90] comparing BOLD effect in macaque placenta and human placenta demonstrated some discrepancies in human data that are thought to be due to fetal and maternal motion.

Biological: Even though animal studies have been performed to better understand placental structure and function, differences between the human placenta and animal placenta complicate extrapolation of the findings to humans. Specifically, IUGR rat models do not fully represent human IUGR in which the lesions affect placental microcirculation and become more progressive.[81] Although sheep models have often been used to study fetal physiology, differences in placentation make this model less attractive for placenta studies.[87] Especially to characterize oxygen transport in placenta, the sheep placenta is not an effective analogue to the human placenta.[80] Macaques are the best models to represent the human placenta in the way spiral arteries are invaded and transformed.[87] However, differences between the macaque placenta and the human placenta should still be further investigated as the number of spiral arteries and the penetration depth of the trophoblast in the decidua may change blood flow.[82] Moreover, experimental settings involving anesthesia may affect placental physiology. In addition, when a surgical procedure necessary for the experiments causes an acute stress in the fetus, fetal/placental response to an oxygenation paradigm may be altered.[14,83]

Human Studies

Studies of oxygen transport in the human placenta using MRI have focused on using aspects of the relationship between oxygenation and relaxation time coupled with protocols that involve oxygen administration to characterize placental wellbeing. The primary differences between studies consist of using relaxometry versus BOLD imaging alone, and observing a single time point or a time course.

Single time point relaxometry observations were among the earliest MRI-based observations of the placenta. Gowland et al. and Duncan et al. scanned pregnant mothers at 0.5T and observed a negative linear correlation between both T_1 and T_2, and gestational age, and that T1 was significantly lower in fetuses with IUGR compared to those appropriate for gestational age.[91,92] Though published before much of the work linking relaxation time and blood oxygenation, these results would be consistent with a lower overall blood oxygen saturation both later in gestation and in those pregnancies with IUGR. Wright et al. again found a negative linear relationship between relaxation time and gestational age, but this time at 1.5T, as well as a positive linear relationship between T_2 and fibrin (intervillous-fibrin volume) volume density.[46] They speculated that the increased T_2 with fibrin deposition may be due to a decrease in blood oxygenation, variations in fluid in stromal channels or changes in the hydration fraction of the tissue. In order to confirm the posited relationships between hemodynamics, blood oxygenation and relaxation times, Derwig et al. compared doppler ultrasound hemodynamic and MRI placental T_2 measurements between normally developing fetuses and those born small for gestational age. They found small for gestational age fetuses had a lower T_2 and uterine artery pulsatility index, and a negative linear relationship between T_2 and $\log_{10}$ of the pulsatility index.47 Interestingly, a

correlation between T_2 and gestational age at MRI exam was not observed in contrast to the studies performed at 0.5T and animal studies.[88,89,91,92]

To visualize changing placental physiology over time, some researchers used BOLD imaging to observe relative changes in R_2* instead of absolute relaxometry. Sorenson et al. performed the first human study using BOLD MRI to visualize the placental oxygenation change.[93] In this study, they demonstrated an increase in average BOLD signal in the placenta (three cross sectional slices through the placenta center) in eight healthy pregnant women following an oxygenation paradigm of 5 minutes normoxia (21% O2) and then 5 minutes hyperoxia (12 L O2/min). (Figure 2) In a follow up study, placental BOLD MRI data collected from 21 healthy women were compared with the ones collected from 4 women diagnosed with severe IUGR.[94] They reported no BOLD signal increase in a case with severe histological findings reflecting maternal hypoperfusion of the placenta. In addition to the IUGR population, the BOLD MRI protocol was also tested in a CHD population including 51 healthy and 34 CHD fetuses, but no significant difference was reported in placental BOLD signal response between these two groups.[95] Luo et al. performed voxel-wise analysis for the whole placenta for the first time and proposed the quantitative biomarker time to plateau (TTP), derived from a spatiotemporal analysis of BOLD MRI time series collected during an oxygenation paradigm of 10 minutes normoxia, 10 minutes hyperoxia and 10 minutes normoxia in monochorionic diamniotic twins.[42] It was reported that mean placental TTP was positively correlated with placental pathology ($p < 0.01$) and negatively correlated with birth weights ($p = 0.0003$). Additionally, average TTP was significantly correlated with fetal brain volume ($r=-0.86$, $p= 0.02$), and fetal liver volume ($r=-0.79$, $p=0.05$) at time of MRI, with the longer placental TTP value associated with smaller brain and liver. (Figure 3) A more recent study[54] reported BOLD signal change together with susceptibility maps and showed that homogeneity of the susceptibility map increases with hyperoxia, which might be another marker of oxygen transport in the placenta.

Other studies set out to observe absolute changes in relaxation time during the oxygenation paradigm (Figure 4). Huen et al., and Ingram et al. found that the magnitude of the increase in R_1 ($=1/T_1$) after maternal 100% oxygen exposure decreased with gestational age, which was evidence that placental pO_2 increased during hyperoxia and that a lower baseline blood oxygen saturation existed later in gestation.[48,49,96] Taking place at both 3T and 1.5T using the same basic methodology (IR-HASTE), these studies had congruent results nicely demonstrating the suitability of placenta examinations at 3T. Huen et al. included a measurement of R_2* before and after oxygen breathing and consistent decreases in R_2* with oxygen were observed. There was no correlation with gestational age.[49] Notably, the previously observed decrease in T_1 with gestational age was not found in any of these studies, likely due to lower subject count. Ingram et al. introduced a predictive model of fetal growth restriction as a step toward providing diagnostic information, and found that it performed best when both ΔR_1 in addition to a baseline relaxation rate (either R_1 or R_2*) was included.[48] Recognizing that simultaneous quantitative estimates of both T_1 and T_2 could mean better inference of placental oxygenation, due to the previously discussed sensitivities of each relaxation time, magnetic resonance fingerprinting has been proposed

for placental imaging and used to acquire relaxometry in under ten seconds (Figure 4), showing a significant change during the oxygen paradigm for T_2, but not T_1.[97]

In order to streamline MRI scans while moving toward a diagnostic test, researchers have maintained focus on single-time point relaxometry, particularly on R_2* (=1/T_2*).[43,44,48,49,69,98,99] Placental T_2* was proposed as a strong predictor of low birth weight as it performed better than the uterine artery pulsatility index.[100] Studies evaluating T_2* estimates with respect to gestational age reported a negative correlation in healthy placentas.[44,69] Only a few studies included pregnancies complicated with IUGR or preeclampsia and reported significant difference in T_2* measurements.[44,48,69] Sinding et al. compared the the relative BOLD signal change to the magnitude of the T2* change when going from normoxia to hyperoxia periods and reported high relative BOLD signal change in dysfunctional placentas with signs of vascular malperfusion at pathological examination (i.e. $S_0[e^{-TE/T_2^*O_2} - e^{-TE/T_2^*air}]_{days\,functional} > S_0[e^{-TE/T_2^*O_2} - e^{-TE/T_2^*air}]_{healthy}$), while there was no significant difference in the magnitude of the T2* change between healthy and dysfunctional placentas (i.e. $[T_2^*O_2 - T_2^*air]_{days\,functional} \approx [T_2^*O_2 - T_2^*air]_{healthy}$).[43] As a result they concluded that the increased relative BOLD signal change in abnormal placenta may be explained by altered baseline oxygenation.

Limitations

Technical: None of the current MRI measures directly provide quantitative baseline oxygenation in the placenta. Relaxometry has shown changes in oxygenation state, and if a pure blood signal can be isolated oxygenation can be quantified. However there is no work yet that describes non-invasive quantitative measurement of placental oxygenation. In part this is due to the spatial heterogeneity of the placenta, thus methods for isolating certain blood compartments in the placenta based on their anatomical location[101] or physiological properties[102] would permit more accurate estimates of the the oxygenation state in each compartment, and provide more information about oxygen exchange dynamics. Although BOLD MRI provides useful information related to the relative change in deoxyhemoglobin concentration with oxygenation paradigm, there are large intersubject variations in signal amplitudes since the BOLD effect depends not only on the deoxyhemoglobin level but also on blood volume in the tissue, blood flow and baseline oxygenation.[14,103] Additionally, several biological factors (described below) could confound analysis of the temporal BOLD response.

In order to perform spatio-temporal analysis and develop better regional measures to characterize placental oxygenation it is necessary to eliminate motion artifacts due to unpredictable fetal movements, uterine contractions, and maternal breathing as well as signal non-uniformities caused by motion and field inhomogeneity especially in T_2* imaging. There are a few pipelines proposed to mitigate motion in the placenta[104-106] but there is still a need to make these pipelines easily accessible. Besides retrospective approaches, developments in MRI sequences (e.g. a new free-breathing BOLD sequence[107] or multiecho 3D stack-of-radial technique[108]) could provide an opportunity to collect high resolution T_2* maps of the entire placenta without motion artifacts.

The studies we have discussed are mostly focused on developing robust and reliable measurement techniques appropriate to Phase 1 studies. As such, there is significant diversity in the subject populations studied (e.g. normally developing, small for gestational age and preeclampsia), in imaging protocols (e.g. single slice versus whole placenta coverage, various resolutions both spatial and temporal, different MRI field strength, and different image acquisition strategy), and in processing approaches (e.g. method of relaxometry fitting, strategy for motion correction incorporating machine learning approaches) making comparisons between studies somewhat difficult. Particularly where an observation with many subjects scanned with older systems and protocols,[91] is compared to a more recent observation with fewer subjects but with more advanced imaging techniques, [49] it is very difficult to see where the truth lies. This diversity obscures a clear path toward predictive diagnostic models or establishing clinical benefit.

Biological: Baseline oxygen content in maternal and fetal blood, placental blood flow, oxygen diffusion, and placental oxygen consumption all affect oxygen transport in the placenta.[27] While placental pathology may affect oxygen transport by modulating any of these factors, intermittent fetal muscular activity, myometrial contractions and changes in maternal position may affect placental oxygenation temporally.[109] Therefore, for studies performing cross-sectional analysis of placental function, it is critical to take into account such variables. For example, changes in placental blood flow due to vena-cava compression in supine position may disturb placental hemodynamics and cause utero-placental hypoperfusion,[110] which might in turn affect placental oxygen transport. In a recent study, [111] higher BOLD signal change was reported in the supine position compared to the left-lateral position, which might be related to decreased baseline oxygenation in the placenta in the supine position due to aortacaval compression. Moreover, spontaneous non-labor contractions can change the utero-placental circulation and changes in the circulation affect the placental oxygenation.[112,113] The global effect of contractions on the placental oxygenation transport has been previously observed in BOLD MRI studies.[114,115] Thus, there are many biological factors that will need to be controlled to decrease variance in MRI-based oxygenation measures.

Future of Human *in vivo* Placental MRI

As described, there has been tremendous progress in MR imaging of the placenta with numerous studies assessing placental oxygenation via single time point relaxometry measurements and via temporal analysis of BOLD imaging during maternal hyperoxygenation in different placental pathologies. Many of these studies have demonstrated the potential of such measurements to distinguish abnormal from normal placentas in group comparisons and to characterize changes with gestational age. Although progress has been made with motion, it remains a confounder that future developments must continue to address. In addition, the link between MRI based measurements of oxygenation and individual placental physiology (ex. placental perfusion pressure, non-labor contractions) and pathophysiology (ex. altered spiral arteries or fetal microvasculature) requires further supplementation with other imaging modalities, model development and validation. In addition inclusion of MRI based measurements of oxygenation in future

clinical trials and complimenting MRI studies with additional data such as cell free mRNA/DNA may further improve our ability to phenotype placental function.

For example, multiple MRI modalities can be combined to infer specific quantitative information about oxygen delivered to and consumed by the placenta. Measurements of intravascular blood relaxation times coupled with blood flow measurements could be used to quantify placental VO_2. Techniques are available to obtain these measurements,[45,116-118] though these studies were focused on understanding whole fetal and cerebral oxygen demand in cases of congenital heart disease. One study found that fetal oxygen delivery increased exponentially between 23-34 weeks, but was invariant when normalized to fetal mass.[45] A similar framework could be implemented for the placenta, to characterize placental oxygen consumption across gestation and with pathology.

Another approach to improve the ability of MRI measures to characterize individual placental oxygen physiology is to explore ways in which MR measures could inform and build on current mathematical models. Using fluid dynamics in combination with structural information obtained via segmented digital photomicrographs of the villous network, models of microscopic oxygen transport dynamics are under development.[119-121] Based on simulations, a considerable degree of spatial heterogeneity in oxygen saturation of fetal and maternal blood over regions on the scale of a single voxel in MR images has been posited. A more detailed understanding of the relationship between tissue microstructure and abnormal oxygen transport may result from further elaboration of the relationship between numerical models and MRI-based measurements that occur on a larger scale.

Linking the measured regional physiology of oxygen metabolism to regional placental pathology remains a critical, yet difficult step toward using MRI for individual diagnosis. Comparing quantitative regional maps with an *ex vivo* placenta is challenging due to the differences in shape. In order to simplify this comparison and to guide pathological examination based on MRI measures, there are studies pursuing a placental flattening approach.[122,123] These studies can be thought of as a first step towards developing a common coordinate system to visualize, examine and compare the complex spatiotemporal dynamics of placental function before birth and obtain region pathological correlates after birth.

A more nuanced perspective of placental oxygen metabolism provided by MRI may eventually guide placental therapy, by helping to both better stratify disease severity and providing relevant outcome measurements. To date, there have been several attempts to treat placental dysfunction, but none of them have made it to clinical practice.[124] Early indications of benefit from pre-clinical or clinical case studies have failed to produce results at scale,[125-128] emphasizing the importance of the stratification of different phenotypes of placental dysfunction that need further investigation. Standardized MRI measures have the potential to provide such stratification of placental disease, possibly with machine learning approaches in retrospect, and future opportunities to develop phenotype specific drugs.

We recognize that MRI provides only one view of placental development, and that information from a variety of sources could enhance diagnosis and clinical decision making.

Specifically micro-RNA and cell-free fetal/placental DNA based screening may enable increased specificity of an individual diagnosis, and efforts should continue to understand the large shift in the gene expression of the placenta caused by hypoxia.[129-131] We imagine that there will be considerable synergy in both the development and eventual use of biochemical and imaging approaches to more accurately phenotype placental function. For example, although micro-RNA is correlated with the severity of fetal hypoxia, there is still the question of how hypoxia affects fetal and placental oxygen consumption. Micro-RNA indications of hypoxia could be compared with quantitative evaluations of placental VO_2 if those imaging-based techniques were to exist.

Thus there are many potential strategies to improve MRI assessment of placental oxygen metabolism but major barriers to the use of MRI remains. Placental dysfunction begins early (for example by 10 gestational weeks in preeclampsia),[132] but MRI use during the first trimester of pregnancy is controversial. Although MRI is recommended to further assess many fetal abnormalities, these recommendations and statements on the fetal safety of MRI only begin at 18 weeks gestational age.[133] The determination of fetal MRI safety involves the assessment of the biological risks to the fetus associated with all aspects of the MRI examination, but potential heating from the applied radiofrequency (RF) fields is a prominent concern since temperature increases can cause fetal harm.[134,135] Thus, the use of MRI to assess placental function in the first trimester will require that these safety concerns be addressed. In addition, the ability of MRI to assess placental function in high body mass index (BMI) women is limited primarily due to decreased signal to noise of images obtained. Although higher RF power could lead to improved image quality, the International Electrotechnical Commission (IEC) recommendations limit RF exposure to normal operating mode whole-body specific absorption rate (SAR) of 2W/kg in all pregnant women to provide conservative safety margins. However, conservative safety margins impair image quality especially in high BMI women because they need the most RF power. Hence more individual specific SAR management would be helpful especially for high BMI women and low GA women. Thus, although electromagnetic simulations using pregnant body models have been performed and studies with additional pregnant models are ongoing,[136-143] more needs to be done to clarify safety at early gestational ages and determine appropriate margins of safety for individual pregnant women.[144,145]

Finally, personalized measures of placental function may also give an opportunity to understand the complex effect of placental function on structural and functional fetal heart, lung and brain development. These are complex interacting systems that are all likely to impact neurodevelopmental and the emergence of brain disorders later in life. For example, placental insufficiency resulting in malnutrition, hypoxia and an altered endocrine status can alter cerebral cortical brain development and result in long-term deficits in neural connectivity and myelination.[146-148] However, direct measures of placental function may better highlight the important interactions between placental development, major fetal organ development and later brain development, as one-to-one correspondence between placental lesions and the integrity of the fetal brain are difficult to establish.[149]

Conclusion

We have made significant progress on imaging placental oxygenation and oxygen transport with MRI, with much of the recent progress fueled by the Human Placenta Project. However, the placenta presents numerous technical and physiological challenges that are unlike any other organ system, as motion is challenging and there are many complex interactions with the fetus and mother. Thus, there is a long road before robust, reliable and standardized approaches, with known diagnostic accuracy, are available for phase 3 and phase 4 studies. While we recognize that oxygen metabolism is only one window into placental function, of all the imaging modalities, MR continues to provide the most promise given its potential to quantify oxygen content and blood flow. With the urgent unmet need for better measures of placental health and response to novel interventions throughout pregnancy, we hope support for placental MRI research will continue. In addition, we hope that MRI methods of placental disease monitoring will be integrated other diagnostic tests using computational tools to better understand the link with developmental outcomes, setting the stage for improved life long health.

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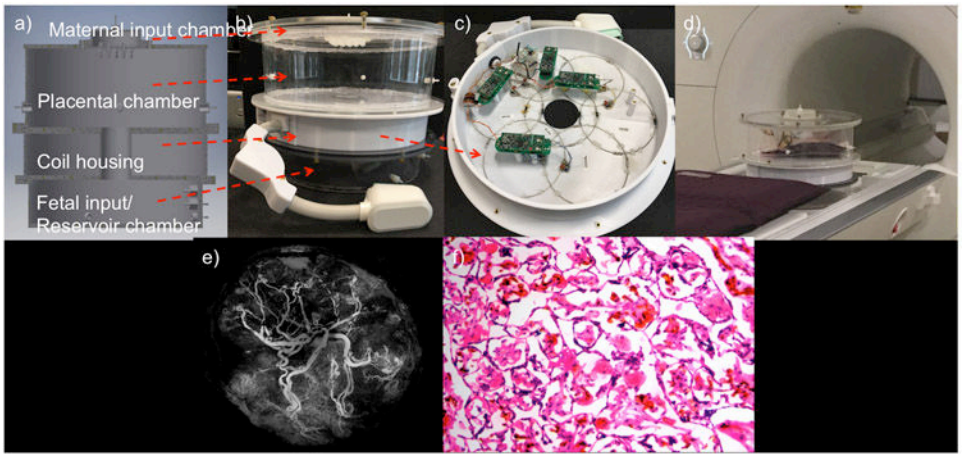

Figure 1.

a) Cross-sectional model of dual perfusion chamber, b) Assembled *ex-vivo* placental dual perfusion chamber and coil array, c) 7 Channel MRI coil chamber and array, d) Perfusion chamber and coil on MRI table, e) Maximum intensity projection of peristaltically perfused placenta acquired using the coil array. The placenta was imaged flat with the umbilical cord side down in room air. b) 20X photomicrograph of the syringe-pump perfused placenta (H&E Frozen section) showing yellow dye in ~90% of the distal capillaries in the region sampled.

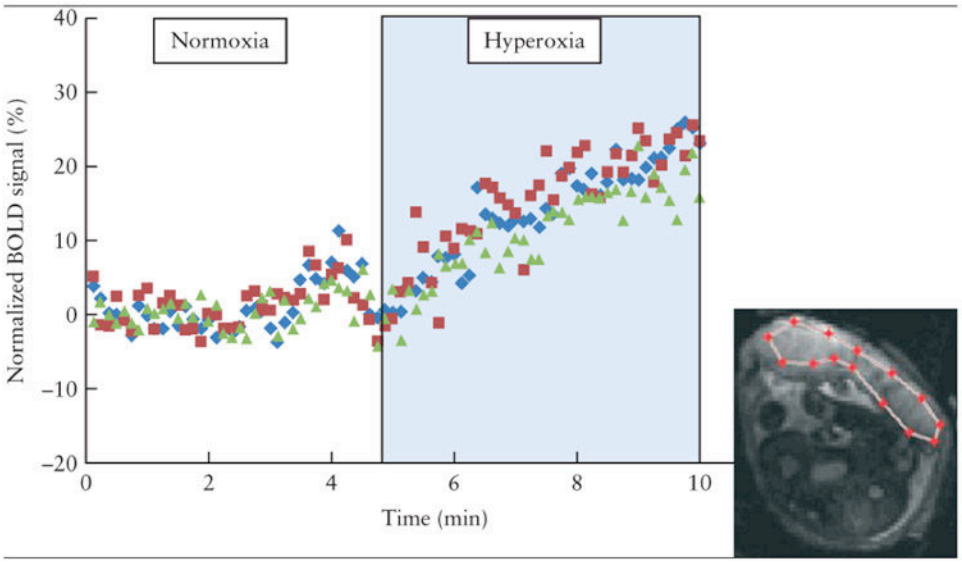

Figure 2.

Normalized blood oxygen level-dependent (BOLD) signal vs time curves of total placenta during 10-min BOLD scan: three curves represent three slices within the same placenta (Case 3). Region of interest is shown in inset BOLD image. (Reproduced with permission from Sorenson et al.[41])

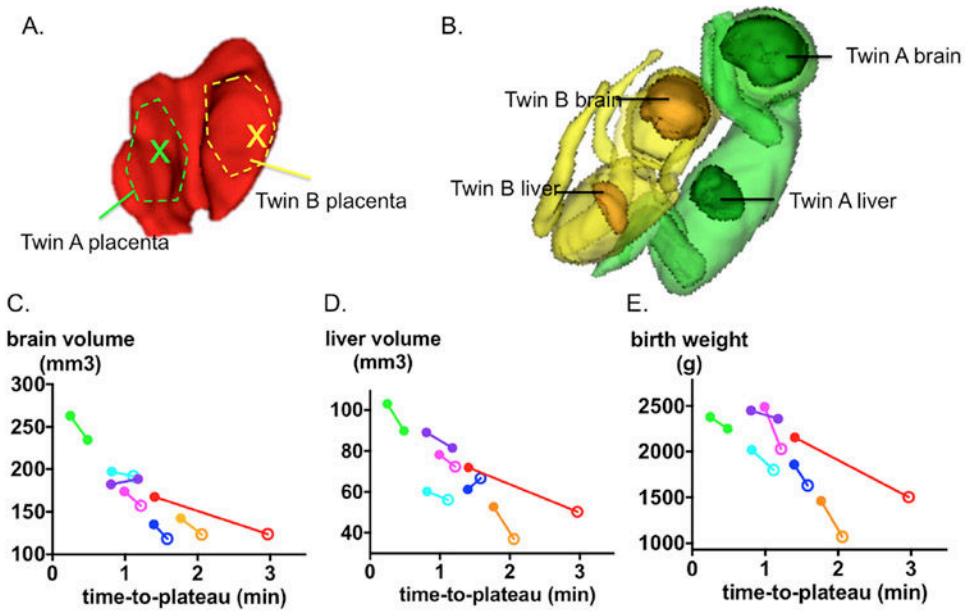

Figure 3.

Illustrations of segmentation volumes and of mean time-to-plateau (TTP). (A) placenta for the discordant twin pair with indication of ROI segmentation used for the average TTP calculation. (B) 3D view of segmented fetal brains and livers in the corresponding discordant twin pair (red points in (C–E) below). (C–E) Brain volume, liver volume and birth weight respectively as a function of the average TTP. The brain and liver volume were measured at the time of the scan. Twin pairs are connected by solid line, and are assigned same color. Hollow circles denotes fetuses that proved to be small for gestational age at birth. (Reproduced with permission from Luo et al.[42]).

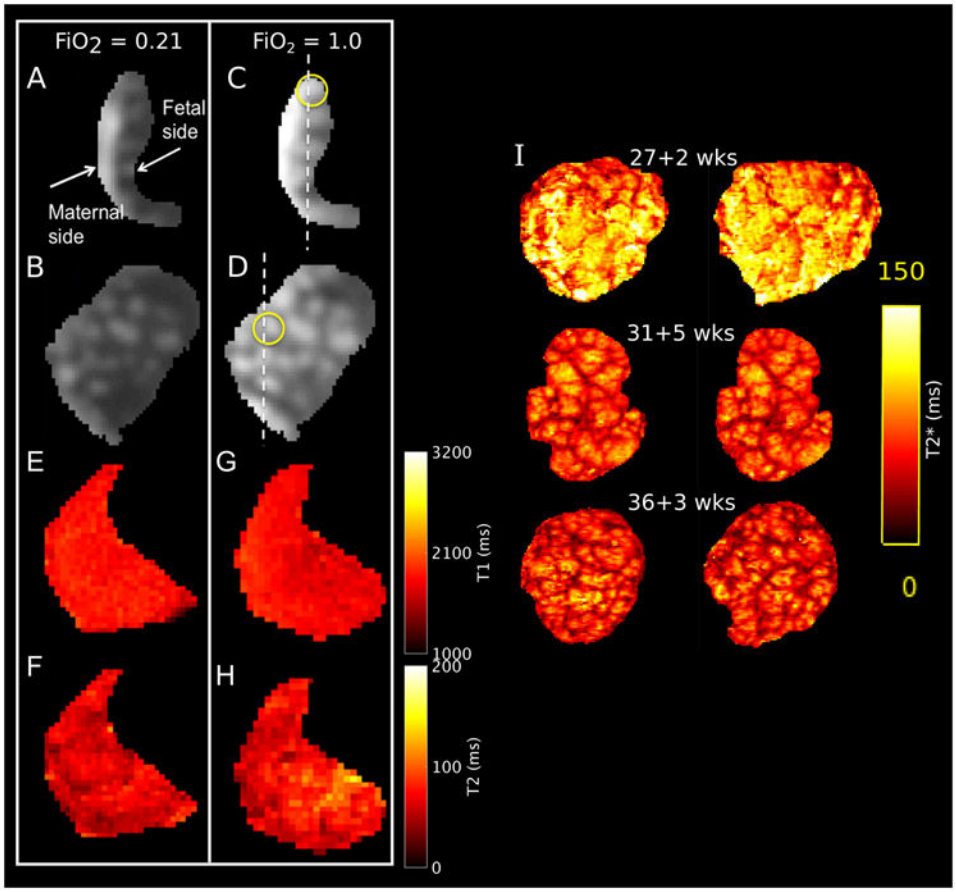

Figure 4.

Example BOLD images in two orientations from a placenta at 31+3 weeks (A-D). (Reproduced with permission from Luo et al.[42]) T_1 (E,G), T_2 (F,H) maps acquired using magnetic resonance fingerprinting from a placenta at 29+6 weeks. Images and maps during air breathing (A,B,E,F) and during maternal hyperoxia (C,D,G,H) show contrast between the two states. T_2* maps (I) from placentas at different gestational ages demonstrating changes during development. (Reproduced with permission from Hutter et al.[151])