Changes in human fetal oxygenation during maternal hyperoxia as estimated by BOLD MRI

Sørensen, Anne Nødgaard; Peters, David Alberg; Simonsen, Carsten; Pedersen, Michael; Stausbøl-Grøn, Brian; Christiansen, Ole Bjarne; Lingman, Göran; Uldbjerg, Niels

Published in:
Prenatal Diagnosis

DOI (link to publication from Publisher):
10.1002/pd.4025

Publication date:
2013

Document Version
Publisher's PDF, also known as Version of record

ORIGINAL ARTICLE

Changes in human fetal oxygenation during maternal hyperoxia as estimated by BOLD MRI

Anne Sørensen[1]*, David Peters[2], Carsten Simonsen[3], Michael Pedersen[4], Brian Stausbøl-Grøn[5], Ole Bjarne Christiansen[1], Göran Lingman[6] and Niels Uldbjerg[7]

[1]Department of Obstetrics and Gynecology, Aalborg Hospital, Aalborg, Denmark
[2]Department of Clinical Engineering, Aarhus University Hospital, Aarhus, Denmark
[3]Department of Radiology, Aalborg Hospital, Aalborg, Denmark
[4]Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark
[5]MRI Research Center, Aarhus University Hospital, Aarhus, Denmark
[6]Department of Obstetrics and Gynecology, Lund University Hospital, Lund, Sweden
[7]Department of Obstetrics and Gynecology, Aarhus University Hospital, Aarhus, Denmark
*Correspondence to: Anne Sørensen. E-mail: annenoedgaard@hotmail.com

ABSTRACT

Objective Changes in blood oxygen level dependent (BOLD) magnetic resonance imaging (MRI) signal are closely related to changes in fetal oxygenation. In this study, we aimed to investigate the changes in human fetal oxygenation during maternal hyperoxia by using the non-invasive BOLD MRI technique.

Method Eight healthy pregnant women in gestational week 28 to 34 were included. With the use of a facial oxygen mask, we induced maternal hyperoxia and measured changes in the BOLD MRI signal of selected fetal organs.

Results In a number of fetal organs, the BOLD MRI signal increased significantly ($P < 0.01$) during maternal hyperoxia (mean change in % ± SEM): liver (14.3 ± 3.7%), spleen (15.2 ± 3.5%) and kidney (6.2 ± 1.8%) as well as the placenta (6.5 ± 1.6%). In the fetal brain, however, the BOLD MRI signal remained constant (0.3 ± 0.2%).

Conclusion During maternal hyperoxia, we demonstrated an increased oxygenation in a number of human fetal organs by using the non-invasive BOLD technique. The oxygenation of the fetal brain remained constant, thus a 'reversed' brain sparing mechanism could be considered in healthy fetuses subjected to hyperoxia.

Funding sources: None
Conflicts of interest: None declared

INTRODUCTION

The fetal effects of antepartum maternal hyperoxia in uncomplicated third trimester pregnancies have been investigated in several studies.[1–4] Cordocentesis performed during maternal hyperoxia showed the pO_2 in the umbilical vein to increase above the normal range.[1] Unfortunately, cordocentesis is associated with an increased risk of fetal mortality of 1%; therefore, it is not justified to perform it unless clinically indicated.[5] Furthermore, the oxygen content of the umbilical vein reflects the total oxygen supply to the fetus, but it does not provide information about the tissue oxygenation in individual fetal organs. By using the non-invasive blood oxygen level dependent (BOLD) technique, it is now possible to investigate oxygenation changes in different fetal organs.

BOLD magnetic resonance imaging (MRI) is widely used in clinical neuroimaging as it links brain anatomy and cognitive function.[6,7] This technique is based on the magnetic properties of hemoglobin. Deoxyhemoglobin is paramagnetic in contrast to oxyhemoglobin, which is diamagnetic. During hyperoxia, the concentration of deoxyhemoglobin decreases. Consequently, the local magnetic field changes thereby increasing the T2* relaxation time of the neighboring protons. This produces a measurable increase in the local BOLD MRI signal.[8] Studies in sheep fetuses have shown that changes in fetal BOLD MRI signal are closely related to changes in fetal oxygenation estimated by fetal arterial hemoglobin saturation[9,10] and by fluorescent oxygen sensors inserted into the fetal liver.[11]

The purpose of this present study was to investigate oxygenation changes in a number of fetal organs during maternal hyperoxia by using the non-invasive BOLD technique.

METHODS

The study was approved by the regional Committee on Biomedical Research Ethics (Journal number M-20090006). Oral and written informed consent was obtained from all

participating women. Eight healthy pregnant women carrying uncomplicated singleton pregnancies were included in the study. On the day of the examination, the fetal weight was estimated by ultrasound, and Doppler flow measurements of the umbilical artery, the middle cerebral artery and maternal uterine arteries were performed. All measurements were within the normal range. During the BOLD MRI scan, the maternal oxygen supply was controlled by a non-rebreather facial mask (Hudson Respiratory Care, Durham, NC, USA). Three consecutive maternal oxygenation episodes were induced: (1) a normoxic level (room air: 21% O_2) lasting 5 min, followed by (2) a hyperoxic level (12 L O_2/min corresponding to approximately 60% O_2) lasting 10 min, and finally (3) a normoxic level (air: 21% O_2) lasting10 min. The facial mask was applied without interfering with the BOLD MRI scan while the pregnant woman remained in the bore magnet in the left lateral position.

The BOLD MRI scan was performed with a 1.5 Tesla MRI System (Philips Medical Systems, Best, The Netherlands). A multi-receiver cardiac surface coil was placed over the abdomen covering the entire fetus. Data were acquired with a gradient echo-planar-imaging sequence with the following parameters: repetition time = 1800 ms, echo-time (effective) = 39.4 ms, number of averages = 3, flip angle = 30 and 15 slices of 6 mm with varying slice gap depending on the size of the fetus. The acquisition matrix was adjusted accordingly resulting in an in-plane spatial resolution of 2.8×2.8 mm, and spectral fat saturation was applied.

The BOLD MRI raw data were streamed to an external workstation and filtered by using dedicated custom software. Regions of interest (ROIs) were plotted in each dynamic BOLD image corresponding to the selected fetal organs and the placenta as presented in Figure 1. The ROI size depended on the size and shape of the investigated organ. In each organ, the ROI was drawn as big as possible, which meant that the placenta ROI was the biggest (approximately 670 pixels), and the kidney ROI was the smallest (approximately 45 pixels). The ROI was moved manually in each dynamic image to adjust for fetal movements, and less than 5% of the images were discarded because of severe movement artifacts. The change in BOLD signal during the entire 25-min BOLD MRI scan was obtained for each organ. For each ROI, the average BOLD signal of the initial normoxic episode (5 min) was used as a reference. The increase in BOLD signal was calculated as the average BOLD signal during the last 5 min of the hyperoxic episode. The values obtained for calculation are marked with blue bars in Figure 2.

The increase in the BOLD MRI signal during hyperoxia (ΔBOLD) was tested against the initial normoxic BOLD signal level for each organ by using a paired *t* test. A *P*-value <0.05 was considered statistically significant. The statistical analysis was performed with STATA®11 (StataCorp LP, College Station, TX, USA) statistical package.

RESULTS

Changes in the BOLD MRI signal during hyperoxia in one case (fetus number five) are shown in Figure 2. In Figure 3, data from the eight cases are pooled together, and each graph represents changes in BOLD signal (mean ± SEM) values of one fetal organ. During maternal hyperoxia, we observed an abrupt increase in the BOLD MRI signal of the fetal liver, spleen and kidney as well as the placenta; and within a few minutes, the MRI signal reached a steady-state plateau. During normoxia, the BOLD MRI signal returned to the initial reference level at a markedly slower pace. In contrast to the organs just mentioned, the BOLD MRI signal of the fetal brain remained constant during all three oxygenation periods.

Table 1 presents the eight cases and the ΔBOLD in all selected organs. The ΔBOLD was calculated for each organ. During hyperoxia, we found a significant increase in the BOLD MRI signal (ΔBOLD) of the three fetal organs (mean ± SEM): liver (14.3 ± 3.7%), spleen (15.2 ± 3.5%), kidney (6.2 ± 1.1%) and the placenta (6.5 ± 1.6%). Interestingly, the BOLD MRI signal of the fetal brain did not change during hyperoxia (0.3 ± 0.2%). We found, that the observed ΔBOLD in response to maternal hyperoxia varied among organs. For example, the

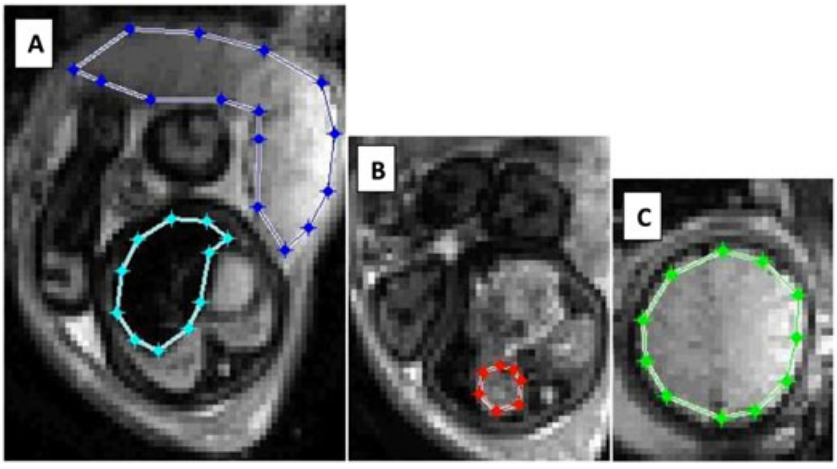

Figure 1 BOLD images of the fetus and the placenta (axial plane). Regions of interest (ROIs) are drawn in different locations. (A) the placenta (blue) and in the fetal liver (turquoise). (B) the fetal kidney, (C) the fetal brain

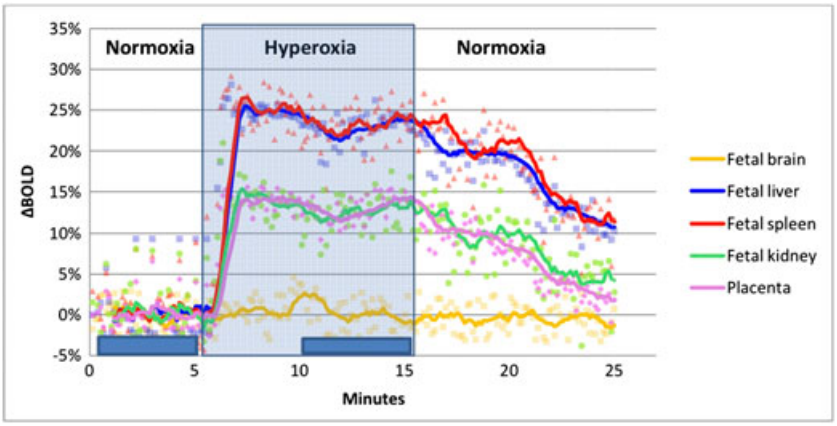

Figure 2 Changes in BOLD signal during maternal hyperoxia. Each fetal organ is represented by a different color. (Fetus number 5). The blue bars indicate the values obtained for calculation of ΔBOLD

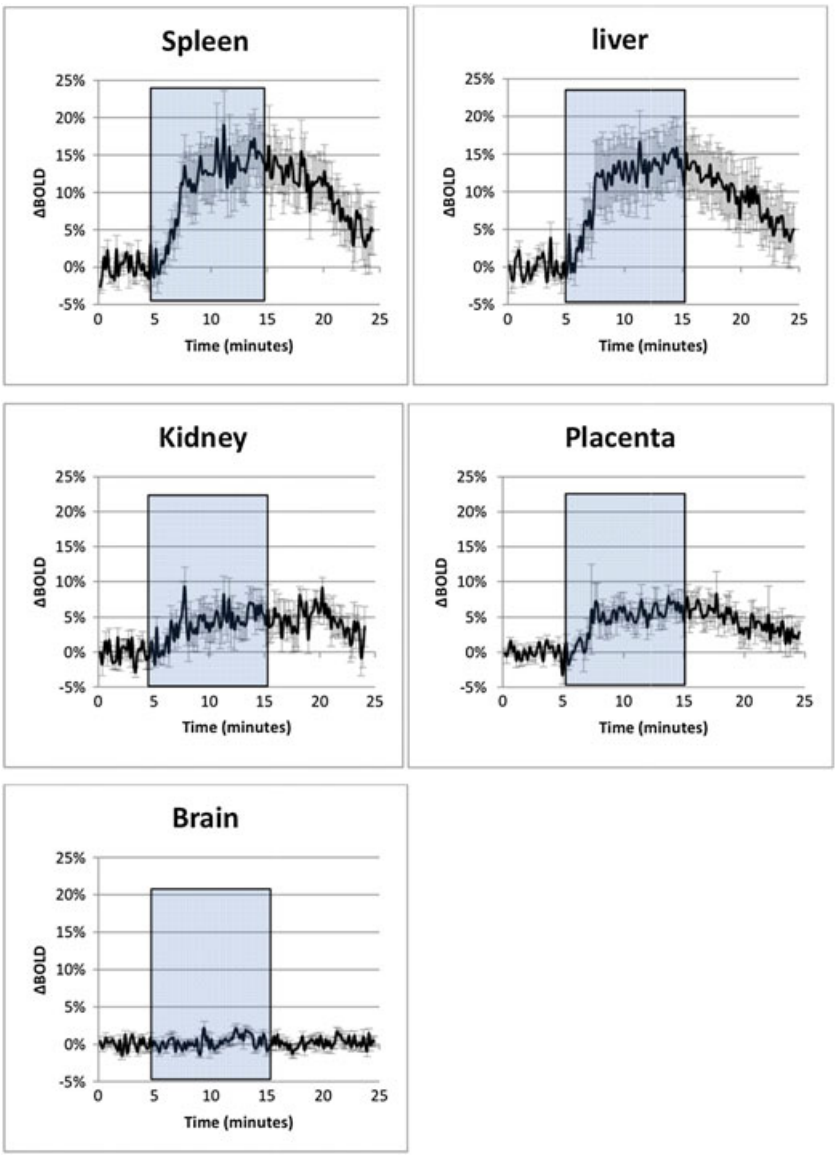

Figure 3 Data are pooled for the eight participants and each graph represents the BOLD signal changes (mean ±SEM) for one fetal organ. The gray box marks the hyperoxic episode

Table 1 The eight participants are presented and the average BOLD for each organ (mean ± SEM) are calculated. The *P*-values are based on a paired *t* test, and $P < 0.05$ is considered significant

Fetus number	Gestational age (weeks + days)	Fetal weight UL estimated (gram)	ΔBOLD fetal liver (%)	ΔBOLD fetal spleen (%)	ΔBOLD fetal kidney (%)	ΔBOLD placenta (%)	ΔBOLD fetal brain (%)
1	28 + 2	1381	14.6	15.3	5.2	5.5	−0.3
2	28 + 0	1350	−0.6	2.2	0.5	0.5	−0.01
3	28 + 6	1555	33.3	33.2	14.4	13.1	0.8
4	27 + 4	1038	13.9	16.0	5.3	4.7	0.7
5	34 + 1	2227	22.9	23.2	12.7	12.9	−0.3
6	33 + 6	2392	4.8	5.6	0.3	2.2	0.1
7	33 + 2	2190	9.1	9.0	3.8	4.6	1.5
8	33 + 6	2273	16.0	17.4	7.3	8.5	0.3
Mean (±SEM)			14.3 (±3.7)	15.2 (±3.5)	6.2 (±1.8)	6.5 (±1.6)	0.3 (±0.2)
P-value			0.006	0.003	0.006	0.005	n.s.

ΔBOLD of the liver and spleen were approximately twice the ΔBOLD of the kidney and the placenta.

DISCUSSION

This present study demonstrated that during maternal hyperoxia, oxygenation changes in a number of human fetal organs could be estimated by using the non-invasive BOLD technique.

The BOLD MRI technique provides information about changes in the fetal oxygenation status, as previously demonstrated in a study using oxygen sensitive optodes as a reference.[11] Furthermore, this technique allows real-time assessment of oxygenation changes in a number of fetal organs simultaneously. It is considered safe when performed in the second and third trimester at a magnetic field strength of 1.5 Tesla.[12]

One limitation of BOLD MRI is that oxygenation is measured in relative hence not in absolute values. The acquired BOLD MRI signal depends not only on the proportion of paramagnetic deoxyhemoglobin but also on physical parameters such as the distance to the radiofrequency coil, the magnetic shimming, sequence parameters (especially the echo-time) and physiological conditions including the blood flow, the volume fraction of blood in the fetal tissue, the hematocrit, and the hemoglobin concentration within fetal erythrocytes and so forth.[13] Therefore, the absolute BOLD MRI signal is expected to vary not only between individuals but also from day to day in the same individual.

Reducing the movement artifacts and keeping the ROI in the exact same position in the fetal organs during the BOLD MRI acquisition are important for acquiring accurate assessment. In this study, the pregnant woman remained inside the magnet bore during the entire BOLD MRI scan. No interruption was made for application of the facial mask. In case of fetal movements, the ROI position was adjusted by hand in each BOLD image.

In this present study, we did not include assessment of maternal arterial pO_2. Previously, however, in unpublished data, we have demonstrated an increased maternal arterial pO_2 to (mean ± SD) 45.0 ± 7.6 kPa (data not shown) when using the exact same facial mask for maternal hyperoxia. The differences in pO_2 were mainly due to inaccurate maternal oxygen supply. The facial mask administered oxygen at a flow rate of 12 L per minute. However, the mask was not completely tight; and therefore, some inhalation of room air was allowed. This variation in maternal pO_2 might to some extent explain the observed differences in ΔBOLD MRI signals among the fetuses.

The graphs in Figures 2 and 3 all showed a rapid increase in BOLD signal during hyperoxia and a decrease at a much slower pace when the oxygen was reduced to normoxia. The oxygen binding capacities of fetal hemoglobin might explain the shape of the graphs. Fetal hemoglobin has high oxygen affinity when compared with maternal hemoglobin, which facilitates fetal tissue oxygenation and hampers fetal hemoglobin unloading of oxygen.

Another interesting observation was that the oxygenation of the fetal brain remained unaffected by maternal hyperoxia. It is well known from Doppler flow measurements that cerebral blood flow is subjected to autoregulation.[14] During hypoxia, a compensatory increase in the cerebral blood flow is seen, known as the brain sparing mechanism.[15] The fetal hemodynamic response during hyperoxia is sparsely described, but a few studies have shown a decrease in the cerebral blood flow[16–18] during maternal hyperoxia, which could be considered as a 'reversed' brain sparing mechanism. The lack of oxygenation changes in the fetal brain observed in our study may therefore support the view that the cerebral blood flow is reduced during hyperoxia.

In addition, we found a fixed relationship between the ΔBOLD signals of the different organs in each individual. In each fetus, the ΔBOLD signal of the fetal spleen and liver were similar, and it was nearly doubled when compared with the ΔBOLD signal of the fetal kidney and placenta. These observations are likely explained by biological variations among organs, for example, different fractions of blood volume. As mentioned earlier, the imaging parameters, especially the echo-time, are important for the magnitude of the BOLD MRI signal, and the echo-time chosen in this study might favor an increased ΔBOLD in the fetal liver and spleen.

Two previous studies using BOLD MRI, a pilot study of nine fetuses[19] and a larger study including 41 growth restricted

fetuses and 39 normal fetuses,[20] have investigated the human fetal liver oxygenation during maternal hyperoxia. The later study demonstrated no changes in BOLD signal in fetal liver during hyperoxia. The discrepancy between these findings and our present results could be due to differences in experimental design, MRI protocol and in handling of the pregnant woman during the BOLD MRI procedure.

A clinical perspective of this method could be BOLD MRI scans of growth restricted fetuses with impaired placental function. Two previous studies have investigated the potential of maternal hyperoxia as a test of placental function and fetal outcome.[1,21] Cordocentesis in growth restricted fetuses during maternal hyperoxia showed that no increase in fetal oxygenation was associated with severe placental dysfunction and adverse fetal outcome.[1] Another study investigated the changes in fetal cerebral resistance by Doppler ultrasound during maternal hypoxia. In a group of growth restricted fetuses with brain sparing normalization of cerebral flow was associated with better fetal outcome, and no change of cerebral blood flow was associated with adverse fetal outcome.[21] These findings suggest that fetuses with seriously impaired placental function do not respond to maternal hyperoxia; and therefore, fetal non-responsiveness could be a predictor of poor fetal outcome. However, this needs to be tested further. To our knowledge, this is the first study to successfully demonstrate oxygenation changes in a number of human fetal organs during maternal hyperoxia. The BOLD MRI technique provides new possibilities in observing normal fetal physiology, and it introduces a new tool to the field of fetal monitoring and fetal testing. Further research should be conducted in healthy as well as growth retarded fetuses suffering from impaired placental function.

ACKNOWLEDGEMENT

We wish to thank statistician Steffen Falgreen Larsen M.Sc. at the Cardiovascular Research Center, Aalborg Hospital for very helpful advice in statistical matters.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- The BOLD MRI signal depends upon the magnetic properties of hemoglobin.
- In the sheep fetus, changes in the BOLD MRI signal reflect changes in fetal tissue oxygenation.
- Maternal hyperoxia increases the fetal oxygen supply when estimated by cordocentesis.

WHAT DOES THIS STUDY ADD?

- In the human fetus, the BOLD technique is capable of measuring changes in tissue oxygenation in various fetal organs.
- Maternal hyperoxia increases fetal tissue oxygenation in a number of fetal organs.
- The oxygenation of the fetal brain is unaffected by maternal hyperoxia, this could be caused by autoregulation of fetal cerebral bloodflow – reversed brain sparing.

REFERENCES

1. Nicolaides KH, Campbell S, Bradley RJ, *et al.* Maternal oxygen therapy for intrauterine growth retardation. Lancet 1987;1(8539):942-5.
2. Haydon ML, Gorenberg DM, Nageotte MP, *et al.* The effect of maternal oxygen administration on fetal pulse oximetry during labor in fetuses with nonreassuring fetal heart rate patterns. Am J Obstet Gynecol 2006;195(3):735-8.
3. Bartnicki J, Saling E. The influence of maternal oxygen administration on the fetus. Int J Gynaecol Obstet 1994;45(2):87-95.
4. Battaglia FC, Meschia G, Makowski EL, *et al.* The effect of maternal oxygen inhalation upon fetal oxygenation. J Clin Invest 1968;47(3):548-55.
5. Srisupundit K, Wanapirak C, Piyamongkol W, *et al.* Comparisons of outcomes after cordocentesis at mid-pregnancy between singleton and twin pregnancies. Prenat Diagn 2011;31(11):1066-9
6. Logothetis NK. What we can do and what we cannot do with fMRI. Nature 2008;453(7197):869-78.
7. Blatow M, Nennig E, Durst A, *et al.* fMRI reflects functional connectivity of human somatosensory cortex. Neuroimage 2007;37(3):927-36.
8. Thulborn KR, Waterton JC, Matthews PM, *et al.* Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. Biochim Biophys Acta 1982;714(2):265-70.
9. Wedegartner U, Tchirikov M, Schafer S, *et al.* Functional MR imaging: comparison of BOLD signal intensity changes in fetal organs with fetal and maternal oxyhemoglobin saturation during hypoxia in sheep. Radiology 2006;238(3):872-80.
10. Wedegartner U, Kooijman H, Andreas T, *et al.* T2 and T2* measurements of fetal brain oxygenation during hypoxia with MRI at 3T: correlation with fetal arterial blood oxygen saturation. Eur Radiol 2010;20(1):121-7
11. Sorensen A, Pedersen M, Tietze A, *et al.* BOLD MRI in sheep fetuses: a non-invasive method for measuring changes in tissue oxygenation. Ultrasound Obstet Gynecol 2009;34(6):687-92.
12. Kanal E, Barkovich AJ, Bell C, *et al.* ACR guidance document for safe MR practices: 2007. AJR Am J Roentgenol 2007;188(6):1447-74.
13. Lu H, Zhao C, Ge Y, *et al.* Baseline blood oxygenation modulates response amplitude: physiologic basis for intersubject variations in functional MRI signals. Magn Reson Med 2008;60(2):364-72.
14. Kiserud T, Acharya G. The fetal circulation. Prenat Diagn 2004;24 (13):1049-59.
15. Baschat AA. Fetal responses to placental insufficiency: an update. BJOG 2004;111(10):1031-41.
16. Almstrom H, Sonesson SE. Doppler echocardiographic assessment of fetal blood flow redistribution during maternal hyperoxygenation. Ultrasound Obstet Gynecol 1996;8(4):256-61.
17. Hsu YY, Kuan WC, Lim KE, *et al.* Breathhold-regulated blood oxygenation level-dependent (BOLD) MRI of human brain at 3 Tesla. J Magn Reson Imaging 2010;31(1):78-84.
18. Simchen MJ, Tesler J, Azami T, *et al.* Effects of maternal hyperoxia with and without normocapnia in uteroplacental and fetal Doppler studies. Ultrasound Obstet Gynecol 2005;26(5):495-9.
19. Semple SI, Wallis F, Haggarty P, *et al.* The measurement of fetal liver T(*)(2) *in utero* before and after maternal oxygen breathing: progress towards a non-invasive measurement of fetal oxygenation and placental function. Magn Reson Imaging 2001;19 (7):921-8.
20. Morris DM, Ross JA, McVicar A, *et al.* Changes in foetal liver T2* measurements by MRI in response to maternal oxygen breathing: application to diagnosing foetal growth restriction. Physiol Meas 2010;31(9):1137-46.
21. Arduini D, Rizzo G, Romanini C, *et al.* Hemodynamic changes in growth retarded fetuses during maternal oxygen administration as predictors of fetal outcome. J Ultrasound Med 1989;8(4):193-6.

