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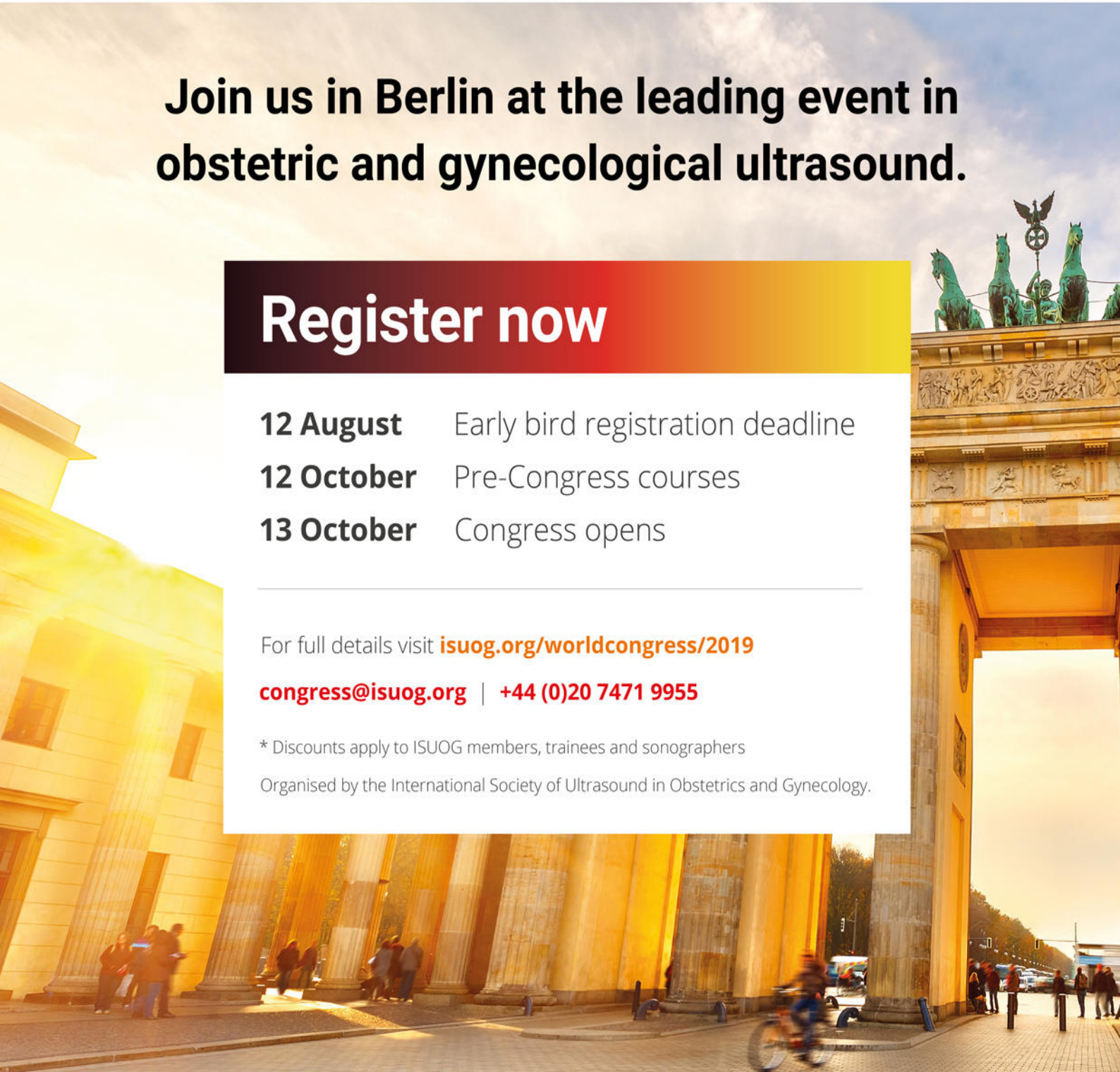

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T2* weighted placental MRI: basic research tool or an emerging clinical test of placental dysfunction?

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Contribution

- *What does this work add to what is already known?*

T2* weighted placental MRI provides antenatal information on placental function. Short placental T2* relaxation time and increased hyperoxic BOLD response are both promising indicators of placental dysfunction.

- *What are the clinical implications of this work?*

T2* weighted placental MRI is fast to obtain and easy to analyse, which makes the method a promising antenatal test of placental dysfunction.

Introduction:

Placental dysfunction is a common obstetric problem that complicates 5 – 10% of all pregnancies (1). It is a progressive condition, in which the fetal supply of oxygen and nutrients is insufficient to maintain normal fetal growth and organ development. The association between low birth weight and adverse neonatal outcome is well described (2). Moreover, there is evidence to support the hypothesis that common adult diseases such as metabolic syndrome and cardiovascular disease originate from abnormal fetal programming due to placental dysfunction – also known as Barker's Hypothesis (3). Currently, there is no available treatment to improve placental function. However, correct antenatal identification of placental dysfunction leads to a four-fold improvement in the neonatal outcome, as it allows for timely delivery and thereby reduces the risk of irreversible fetal organ damage (4).

Current antenatal screening of placental dysfunction focuses on fetal weight estimates and fetal and umbilical Doppler flow measurements. However, fetal size does not exactly reflect placental function. In addition, in late onset placental dysfunction, Doppler flows usually remain normal (5).Therefore, additional markers that directly reflect placental function have the potential to considerably improve the antenatal screening of placental dysfunction.

There is increasing interest in placental MRI, due to its potential to detect placental dysfunction in vivo. In particular, T2* weighted MRI has proven to be a simple and useful method to assess placental health, either studying the quantitative T2* relaxation time or the relative change in the raw T2* weighted signal in response to a given challenge (the BOLD response). T2* depends primarily on oxygenation but also on other tissue factors, including villous density, inhomogeneities in the distribution of oxygenated blood, magnetic field inhomogeneities, and the presence of other paramagnetic molecules (6).

This paper aims to explain the physiological basis for changes in T2* weighted signal intensity in the placenta. Previous literature on T2* weighted placental MR is reviewed and reference values are provided for 1.5 and 3 T. Practical guidance on how to optimize the T2* weighted scans is included, and the clinical potential of T2* weighted imaging as an antenatal test of placental dysfunction is outlined.

Basic concepts of T2* weighted MRI

T2* is the MRI transverse relaxation times which describes the time taken for the observed signal decay. It is a multifactorial, empirical measure that depends on many biological and physical features of the tissue. Specifically, in the placenta it depends on the more fundamental transverse relaxation time (T2) and volume fractions of the maternal and fetal blood, and of villous tissue, and on spatial variations in magnetic field across each voxel. The T2* of blood depends on the oxygen saturation of the blood, as well as other factors such as exchange between water and other molecules in the tissue, and water binding. Spatial variations in magnetic field can arise from a number of factors but primarily the heterogeneous distribution of deoxygenated blood. Oxyhaemoglobin and tissue both have similar slightly diamagnetic (negative) magnetic susceptibility whereas deoxyhaemoglobin has paramagnetic (positive) magnetic susceptibility. Variations in the magnetic susceptibility will lead to variations in the induced magnetic field within the tissue. Therefore, any spatial variations in the concentration of deoxyhaemoglobin across the placenta, for instance deoxygenated blood confined within fetal arterioles, or deoxygenated maternal blood draining from the placental intervillous space, could lead to a variation in magnetic field across the voxel.

However there are other factors that may change the signal in the T2* weighted MRI scan. For instance most T2* weighted images retain some residual dependence on the longitudinal relaxation time (T1), and dissolved oxygen may the T1 of blood which could cause a further increase in the signal in the T2* weighted images (7,8). Biologically, infarcts can contain intracellular methaemoglobin (which is particularly paramagnetic) and fibrosis, which can also reduce T2 (9). In some cases incoherent movement of the blood during the echo time may reduce the signal intensity of the T2* weighted scans. Finally, large-scale magnetic field variations will affect T2*. Static effects can be minimized by shimming but maternal respiration can cause T2* to fluctuate.

T2* forms the basis of the Blood Oxygen Level Dependent (BOLD) effect used in fMRI of the brain, in which changes in blood oxygenation and blood volume in response to neuronal activation lead to a change in the observed MRI signal. In contrast to the absolute T2* value, the BOLD effect is a relative measure, usually given as percentage of the baseline signal intensity. The T2* signal can be monitored over time to determine the relative change in T2* signal, or BOLD effect in response to interventions. However if T2* is measured quantitatively then normal reference values can be established to differentiate between normal and pathological placentas.

In utero the placenta consists of a large proportion of maternal blood. If the oxygen saturation of maternal blood is increased (by the mother breathing 100% oxygen) and assuming that there is no other physiological effects of the hyperoxic challenge, then the change in the placental T2* weighted signal (the BOLD effect) would be caused by the change in placental oxygenation.

How to obtain placental T2* images

There are several ways to obtain T2* weighted images of the placenta; fast gradient echo sequence (GE) or gradient-echo echo planar imaging (EPI) sequences, run in either single or multi-echo mode. GE sequences can achieve higher spatial resolution but take longer to acquire which makes them more sensitive to motion artefacts. For multi-Echo EPI data there is effectively no motion during the time required to acquire for each slice (<200ms), rendering it very robust to intra-slice motion, although the spatial resolution achievable is generally lower than for GE scans. At term the whole placenta can be scanned with EPI in a single breath hold using MultiBand/Simultaneous Multislice approaches. In principle GE-EPI will be affected by susceptibility artefacts in the abdomen, but the spherical nature of the pregnant uterus and the fluid filling the uterine and fetal cavities, make GE-EPI a very robust sequence for use in pregnancy even at 3T. It is preferable, however, to use image based B_0 shimming for GE-EPI at 3T where available.

We recommend using a trans-axial imaging plane with the field of view aligned with the scanner coordinates, to simplify planning. While coronal and sagital imaging planes are also possible the transaxial plane is commonly the most usefull, as the trans-axial imaging plane assures coverage of the main functional placental direction (maternal basal plate to fetal chorionic plate) within each image (without having to consider movement between slices). It is important that the field of view covers the whole of the abdomen to avoid artefacts from parallel imaging reconstruction techniques (e.g. SENSE artefacts). Similarly good fat suppression is required, for which the B_0 shim box must cover all the maternal subcutaneous fat.

In addition, we suggest, that the subject lies in the left lateral position (10° - 20° tilt) mainly to avoid caval vein compression, as even minor changes in the maternal circulation may have a detectable impact on the placental T2* value. A recent paper by Humpries et al (10) suggests that maternal supine position in late pregnancy may reduce the flow in the inferior caval vein by 85%. The venous return in the azygos vein is compensatory increased however; the cardiac output is reduced by 16%. We also find that left lateral position makes it easier to image posterior placentas,

as we can often place the receiver coils closer to the placenta. If scanning supine, we recommend ensuring frequent contact with the mother, monitoring maternal blood pressure, heart rate and oxygen saturation using MR compatible monitoring equipment. In addition splitting the scanning session into shorter sessions lasting no longer than 30-45 minutes will ensure maternal comfort. Accurate recording of the position and tilt angle is important for analysis purposes, given the possibility that the maternal position may influence the physiology.

Using this approach, a baseline T2* weighted data set covering the entire placenta can be acquired within 5 minutes from entering the scanner room to leaving it again, which suggests that this simple measurement could be used for rapid monitoring of placental health.

We are often asked 'what field strength should I use for placental imaging?' 1.5T is the field strength used in most placental MRI studies reported so far, however 3T field strength is replacing the 1.5T systems in many centers and therefore it is likely, that 3T will be increasingly used in future placental MRI studies. As the field strength increases, the sensitivity of MRI increases and the sensitivity to the BOLD contrast increases super linearly. 3T images can provide exquisite detail on oxygenation in the human placenta but for a standard clinical test of placental dysfunction, 1.5T can give sufficient information. In addition, the intrinsically shorter T2* values at higher field strength can make it difficult to acquire data at sufficiently short echo times to provide sufficient sensitivity to changes in T2*. In addition, at 3T the RF fields can be very inhomogeneous leading to signal drop out in the center of the field of view particularly with the larger abdomen at late gestation, which can make it harder to image posterior placentas. Furthermore, higher field strength increases the risk of geometric distortions due to air-tissue interfaces, requiring special attention to B_0 shimming especially if using high resolution EPI. While RF heating and acoustic noise are general safety concerns for fetal MRI, 3T magnets tends to have in general stronger gradient coils and hence higher acoustic output. For our current state of knowledge, we recommend using Level 0 normal operating mode of RF or 2 W/kg, labelled by some vendors as 'low SAR' or 'fetal MRI', since the fetus has reduced heat loss mechanisms compared to the adult. Similarly, we recommend not using parallel transmit approaches unless the system vendor explicitly advises their use in pregnancy. For acoustic noise we recommend using reduced acoustic noise options available on the scanner.

Data analysis

The quantitative placental T2* relaxation time

For more detailed placental assessment it may be preferable to measure the absolute T2* relaxation time rather than just acquiring a T2* weighted image, since quantitative measurements make the results more comparable over time for longitudinal studies, between patients in cross sectional studies, and between scanners and sites for a given field strength in multicenter studies.

We generally assume that T2* describes a mono-exponential decay. In that case in principle T2* can be estimated by a measurement at two echo times: the first being the shortest possible echo time and the second being at an echo time approximately equal to TE. The two echoes can either be collected from a single RF pulse (double echo sequence) or by repeating a single echo acquisition at two echo times which for the fast gradient echo sequence is the same sequence as used for IDEAL or DIXON fat/water scanning. T2* can then be estimated by calculating –dTe ln (S1/S2) where S1 and S2 are the signals from the first and second echo images respectively and dTe is the difference in the echo times of these two images.

Alternatively multiple echoes can be fitted for T2*. Comparing the signal decay to a monoexponential function will highlight any systematic errors in the data e.g. from shimming errors or high noise floors due to Riccian noise. We therefore recommend sampling the signal decay of at least three echo times (with the longest echo time providing a signal that is above the noise floor). If the data is fitted for a mono-exponential decay then a weighted linear fit should be used and efforts should be made to eliminate data points influenced by the noise floor. Otherwise, the data could be fitted to a more complex function for instance to take account of the effects of through slice dephasing(11). Multi-echo sequences are automatically co-registered but will be more sensitive to motion during the acquisition, and repeated single echo acquisitions allow a wider range of echo times to be explored, which can provide better discrimination of the signal decay curve (Figure 1).

Because of the heterogeneous nature of placental tissue and placental oxygenation, we recommend including as much placental tissue as possible in the region of interest (ROI) to improve the reproducibility of the T2* measurements. If possible a 3D volume should be obtained, or the T2* estimate should be based on an average of at least three slices spaced across the placenta. In each slice, the ROI should cover the entire placenta in a cross section perpendicular to the placental surface but amniotic fluid and large maternal vessels should be avoided by careful segmentation (Figure 2). In inhomogeneous appearing placentas, the segmentation should include all placental tissues, even regions with very low T2* values appearing almost homogeneously black. If necessary, segmentation can be assisted by checking the placental outline in T2 weighted

(fast spin echo) anatomical images (taking into account any movement between the acquisitions. The T2* measurement should be repeated at least 3 times with a minimal spacing of 3 minutes in order to identify artifacts related to uterine contractions (12). Extreme T2* values should be checked for susceptibility artifacts, movements artifacts (maternal and fetal) or contractions and excluded from the analysis. If both magnitude and phase maps are stored for T2* mapping data sets, then susceptibility weighted imaging and susceptibility mapping can be performed providing information that is more specific to oxygenation than T2* alone.

Placental T2* mapping

In addition to reporting the mean T2* relaxation time for the entire placental slice (2D) or placental organ (3D), a map of the different T2* value of each pixel can be created, to illustrate the T2* heterogeneity (Figure 6). Histogram distribution of the T2* values normalized by placental volume may provide a quantitative evaluation of the degree of tissue heterogeneity, which may be related to placental pathology (13,14). It also provides an opportunity to relate the T2* values to specific anatomic features.

The placental BOLD effect

If a time series of T2* weighted MRI scans is acquired across the placenta then the dynamic change in signal intensity can be estimated, this is generally known as the BOLD effect (ΔBOLD) (Figure 3). For instance experimental studies have investigated the placental response to maternal hyperoxia using the following equation to estimate the hyperoxic BOLD effect (15):

$$\Delta BOLD = (S_{Hyperox} - S_{Normox})/S_{Normox} \times 100\%$$

In order to achieve reliable estimates of the hyperoxic BOLD effect the dynamic scan should be continued until the placental response reaches the steady-state level. In the normal placenta the steady state level is reached within 5 minutes of maternal hyperoxia. However, in the dysfunctional placenta the time to steady state can be prolonged, sometimes even beyond 10 minutes. If the scan is stopped before the steady state level is reached, it may lead to an underestimation of the BOLD effect. Also, the T2* weighted scans are very sensitive to uterine contractions, which may also lead to an underestimation of the hyperoxic BOLD effect. Uterine contractions maybe identified by uterine movements in the dynamic scan or by the pregnant women. A recent publication suggests, that most contractions are subclinical, and therefore you cannot rely on

maternal reports alone (12). Alternatively, if T2* is measured then the BOLD signal can be characterized by the absolute change in T2* (ΔT2***).**

$$\Delta T2^* = T2^*(\text{Hyperoxia}) - T2^*(\text{Normoxia})$$

Literature search

A systematic search was performed in Pubmed/Medline (last updated November 8th, 2018) by combining the following terms “Placenta” AND “MRI” AND “T2* OR “BOLD”. This search yielded 142 results. These papers were reviewed by title and abstract using the pre-specified inclusion criteria that required papers 1) were original studies and 2) included T2* weighted MR imaging of the placenta. There were no language restrictions, and we included both human and animal studies. The resulting 37 studies were then assessed by full text review, and a total number of 24 studies fulfilled the inclusion criteria. Additional literature search by the reference lists of the included studies revealed no further studies for the review. The included papers are listed according to their date of publication and are separated into studies on the Placental BOLD effect (Table 1) and Placental T2* (Table 2).

Dynamic T2* weighted placental MRI – Placental BOLD MRI

Most human studies have investigated the changes in placental signal intensity during maternal hyperoxia (3 – 10 minutes of oxygen breathing) (15–21), and a single study investigates the effect of uterine contractions (21). In addition, three animal studies describe changes in placental signal intensity during maternal hypoxia (22), normoxic hypercapnia (23) and injection of vasoconstrictor (24).

Human studies were performed at both 1.5T (12,15–18,21) and 3T (19,20) using single shot gradient echo EPI sequences. However, the specific echo-time (TE) and repetition-time (TR) varied between studies as presented in Table 1.

Placental BOLD effects in experimental animal studies

Experimental animal studies have investigated the correlation between acute changes in placental oxygenation and changes in placental BOLD signal intensity. In a sheep model maternal hypoxia lead to a mean reduction of the BOLD signal of a placental cotyledon by 29% (range 9-43%) (22).

In a rat model injection of Prostaglandin $F_{2\alpha}$, which is known to cause placental vasoconstriction, lead to a 10% reduction on placental BOLD signal intensity (24). Recently, a study conducted in mice investigated the effect of normoxic hypercapnia on the placental BOLD signal. A 44% reduction in placental BOLD signal was demonstrated, probably caused by placental hypo-perfusion due to the vasoconstrictive effect of hypercapnia (23).

The hyperoxic BOLD effect (ΔBOLD) in normal human pregnancies

In normal human pregnancy the placental hyperoxic BOLD effect have been addressed in four studies (15,16,19,21). A significant increase in the placental signal intensity (ΔBOLD) was demonstrated during hyperoxia (15,16,21), and a positive correlation between ΔBOLD and gestational age was demonstrated (21). In normal pregnancies at term ΔBOLD was 20% (21).The findings are presented in Figure 3.

The hyperoxic BOLD effect (ΔBOLD) in human pregnancies complicated by IUGR

Three studies included IUGR pregnancies, and in these studies IUGR was defined by low birthweight (15,19) or low birthweight in combination with abnormal postnatal placental examination (21). Initially, a small study including four IUGR cases demonstrated inconsistent results regarding the hyperoxic BOLD effect (15). However, a larger case-control study including 13 IUGR cases and 49 healthy controls demonstrated that placental ΔBOLD was significantly increased among IUGR cases (21), Figure 4. In addition, the study by Lou et al. demonstrates that in monochorionic twin pairs complicated by selective IUGR the time to reach hyperoxic steady state is prolonged in the smaller twin (19).

Quantitative placental T2* relaxation time (Baseline T2*)

The placental T2* relaxation time has been estimated in seven human studies (7,8,13,21,25–27) and six animal studies (14,28–32). The main purpose of these studies was to estimate the baselineT2* value in normal pregnancies and in pregnancies complicated by IUGR. In addition the hyperoxic placental T2* response (ΔT2*) has been addressed in five of these studies (16,23–25,30). The studies are presented in Table 2.

Five human studies were performed at 1.5T (7,8,21,25,27) and two human studies were performed at a 3T system (13,26) using a multi-echo gradient-recalled-echo (GRE) sequences. However, the

MRI protocols were different in regards to the number and values of the included echo-times as presented in Table 2. The protocol differences result in different accuracies in short and long T2* measurements. In all human studies the T2* value was obtained in large regions of interest (ROI) covering the entire placental cross section. Moreover, in the studies by Sinding et al. the T2* value was calculated as an average of three slices (21,25,27). The studies by Hutter et al. (13) and Armstrong et al. (26) are based on 3D placental models. In the remaining studies the T2* value was based on a single slice only (7,8).

Quantitative placental T2 relaxation time in normal pregnancies (Baseline T2*)*

In normal pregnancies the association between the baseline T2* and gestational age has been investigated in a total of six studies; one study in a 3T MRI system (13) and five studies in a 1.5T MRI system (7,8,21,25–27). The largest studies have found a strong negative correlation between baseline T2* and gestational age (13,21,25,27). Ingram et al found a non-significant negative correlation (7), and a small study on 14 pregnant women failed to demonstrate such correlation (8). In normal pregnancies at term the placental baseline T2* was estimated to be 47-58 ms at 1.5T (7,8,25,27) and 25 ms at 3T (13) demonstrated in Figure 5 and Figure 6, respectively. The reproducibility of the baseline T2* measurements have been addressed by Sinding et al at 1.5T (25). In this study, the 95%-limits of agreement for within- and between-session variation for a single slice placental T2* measurement was -2.1±10.4ms and -0.6±22.6ms, respectively. In addition, this study demonstrated, that including large regions of interest and average of more slices improves the reproducibility of the T2* measurement. A recent publication by Hutter et al. have demonstrated that the within and between-session variation of T2* at 3T was 1.83+-2.42ms and 1.91+-21.60ms (13).

Placental T2* mapping have demonstrated that the within placental heterogeneity of T2* is in the range of 10 – 200 ms, and the hyperintense areas are corresponding with the center of the cotyledons. In addition, the degree of heterogeneity is increased as pregnancy advances (13). The placental histogram is presented in Figure 6.

Baseline T2 in pregnancies complicated by IUGR*

Four human studies included IUGR pregnancies (7,21,25,27). In these studies IUGR cases were defined by either low birth weight (25,27), a combination of low birth weight and abnormal umbilical Dopplers (7) or low birth weight and abnormal postnatal placental examination (21). Three studies

were designed as case-control studies (7,21,25). In each of these studies the baseline placental T2* value was significantly reduced in IUGR cases when compared to normal controls asdemonstrated in Figure 5. In a prospective cohort study, low placental T2* value was a strong predictor of low birth weight, and it performed significantly better than uterine artery Doppler flow measurements (27).

The hyperoxic T2 response (ΔT2*)*

ΔT2* in response to maternal hyperoxia has been investigated in three human studies (7,8,21), which all found a significant increase in placental T2*. The largest study was conducted in 49 normal pregnancies, and this study demonstrated a strong positive correlation between the ΔT2* and gestational age (21) (Figure 5). In the remaining two smaller studies Ingram et al. (7) (n=28) and Huen et al. (8) (n=14) failed to demonstrate such correlation. The increase in placental T2* during hyperoxia is supported by two experimental animal studies in rats (32) and mice (28).

Two human studies included ΔT2* in IUGR pregnancies (7,21). In these studies IUGR was defined by either low BW and abnormal postpartum placental examination (21) or low BW and abnormal Doppler ultrasound findings (7). These studies found no significant difference between ΔT2* in IUGR pregnancies and normal controls. In animal studies there have been conflicting results concerning ΔT2* in IUGR cases. One experimental rat study by Chalouhi et al. reported that placenta ΔT2* in response to hyperoxia was reduced among IUGR cases (32), whereas a recent experimental study in mouse by Collinot et al reported that placental ΔT2* in response to hyperoxia was increased in IUGR (28).

Discussion

Based on the literature review we conclude that T2* weighted placental MRI is a promising marker of placental dysfunction. Approximate reference values for the placenta at 1.5T and 3T, and tips and guidance on how to obtain placental baseline T2* values are presented in Table 3.

It is a consistent finding, that placental dysfunction is associated with a lower baseline T2* value (7,14,21,25,28). The underlying physiological explanation for the low T2* in placental dysfunction is not fully understood. It is well known that placental dysfunction is associated with impaired maternal placental perfusion due to defective transformation of the spiral arteries, which may lead to placental hypoxia (33). As T2* weighted MRI is particularly sensitive to the amount of deoxyhemoglobin present in the tissue, placental hypoxia may reduce T2*. However, in addition, changes in placental morphology such as altered villous density, deposits of fibrin and infarcts may also contribute to a lower T2* value. The latter is supported by a study by Wright et al demonstrating a significant positive correlation between placental T2 and morphological findings such as the relative density of fibrin deposition and villous volume (34).

The majority of studies support a negative correlation between baseline T2* and gestational age (7,13,21,25). Direct measurements of the oxygenation in the intervillous space have demonstrated that oxygenation decreases as gestation advances (35), probably as a result of an increased extraction of oxygen from the intervillous space due to an increased feto-placental metabolic demand as pregnancy advances. In addition, normal physiological placental maturation is associated with morphological changes that may also alter the placental MRI signal intensity. Any comparison between groups should always include adjustment for gestational age at MRI.

It has been demonstrated that the placenta has a heterogeneous appearance in T2* weighted images (15)**,** and maps of T2* demonstrate that the heterogeneity increases with gestational age (13). The heterogeneity may reflect the oxygenation of the placental cotyledons. The cotyledon has a highly oxygenated center, where the maternal spiral arteries enters the intervillous space, and the oxygenation decreases toward to margins of the cotyledon where maternal blood drains back into the maternal venous circulation. Combining contrast enhanced MRI and placental T2* maps in non-human primates supports this hypothesis, as areas with a higher T2* value corresponds with the entrance of the spiral artery in the center of the cotyledon (31).

Several studies have demonstrated that maternal hyperoxia increases the placental signal intensity in the T2* weighted image, also known as the hyperoxic BOLD effect (ΔBOLD) (15,16,18). The direct correlation between changes in placental signal intensity and changes in placental

oxygenation has been confirmed by an invasive experiment in a sheep model (22). In these experiments deoxyhemoglobin can be regarded an intrinsic contrast agent (31). At room air maternal arterial blood is already fully saturated, however hyperoxia leads to an increased saturation of the maternal venous blood in the intervillous space, which is generally accepted to be the main contributor of the hyperoxic BOLD effect. Fetal blood may also contribute to the hyperoxic BOLD effect, however this contribution is expected to be marginal as the proportion of fetal blood is markedly lower than the proportion of maternal blood in the placenta.

In the dysfunctional placenta, ΔBOLD is increased when compared to the normal placenta (21). To understand this finding, one should remember that ΔBOLD is a relative measurement. Any increase in ΔBOLD may be due to an increase in absolute signal intensity and/or a reduced baseline absolute signal intensity. In the dysfunctional placenta, it has been demonstrated that the baseline T2* is markedly reduced when compared to normal controls (21). However, the change in absolute placental oxygenation, estimated by ΔT2*, did not differ between the normal and the dysfunctional placenta (21). This finding indicates, that the higher hyperoxic BOLD effect in dysfunctional placentas may simply reflect a lower T2* baseline value. Similarly, the positive correlation between ΔBOLD and gestational age in normal pregnancy may also be explained by a decreasing baseline T2*. These findings suggest, that as an initial clinical biomarker the fast and simple baseline T2* signal may provide sufficient information to discriminate between the normal and the dysfunctional placenta.

Placental dysfunction is a main challenge in modern obstetrics and today it remains the leading cause of stillbirth (36). Baseline T2* may provide a valuable tool to differentiate between the constitutionally small fetus and the fetus suffering from placental dysfunction. A reliable marker of placental dysfunction in-vivo may increase the antenatal identification of placental dysfunction, which would allow for timely delivery and thereby reduce the number of stillbirths. Baseline T2* may provide early subclinical identification of placental dysfunction before abnormal fetal growth occurs. In addition, longitudinal studies based on baseline T2* offer an opportunity to evaluate the effect of treatment to improve placental function. An area of particular interest will be late onset placental dysfunction, which can present with appropriately grown fetuses and normal umbilical Doppler, so that the dysfunction often remains undetected. Other MRI markers of placental function such as baseline T1, T2 and diffusion weighted MRI still needs to be properly evaluated, since a combination of different MRI markers may further improve the antenatal detection of placental dysfunction.

Conclusion

This review provides approximate reference values on 1.5T and 3T and useful guidance on how to obtain and analyze T2* placental values. Based on the previous literature, placental T2* is a promising marker to discriminate between the normal and dysfunctional placenta in-vivo. Initial studies suggest, that Placental T2* is a highly reproducible measurement with a great clinical potential. As the value of T2* obtained depends on the exact pulse sequence used pooling of results to provide clear guidelines for a specific T2* cutoff value is difficult at this stage. Future multicenter trials with a consistent MRI protocol performed at specific gestational ages in clinically well-defined population should be the next step to determine the clinical potential of T2* weighted placental MRI.

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Figure legends

Figure 1 Mean signal intensity (S) of the placental ROI at 16 different echo times (TE), with some corresponding MR images. The T2* decay curve was obtain using a non-linear square fitting algorithm. (Reprinted from Ref (25))

Figure 2 T2* weighted MR image (1.5 T) demonstrating the placental image plane . ROI should cover the entire placental area. (Reprinted from Ref (21))

Figure 3 The hyperoxic BOLD response in the normal placenta at 1.5T. Image at top: The visual placental changes during maternal hyperoxia; Figure A (normoxia) and Figure B (hyperoxia). Image at bottom: Changes in the normalized placental signal intensity (ΔBOLD) during maternal hyperoxia. ROI covers the entire placental area, and the colors refers to three different placental slices within the same placenta. (Reprinted from Ref (15))

Figure 4 The hyperoxic BOLD response (ΔBOLD) in relation to gestational age at MRI in normal pregnancies (open circles) and pregnancies complicated by fetal growth restriction (dark circles). The black lines indicate the association between ΔBOLD and gestational age in normal pregnancy (mean, 95% prediction interval). (Reprinted from Ref (21))

Figure 5 T2* weighted placental MRI at 1.5T in normal pregnancies and pregnancies complicated by placental dysfunction.
Top: T2* weighted MR placental images (white arrow) in normal pregnancies and four cases of placental dysfunction. The dysfunction placenta appears markedly darker than normal placentas in the MR images. (Reprinted from Ref (25))
Bottom: The association between placental T2* measurements and gestational age in normal pregnancies (open circles) and pregnancies complicated by placental dysfunction (dark circles). Black lines indicates the least square fit of normal pregnancies; mean and 95% prediction interval. Left: Baseline placental T2*. Middle: Hyperoxic placental T2*. Right: The hyperoxic change in T2* value (ΔT2*). (Reprinted from Ref (21))

Figure 6 T2* weighted placental MRI at 3T in normal pregnancies and in two cases of preeclampsia (PE).
Top: T2* maps of coronal placental planes in two normal pregnancies (A) and two cases of PE (B). The blue lines illustrates the perceived lobules delineation.
Bottom: A: The mean placental T2* value in relation to gestational age at MRI (GA). Normal pregnancies (blue crosses) and PE cases (red circles).B: T2* histogram normalized by placental volume. Color coded by gestational age at MRI. Dotted lines indicate the PE cases. (Reprinted from Ref (13))

Author Year	Design	MRI system	MRI protocol	Population	Exposure	Outcome	Comment.
Human Studies							
Sinding 2018 (21)	Case-control	1.5T GE	Single shot gradient echo EPI TR=8000ms TE=50ms Angle:90° Slice thickness 6 mm Resolution 3.6x3.6mm Mean of 3 slices	Controls: BW>10th centile (n=49) GA at MRI 16-41 Cases: BW<10th centile Abnormal PPE (n=13)	100% O_2 (10 min)	Controls: z-score=0 Cases: z-score=4.94, (95%-CI :2.41 – 7.47)	Postpartum placenta exam (PPE). Adjusted for GA at MRI (r=0.47, p=0.0009)
Luo 2017 (19)	Case-control	3T Siemens	Single shot gradient echo EPI TR=5000-8000ms TE=32-38ms Angle: 90° Slice thickness 3 mm Resolution 3x3 mm^2 Views: Cross	MC twins pairs (n=7 pairs) GA at MRI 29-34 Controls: BW>10th centile Cases: BW≤10th centile	100% O_2 (10 min)	Time-to-plateau (TTP) and slope (ΔR2*) **PPE 2-4** TTP↑ inhomo. (p=0.039) **FGR** TTP↑(P=0.008) ΔR2*↓ (p=0.04) **BW vs TTP**	Postpartum placenta exam. (PPE) TTTS excluded TTP an independent predictor of low BW

			sectional and orthogonal.			r=-0.75, p=0.07 **Small twin vs. large** TTP↓ in small	Adjusted for EFW and UmbA Doppler
Turk 2017 (20)	Cohort	3T Philips	Single shot gradient echo EPI TR= 5.8 – 8ms TE=32-36ms Angle: 90° Slice thickness: 3mm Resolution: 3x3 mm^2	Singletons (n=4) Twins (n=6) GA at MRI=26-34	100% O_2 (10 min)	Pre-processing including intravolume and intervolume correction significantly reduces the variation between estaimates of placental intensity	
You 2016 (17)	Case - control	1.5T GE	Single shot gradient echo EPI TR=2000-3000ms TE=1000ms Angle 90° Slice thickness 5-8mm Mean of 3 slices Resolution Axial and coronal	Controls: Healthy singletons (n=8) Cases: Singletons with CDH (n=8) GA at MRI=25-40	100% O_2 (3-4 min)	Preprocessing pipeline reduces the motion-induced artifacts in the placenta	

You 2015 (18)	Case-control	1.5T GE	Single shot gradient echo EPI TR=2000-3000ms TE=1000ms Angle 90° Slice thickness 5-8mm Mean of 3 slices Resolution Axial and coronal	Controls: Healthy singletons (n=8) Cases: Singletons with CDH (n=8) GA at MRI=25-40	100% O_2 (3-4 min)	Pre-processing pipeline to enhance motion correction in fetal fMRI without large data loss.	
Sinding 2016 (25)	Cohort	1.5T GE	Single shot gradient echo EPI TR=8000ms TE=50ms Angle:90° Slice thickness 6 mm Resolution 3.6x3.6mm	Normal (n=56)	Uterine contractions (n=8)	Δ signal=-17.5%, SD ± 5%	Contractions are identified by changes in uterine shape in the dynamic scan.
Sørensen 2015 (16)	Case-control	1.5T GE	Single shot gradient echo EPI TR=8000ms	Controls (n=21) GA at MRI 24-40 FGR cases (n=4)	100% O_2 (5 min)	Controls: ΔBOLD 12.6% ± 5.4%	Postpartum placenta exam. (PPE)

			TE=50ms Angle: 90° Slice thickness 6 mm Resolution 3.6x3.6mm Mean of 3 slices	Low BW<5th centile GA at MRI 24-31		FGR cases: Inconsistent findings: hyper-response and non-response.	
Sørensen 2013 (15)	Cohort	1.5T GE	Single shot gradient echo EPI TR=8000ms TE=50ms Angle: 90° Slice thickness 6 mm Resolution 3.6x3.6mm Mean of 3 slices	Healthy controls (n=8)	100% O_2 (5 min)	ΔBOLD: 15.2 ± 3.2%	
Animal studies							
Ginosar 2018 (23)	Rat + mice Cohort	4.7T Bruker	TR=147ms TE=10ms FOV=5.4 cm^2 Resolution:256x256 Slice thickness=1mm	(Animal, n=6) Average of number of pups:5	3 episodes: Air Air/CO_2, 5% Hyperoxi 95%/CO_2	 ΔBOLD =-44±5.5% ΔBOLD=+83±23%	Acute fetal asfyxia during hypercapnia indicated by umb. Artery PI↑ and FHR↓

Girsh 2007 (24)	Rat Case-control	4.7T Bruker	TR=230ms TE=10ms FOV=7 cm Resolution:256x256 Slice thickness=0.8mm	(Animal, n=6) 47 placental units (n=4) controls	$PGF_{2\alpha}$ inj.	Case ($PGF_{2\alpha}$) ΔBOLD=-10% Control (saline) ΔBOLD=-1% ($p<0.025$)	Hypothesis: $PGF_{2\alpha}$ → vasoconstriction→ placental hypoxia
Wedegärtner 2006 (12)	Sheep	3T Philips	Single shot gradient echo EPI TR=8000-(16000)ms TE=45ms Angle:90° FOV=180mm Resolution:2.25x2.25 mm Slice thickness 5mm	(n=6) (Cotyledons, n=4)	Hypoxia (5-10 min) Maternal sat. 60-80%	ΔBOLD= mean 29% (range: 9-43%)	Postive correlation between fetal saturation (carotid artery cath.) and Placental ΔBOLD

Table 1: Review Table: Dynamic T2* weighted placental MRI - Placental BOLD scan

Author Year	Design	MRI system	MRI protocol	Population	Baseline T2*	Hyperoxic ΔT2*	Comment.
Human Studies							
Hutter 2018 (13)	Case-control	3T Philips	Multi-echo GRE TR=56.6 ms TE (5)=13.8–240.2 ms FOV:300x360mm Matrix: 150x180 Slice thickness 2.5mm	Controls (n=24) MRI: 20-40	20w: Mean T2*=90ms 40w: Mean T2*=25ms	-	Includes T2* mapping and histograms. Posterior placentas are excluded.
				Cases PE (n=2)	Low T2* value		
Armstrong 2018 (26)	Case - Control	3T Siemens	Multi-echo GRE Stack-of-radial TR=15.9 ms TE(12)=1.23 - 14.76ms Flip angle:5° FOV:380x380 Matrix: 224x224 Slice thickness 4mm	Controls (n=30) MRI: 14-18w	Mean T2*=77.3 ms (Range:49.2 – 126 ms)	-	No difference in baseline T2* between anterior and posterior placentas.
				MRI: 19-23w	Mean 75.8 ms (range: 59.2 – 103 ms)		
				Cases: Ischemic placental disease FGR<10th centile or PE MRI: 14-18w + 19-23w	n.s.		

				(n=3)			
Sinding 2018 (21)	Case - Control	1.5T GE	Multi-echo GRE multishot TR=70.0ms TE (16)=3 – 67.5ms Flip angle= 30° FOV: 360x360mm Matrix:128x128 Slice thickness 8mm Mean of 3 slices	Controls: BW>10th centile and normal Dopplers Mean GA at MRI 27.1w (Range:16-41w) (n=49)	T2* z-score=0	Z-score=0	Adjusted for GA at MRI (z-score) Postpartum placenta exam.
				FGR cases: BW<10th centile and abnormal PPE Mean GA at MRI 32.6w (Range:23-37w) (n=13)	T2* z-score = -3.13 95%-CI:(-3.94 , -2.32)	T2* z-score =0.29	
					P<0.0001	p>0.05	
Ingram 2017 (7)	Case-Control	1.5T Philips	Multi-echo GRE singleshot TR=8000ms TE(10)=5-50ms Flip angle=40° FOV: 450x450mm Matrix=128x128	Controls: BW>20th centile and normal Dopplers Mean GA MRI: 27+5w (Range:21-38w) (n=28)	Mean T2* 58.5 ms 95%-CI: (50 - 71.4 ms)	ΔR2*= -1.3 (-3.0 – 1.0)	No correlation between T2* and GA

			Slice thickness 10mm	FGR: BW<5th centile and UtA PI>1.3 or UmbA PI ≥ class 2 Mean GA at MRI:29+0w (Range:23-35w) (n=23)	Mean T2*: 38.5ms 95%-CI: (31.3 – 45.5 ms)	ΔR2*= -3.0 (-4.6 – 1.4)	
					P<0.0001	P=0.06	
Sinding 2017 (27)	Cohort (mixed)	1.5T GE	Multi-echo GRE multishot TR=70.9ms TE(16):3 – 67.5ms Flip angle=30° FOV=350x350 mm Matrix 265x128 Slice thickness 8mm Mean of 3 slices	Mixed population GA MRI: 20-40w (n=100)	Prediction of low BW. AUC=0.92 (CI 0.85-0.98)	-	Comparison with uterine artery Doppler.
Sinding 2016 (25)	Case - Control	1.5T GE	Multi-echo GRE multishot TR=70.9 ms TE(16):3-67.5 ms Flip-angle=30° FOV=350x350 mm	Controls: BW Z-score>-2 and normal Dopplers GA birth: MRI (Range: 24-40w) (n=24)	Mean T2*; 24w: 120±17ms 32w: 84±16 ms, 40w: 47±17ms		Strong correlation between T2* and GA Adjust for GA at

			Matrix: 256x128 Slice Thickness=8mm	FGR cases: BW<3th centile GA at MRI (Range 24-31w) (n=4)	T2* z-score: Range: -5.24 to -0.34 ms		MRI (z-scores)
Huen 2013 (8)	Cohort (normal)	1.5T Philips	Multi-echo GRE multishot TR:60 TE(10): 5-50 ms Flip angle: 40° FOV: 450x450 mm Matrix=128x128 Slice thickness=10mm	Healthy, BW not indicated GA at MRI (Range:23-37w) (n=14)	Mean T2*: 54.6±15.9ms	ΔR2*=-4.30 ±1.82ms	No correlation betwen T2* and GA No correlation between ΔR2* and GA
Animal studies							
Sollinot 2018 (28)	Mice Cohorte	4.7T Bruker	Multi-echo GRE TR=714 TE(42)=1.8-83.8ms Flip angle:80° FOV:4 x 3.22 cm Matrix=256x256 Slice thickness:1mm	**Wildtype**: 12 mice (57 placentas)			T2* inner > T2* outer
				TgSTOX13: 15 mice (60 placentas) BW↓, PW↓, BT↑	Placenta T2*↓	ΔT2*↑	P<0.005
Lo 2018 (14)	Rhesus Macaque	3T Siemen		Healthy control (n=3)		-	Brain growth and maturity

	Case report	s		Natural occurring IUGR (n=1)	Placental T2*↓		reduced in FGR case Postnatal placental exam.
Lo 2017 (30)	Rhesus Macaque Case report	3T Siemens		Non-alcohol (n=6)			Alcohol reduces placental T2* and is associated with low BW
				Alcohol exposure (n=6)	T2*↓ GA 110 p<0.02 GA 135 p=0.39		
Avni 2016 (29)	Mice	9.4T Bruker		MRI embryonic day 14.5 (n=8) 17.5 (n=10)	P50=0.48±0.19 P50=0.39±0.17		Oxygen affinity (P50) is reduced during pregnancy
Schabel 2018 (31)	Rhesus Macaque	3T Siemens	TR=418 ms TE(6)=4.92-44.28 ms Flip= 30° Slice thickness: 1.5mm Slice orientation: Coronal	MRI at day 110 (n=3)	$R2^*$ is strongly correlated to the distance to the spiral artery		Spiral arteries identified by DCE-MRI and compared to T2* maps.

Chalouhi 2013 (32)	Rat Case-control	4.7T Bruker	TR=800 ms TE(20)=1.8- 49.8 ms Flip=80° FOV= 10 x 7 cm Slice thickness: 2mm	MRI at day 17 (n=16) Control (right horn) FPU=110	T2*:15.2±3.5 ms	ΔT2*=11.3 ±5.7 ms	FGR cases was obtained by ligation of the left uterine artery.
				FGR Cases (left horn) (ligated) FPU=114	T2*:14.8±2.9 ms	ΔT2*=5.3 ±6.0ms	
					n.s.	p<0.005	

Table 2: Review Table 2: Quantitative T2* relaxation time - Baseline T2*

Table 3: Guidance on how to obtain placenta baseline T2* values

Approximate reference values for Placenta T2* at 40w	47-58 ms (1.5T System) 25ms (3T System)
Approximate reference values for Placenta T2* at 20w	150 ms (1.5T System) 90 ms (3T System)
Correlation with gestational age	Negative
Placental T2* value in IUGR cases	Decreased
Approximate reference values for hyperoxic ΔBOLD at 20w	5% (1.5T System)
Approximate reference values for hyperoxic ΔBOLD at 40w	20% (1.5T System)
Correlation with gestational age	Positive
Hyperoxic ΔBOLD in IUGR cases	Increased
Tips for the MRI protocol	• **3-4 echo times, spread across the range of interest are sufficient for a mono-exponential fit** • **Image-based shimming is recommended for 3T if using EPI and/or high image resolution**
Practical guidance	• **Left lateral position (10-20° tilt)** • **Axial scan, cross-sectional placental images** • **Repeat measurement to identify artifacts** • **For patient comfort max. scan-time is 30 minutes**
Tips for image analysis	• **Placental ROI as large as possible, but avoiding maternal vessels and amniotic fluid** • **3D volume coverage when achievable, or average of at least 3 slices**

	• **Adjust for differences in GA at MRI** • **Screen for effects of contractions (change in uterus size, decrease in T2*) and exclude this data** • **Record maternal position**