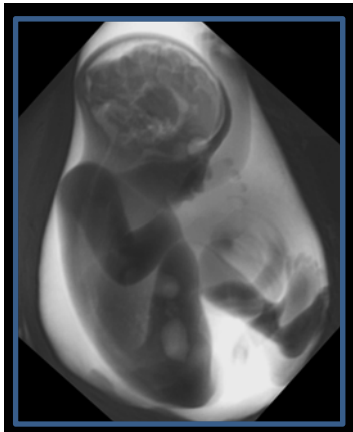

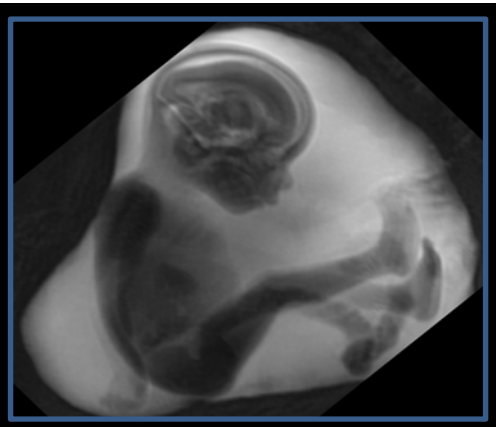

FETAL MAGNETIC RESONANCE IMAGING: BREAKING NEW GROUND

Jaladhar Neelavalli, PhD and E. Mark Haacke, PhD
Department of Radiology, Wayne State University

and the perinatal team of
Uday Krishnamurthy, Brijesh Yadav and Feifei Qu

ACKNOWLEDGEMENTS

Dr. Edgar Hernandez-Andrade
PRB

Dr. Lami Yeo
PRB

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Children's Hospital of Michigan

Dr. Sheena Saleem
Children's Hospital of Michigan

Dr. Homam Saker
PRB

Dr. Maynor Garcia
PRB

Special Thanks to…

All the staff and the Maternal Fetal Medicine fellows at the Perinatology Research Branch (PRB) and the Harper Univ. Hospital

MRI Unit staff at the Children's Hospital of Michigan

Staff at the Wayne State Univ. MR Research Facility

And…to the more than 200 mothers who have participated in these imaging studies

FETAL MR IMAGING RESEARCH

- Choice of field strength (Safety): 1.5T vs 3T
- MR angiography (MRA): Fetal and placental
- Susceptibility weighted imaging (SWI): Oxygen saturation, blood products, calcium and spine imaging
- Motion correction: Self gating for cardiac imaging
- Quantitative imaging: Flow, spin density (water content), T1 and susceptibility maps

FETAL MRI – CHOICE OF FIELD STRENGTH

- Clinically fetal MRI has been performed at ***1.5 Tesla*** field strength

- However, imaging at higher field strengths (***3.0 Tesla***) has several advantages…
  - Better image quality
  - Higher resolution imaging
  - Increased sensitivity to metabolites (spectroscopy)

Krishnamurthy, U et al. MR imaging of the fetal brain at 1.5 T and 3.0 T field strengths: comparing specific absorption rate (SAR) and image quality.
Journal of Perinatal Medicine, *43*(2), 209-220, 2015.

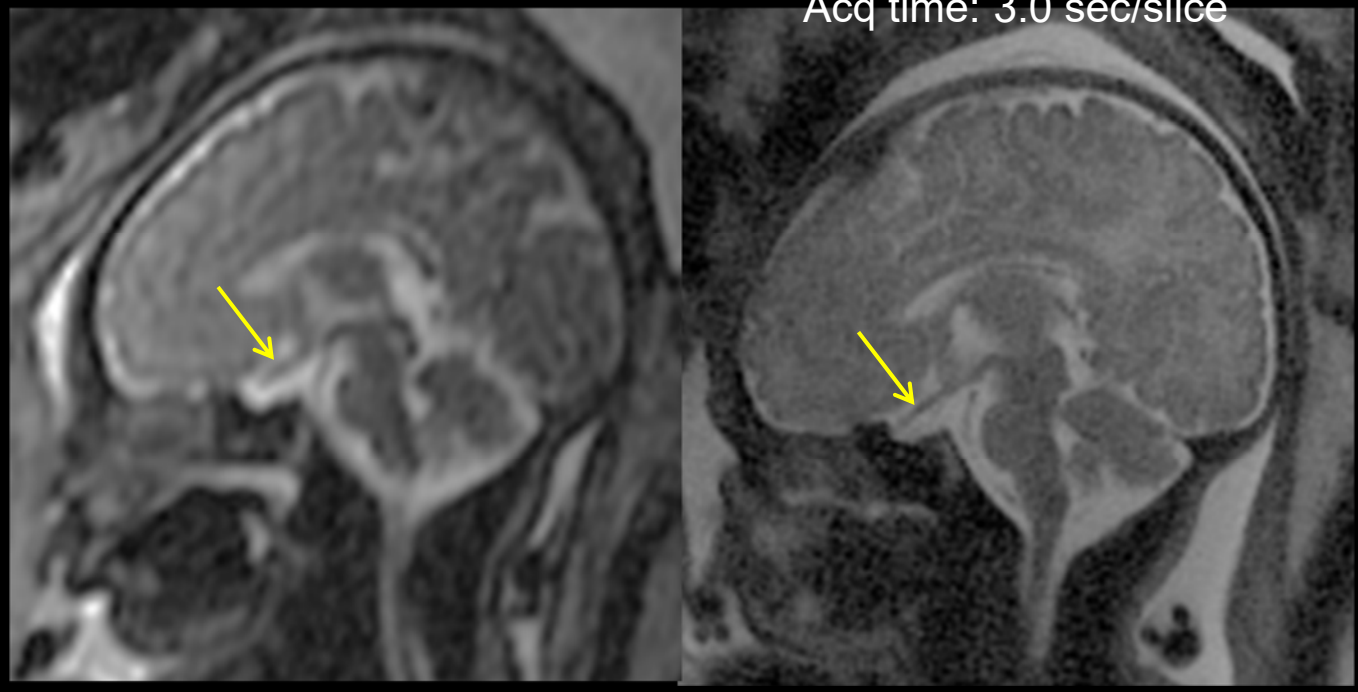
This was recognized as the best poster at the 4th International Congress on Fetal Imaging, Vienna, Austria, 2013.

1.5T VERSUS 3.0 T

Higher resolution at 3T affords better visualization of anatomy

1.5 T
Voxel Size 1.1x1.1x4.0 mm^3
Acq time: 1.2 sec/slice

3.0T
Voxel Size ***0.80x0.80x3.0*** mm^3
Acq time: 3.0 sec/slice



All sequences at 3T were designed to minimize energy deposition.

ANATOMICAL IMAGING SEQUENCES

T_1 Weighted Contrast

GA = 35 1/7 weeks

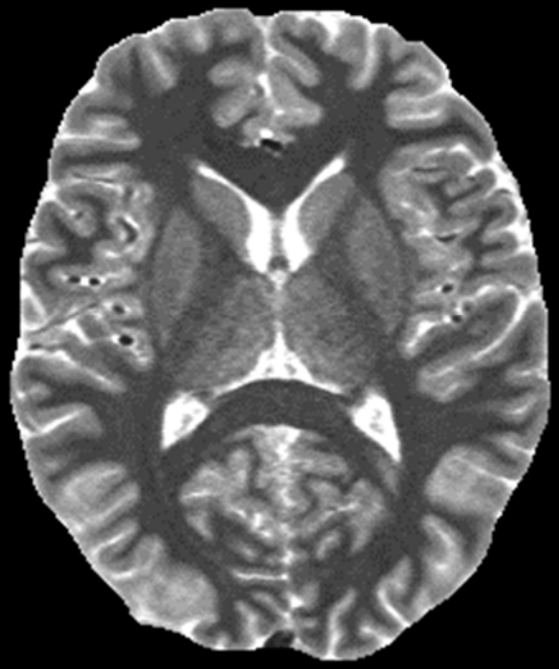
Voxel Size =
0.7 x 0.7 x 3.5 mm^3

Acq. time = ***28 secs***

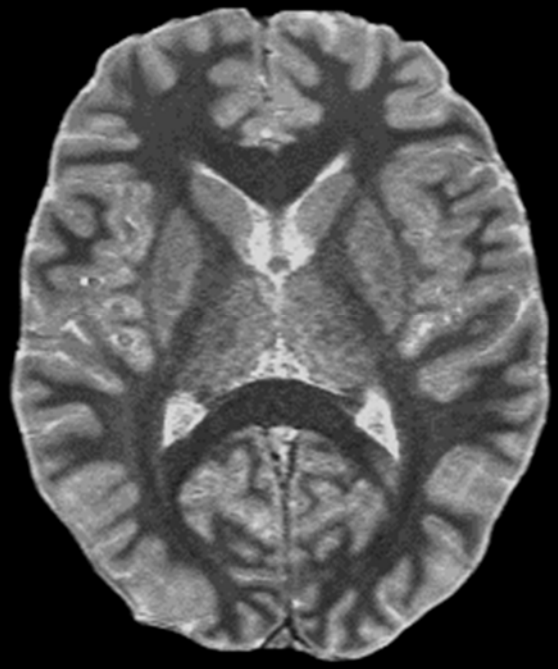
2D T1W : TE=7.64ms; FA=60˚; TR=210ms; 14 slices; Acq. Time=***2sec/slice***

STAGE:
QUANTITATIVE T1 AND SPIN DENSITY MAPS

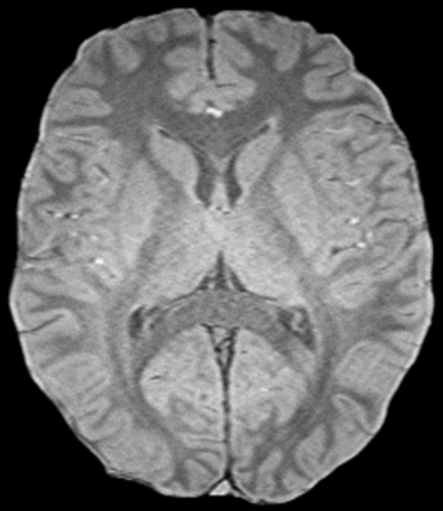
T1 MAP



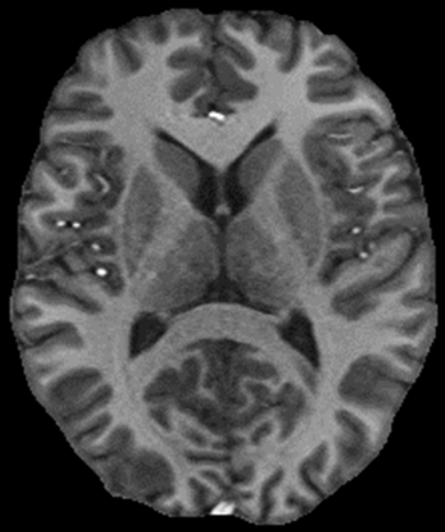
PD MAP



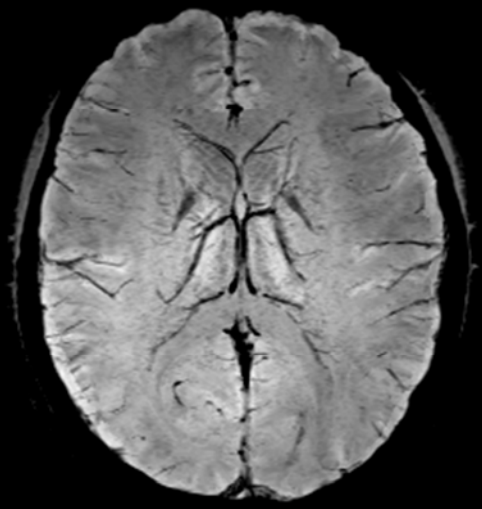
PDW



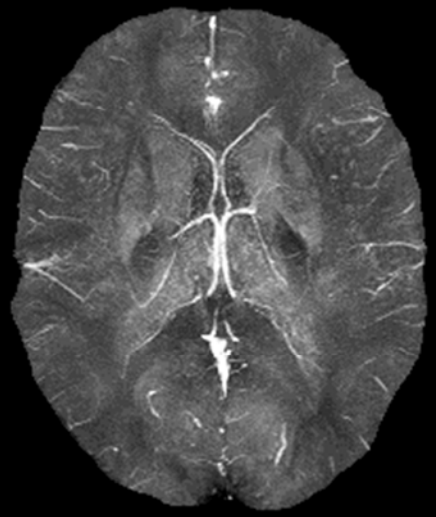
T1WE



SWI



SWIM



STAGE:

- Enhanced T1 contrast whole brain imaging in ***5 minutes.***
- Same scan for fetal imaging will take only ***3 minutes***.

Published/Presented/Submitted Resu

- Oral Presentation at the 25th Annual Meeting ISMRM, Honolulu, Hawaii (2017)

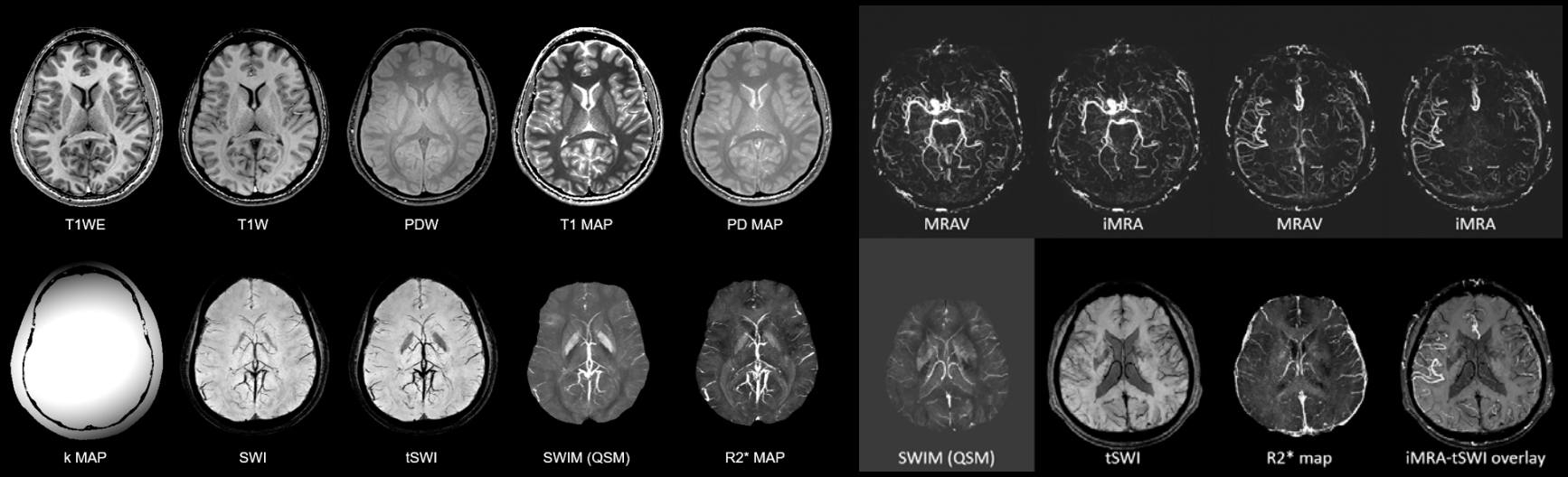
Strategically Acquired Gradient Echo (STAGE) for fetal brain imaging and quantification (pilot study at 1.5T)

Yongsheng Chen, PhD Candidate
Bo Wu, MS
E. Mark Haacke, PhD

Scanner: Siemens Aera 1.5T with 30-channel coil elements (18-body and 12-spine)
Software: Syngo MR D13
Data Collaborator: Dr. Taotao Sun, January 24, 2018. Shanghai International Peace Maternal and Child Health Hospital.

Introduction of STAGE

STAGE [1-4] employs a set of multi-echo GRE acquisitions with optimal echo times, flip angles and flow rephasing/dephasing strategies to obtain multi-contrast qualitative images and quantitative data for studying various neurodegenerative diseases. It takes 5 min at 3T for T1WE, T1W, PDW, T1MAP, PDMAP, SWI, tSWI, QSM and R2*MAP covering the whole brain. With another 5 min, one can also get the MRAV, MRA as well as co-registered QSM, tSWI and R2*map from the same scan for entire cerebral vascular visualization and quantification, especially for small arteries and veins.



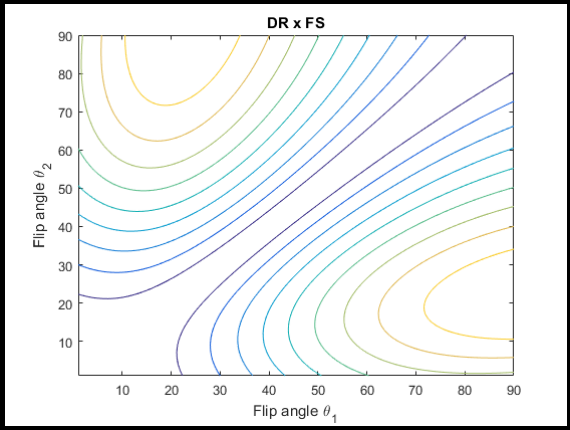
[1] Chen Y, et al., MRI 2017; [2] Wang Y, et al., MRI 2017; [3] Chen Y, et al., MRI 2017; [4] Chen Y, et al., SPIE 2018

STAGE imaging parameters for fetal brain at 1.5T

- Optimized STAGE imaging parameters for this pilot study. This data has 18 slices in 2D acquisition covering the whole fetal brain in a total less than 2 min.

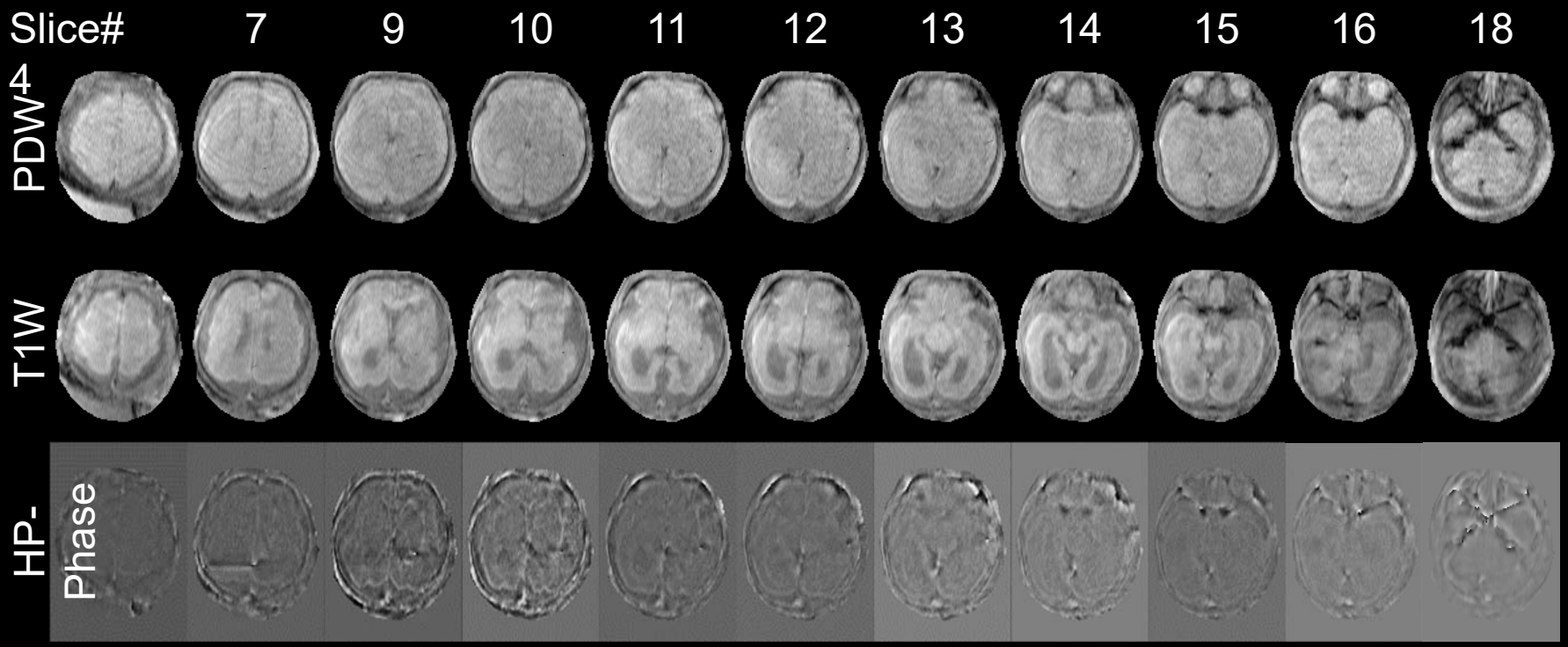
Prot.	Acq.	TR (ms)	TE (ms)	FA (deg)	BW (Hz/px)	Acq. Resolution (mm^3)	FC	GRAPPA Acc./Ref.	Phase PF	Slices	TA (m:s)
PDW-GRE	2D	600	25	15	90	0.85x1.7x3.0	Yes	2/52	6/8	18	0:53
T1W-GRE	2D	600	25	75	90	0.85x1.7x3.0	Yes	2/52	6/8	18	0:53

- The optimal flip angles for STAGE with a TR = 600 ms and T1 = 1200 ms (assuming fetal brain has this T1 at 1.5T) are 20° and 90°.[1] For a lower SAR value, we can use 20° or 15° and 75° instead.



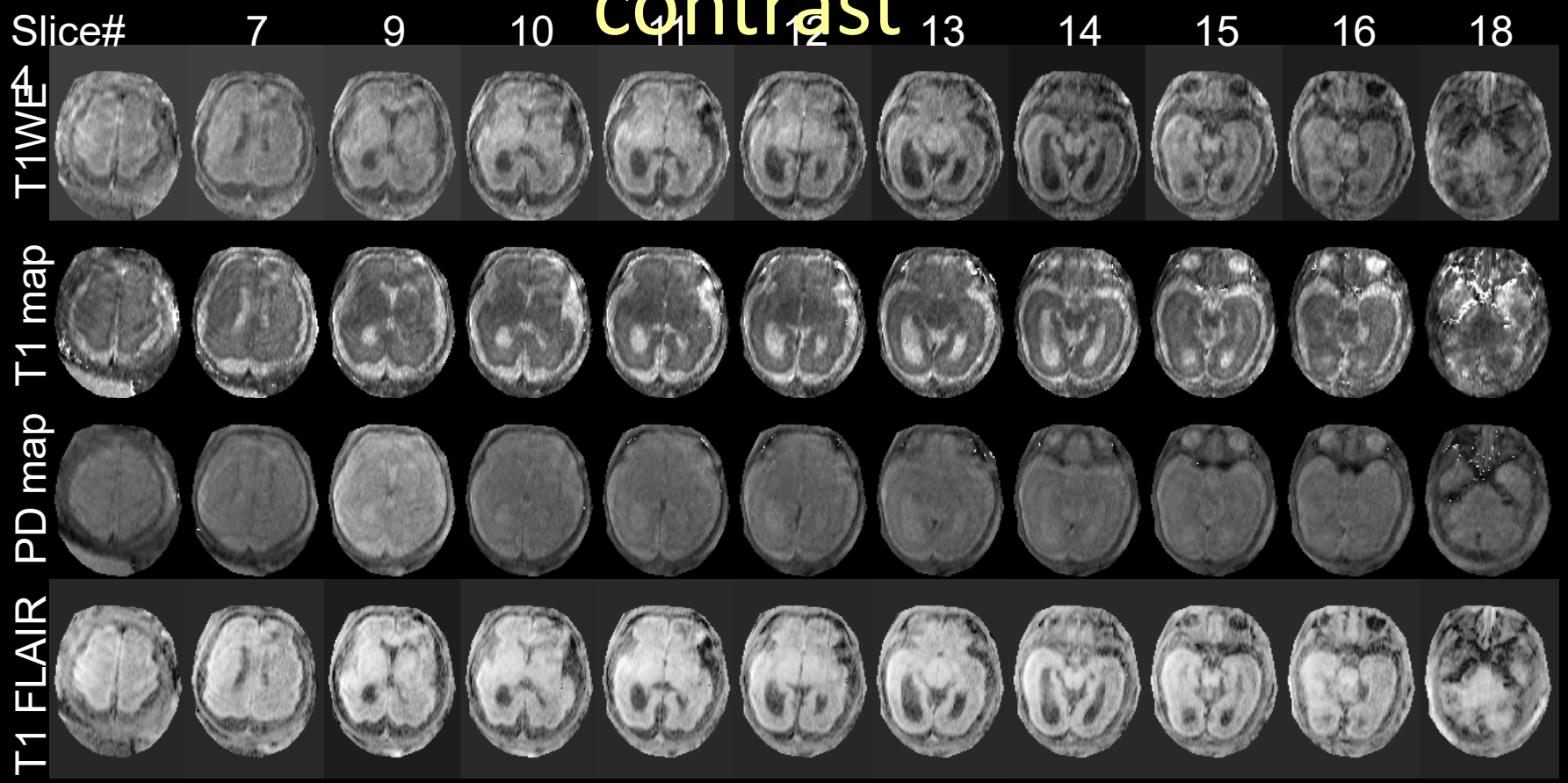
[1] Chen Y, et al., MRI 2017

Preliminary results – Image quality

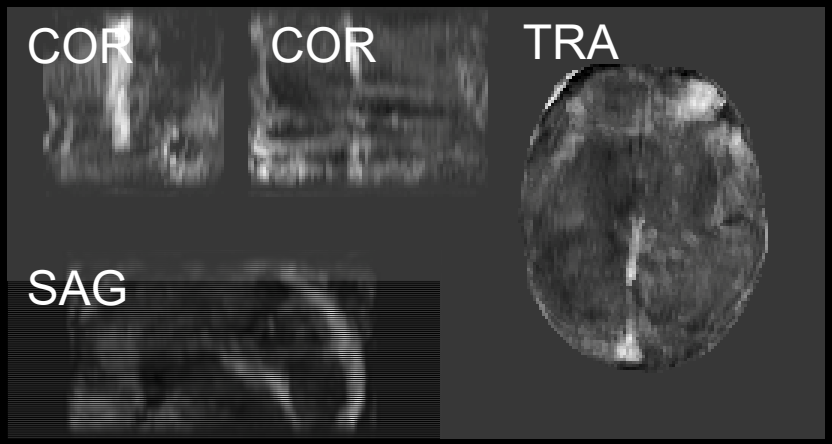


These are original acquired images. Gestational age: 28 weeks.

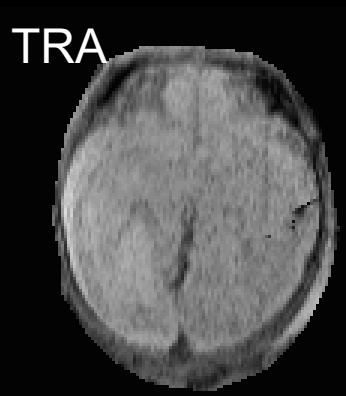
Preliminary results – T1 mapping and contrast



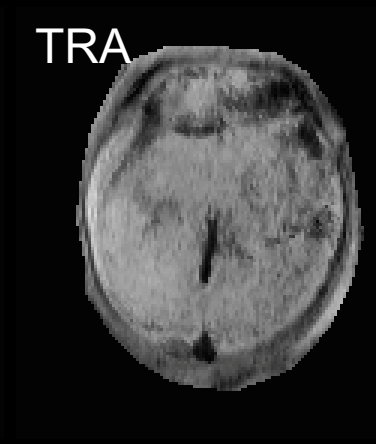
Preliminary results – SWI, tSWI and SWIM



SWIM (QSM)



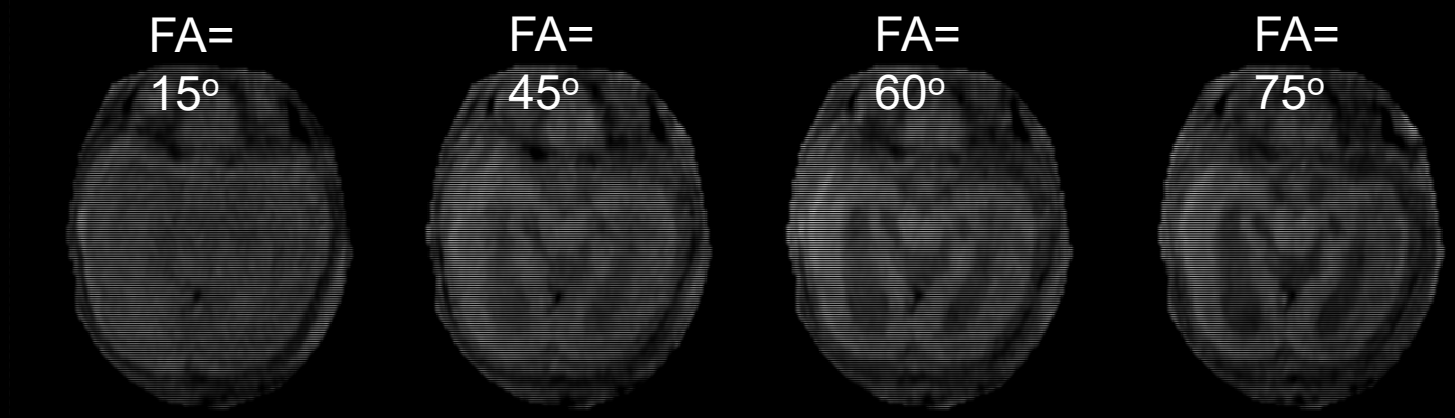
SWI



tSWI

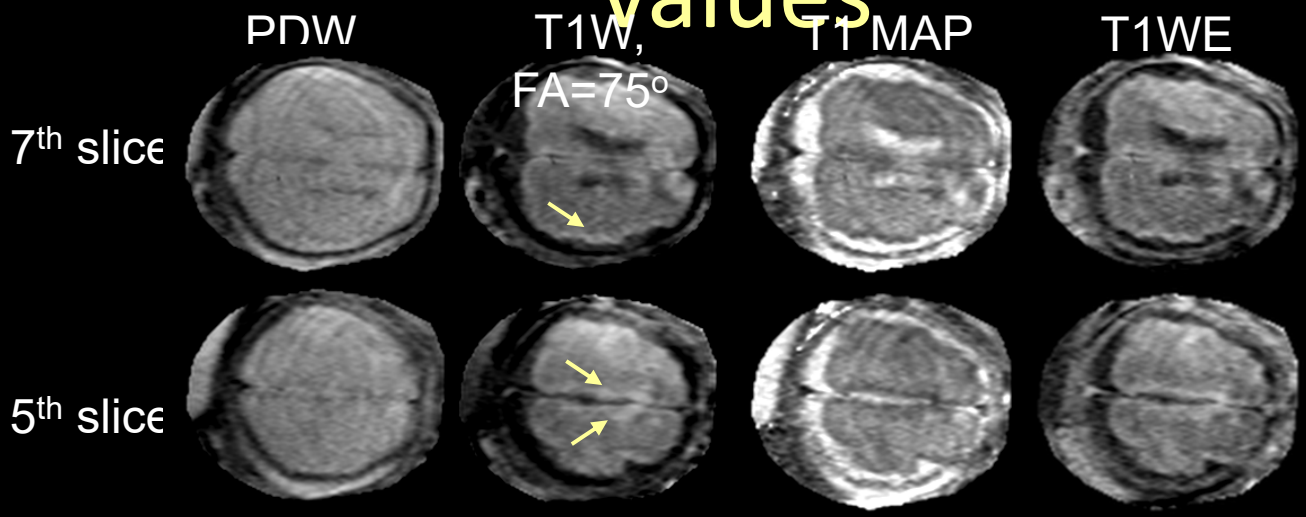
Images are minimum/maximum intensity projection with effective slice thickness of 16 mm over 4 slices for the original axial data, and 18 slices for the reformatted sagittal and coronal data.
Measured susceptibilities for superior sagittal sinuses were 337±46 ppb.

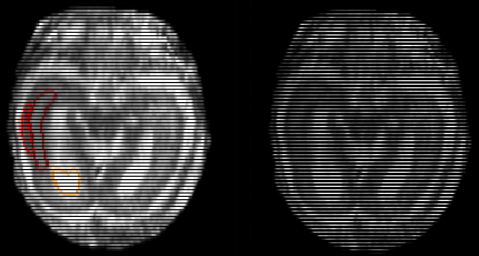
Preliminary results – Contrast and SAR



These are original acquired images. Gestational age: 28 weeks.
SAR value is acceptable even for the scan with FA=75°.

Preliminary results – fetal brain T1 values





T1 map, slice# 14

ROI	T1 (ms)
0-GM	914±159
1-WM	1196±109
2-CSF	2601±209

This data confirms that GM (arrows) has a lower T1 value than WM on fetus at this age.

Summary

- Overall, this first fetal STAGE data has gorgeous image quality.
- The 30-elements coil ensures the data has very good SNR.
- There is no obvious motion in this data even without breath holding. We may do rigid registration for further data processing.
- The known cusp artifacts make some black dots on the magnitude too.
- T1WE and simulated T1 FLAIR has increased T1 contrast than original images.
- T1 mapping is providing not only quantitative values but also a better anatomical image showing water.
- We could have better SNR for T1 mapping and also T1WE if we can do double-echo or multi-echo acquisitions as the echo time is far enough to do double-echo.
- Multi-echo with flip angles of 20^{o} and 75^{o} are preferred for further data acquisition at this 1.5T.
- SAR is acceptable even for the scan with FA=75^{o}.
- GM has a lower T1 value than WM on fetus which is confirmed by this data.

CLINICAL TRANSLATION: FETAL IMAGING PROTOCOL

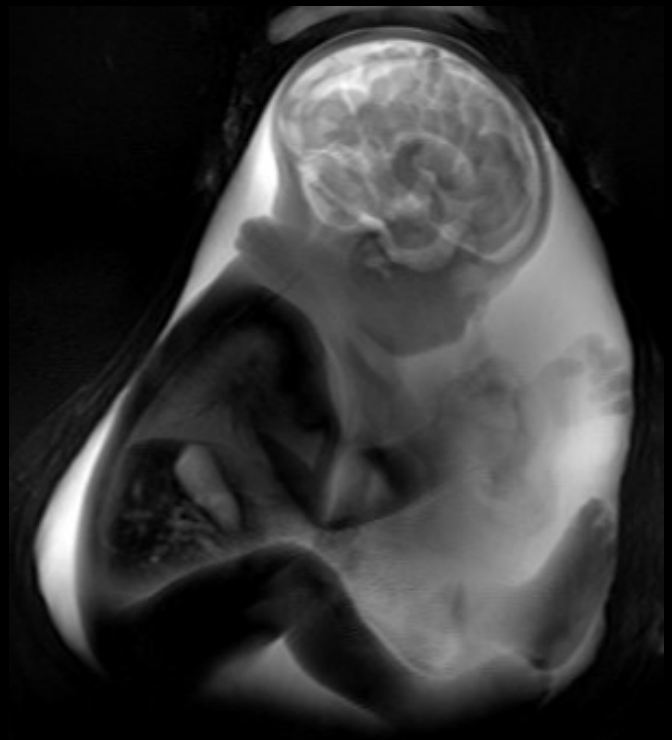
Combining all the methods we have presented today it is possible to collect the data for this quantitative fetal MRI protocol at 3.0T in **~ 25 min**

The detailed protocol will shortly be made publicly available at :
http://www.mrc.wayne.edu/index.php?site=perinatal

Fetal Images: The Thinker

34 weeks: Courtesy of Dr. Tao Tao Sun, Shanghai International Maternal and Fetal Hospital

Fetal Images: The Mathematician



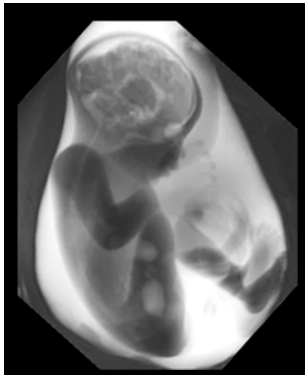
30 weeks: Image courtesy of Drs. Mody and Hernandez and the WSU perinatal MRI team

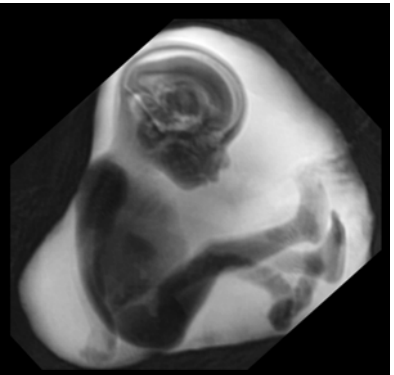
Fetal Images: Playing Checkers

29 weeks: Image courtesy of Drs. Mody and Hernandez and the WSU perinatal MRI team

Fetal Images: Taking a Nap

23 weeks: Image courtesy of Drs. Mody and Hernandez and the WSU perinatal MRI team





Oxygenation Quantification in the Fetal Brain Using Susceptibility Weighted Imaging

Ph.D. Public Defense

by

Brijesh Kumar Yadav

Department of Biomedical Engineering

March 05th, 2018

Committee Members:

Ewart Mark Haacke, Ph.D. (Advisor)
Jaladhar Neelavalli, Ph.D. (Co-Advisor)
Edgar Hernandez-Andrade, M.D., Ph.D.
Zhifeng Kou, Ph.D.
Mohammad Mehrmohammadi, Ph.D.

Outline:

Topic 1 : Model-based approach to measure fetal blood oxygenation

Topic 2 : Association between blood perfusion & oxygenation in fetal brain

Topic 3 : Model-free approach to measure fetal blood oxygenation

Conclusion

Future directions

Topic 1

Imaging Putative Fetal Cerebral Blood Oxygenation Using Susceptibility Weighted Imaging (SWI)

Yadav, B.Y., et al. "Imaging putative foetal cerebral blood oxygenation using susceptibility weighted imaging (SWI)." *European radiology* (2017): 1-7.

Introduction:

- Optimal supply of oxygen is important for normal fetal growth[1,2]
- Obstruction leads to fetal hypoxia [1,2,3]

- Doppler Ultrasound (US) detects secondary change via increased flow
- Doppler US: 15 – 25% of hypoxic fetal cases detected prenatally[4,5]

[1] Maulik, D. Clin Obstet Gynecol, 2006. 49(2): p. 214-8.; [2] Baschat, A.A., Obstetrical & Gynecological Survey, 2004. 59(8): p. 617-627; [3] Longo, S., L. et al, J Matern Fetal Neonatal Med, 2013. 26(3): p. 222-5. [4] Figueras, F. and J. Gardosi, Am J Obstet Gynecol, 2011. 204(4): p. 288-300; [5] Papageorghiou, et. al., Ultrasound Obstet Gynecol, 2001. 18(5): p. 441-9.

Introduction: Motivation

- No non-invasive technique clinically available to quantify blood oxygenation in fetal brain
- Normal blood oxygenation level in fetal brain is not known

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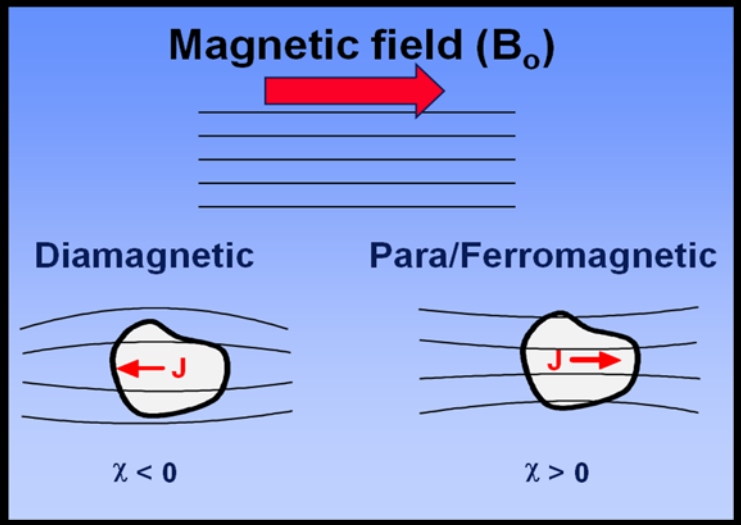
Susceptibility Weighted Imaging

Susceptibility Weighted Imaging (SWI)

χ = Magnetic Susceptibility



Deoxy-haemoglobin

Oxy-haemoglobin
Calcification
Bone

Hemosiderin
Methemoglobin
Ferritin

Diamagnetic Water Paramagnetic

Magnetic susceptibility axis

Image adapted from mri-q.com

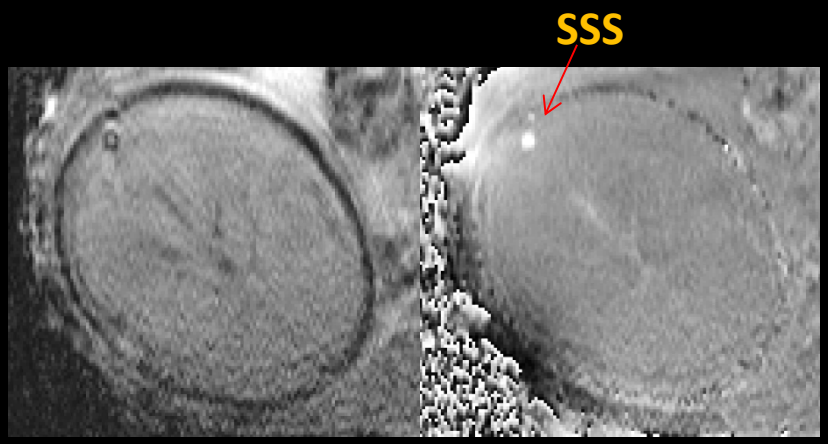
Susceptibility Weighted Imaging (SWI)

$$\Delta\varphi = -\gamma \cdot \Delta\chi_{vein} \cdot B_0 \cdot (\cos^2\theta - 1/3) \cdot TE$$

φ = Phase; γ = gyromagnetic ratio; B_0 = Main magnetic field; TE = Echo time;
θ = angle between blood vessel and B_0

$$\Delta\chi_{vein} = \Delta\chi_{do} \cdot (1 - S_vO_2) \cdot Hct$$

S_vO_2 = Venous oxygenation;
$\Delta\chi_{do}$ = Suceptibility difference between fully oxygented and fully deoxygenated blood;
Hct = Hematocrit



Fetal Brain

Magnitude Image *Phase Image*

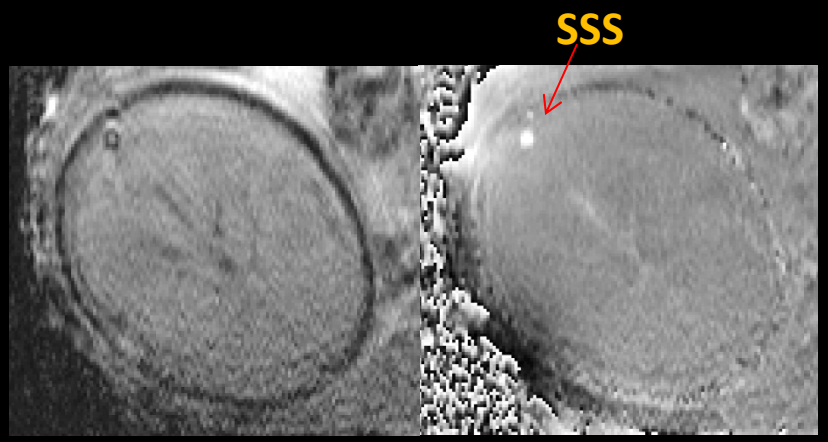
[1] Haacke, E. M. et al., Magnetic resonance imaging: physical principles and sequence design. Vol. 82. New York:: Wiley-Liss, 1999.

Fetal SWI: Model Based Approach

Magnetic susceptibility was estimated by using the long cylinder approximation

$$S_vO_2 = 1 - \frac{6 \cdot |\Delta\varphi|}{\Delta\chi_{do} \cdot Hct \cdot (3\cos^2\theta - 1) \cdot (|\gamma B_0| \cdot TE)}$$

Target Vessel:
Superior sagittal sinus (SSS)



Fetal Brain Magnitude Image ***Fetal Brain Phase Image***

28 6/7 weeks

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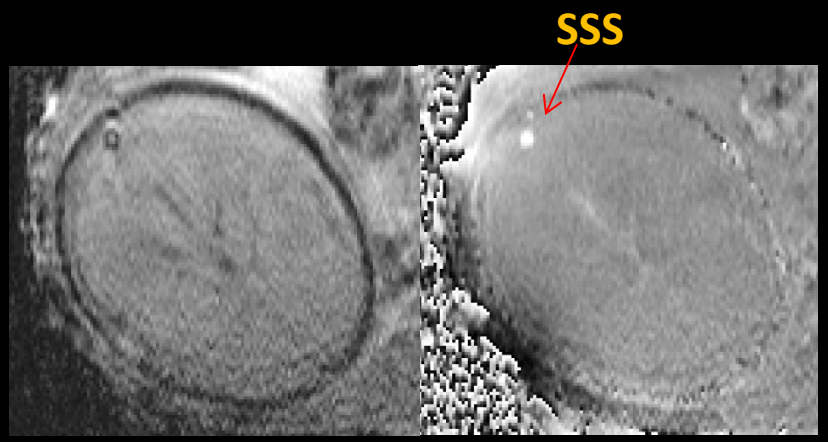

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$\Delta\chi_{do} = 0.27\ ppm$ [1]

$Hct = 22.9\% + GA \cdot 0.5\%$ [2]

GA – Gestation age

[1] Spees W.M., et al. MRM 2001; 45:533–542. [2] Boulot P., FDT 1993; 8: 309-316.

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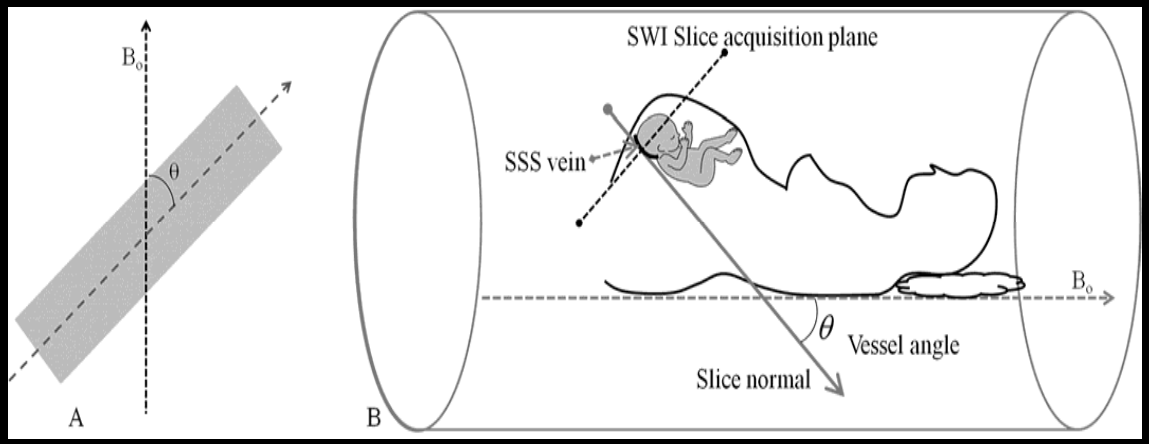


[1] Spees W.M., et al. MRM 2001; 45:533–542. [2] Boulot P., FDT 1993; 8: 309-316. [3] Neelavalli, J., et al. JMRI 39.4 (2014): 998-1006.

Fetal SWI: Sequence

SWI parameters for breathhold scan

Sequence Mode	TR (ms)	TE (ms)	FA (°)	Resolution (mm^3)	BW (Hz/px)	# of Slices	Scan Duration (sec)	SAR (W/Kg)
2D	250-280	15-18.7	32	0.78 x 1.56 x 3.5	199	10-11	24-26	< 0.6
3D	20-23	13.5-17.5	16	0.78x 1.56 x 3-3.5	219	16	32	< 0.6

- Scan at 3.0T MRI Siemens Verio system
- 6 channel body array coil + 4 channel spine coil
- No maternal sedation

Fetal SWI:

Total number of healthy fetuses scanned = **196**

- Fetal Motion
- Vessel curvature
- Vessel orientation
- Maternal breathing
- Partial voluming

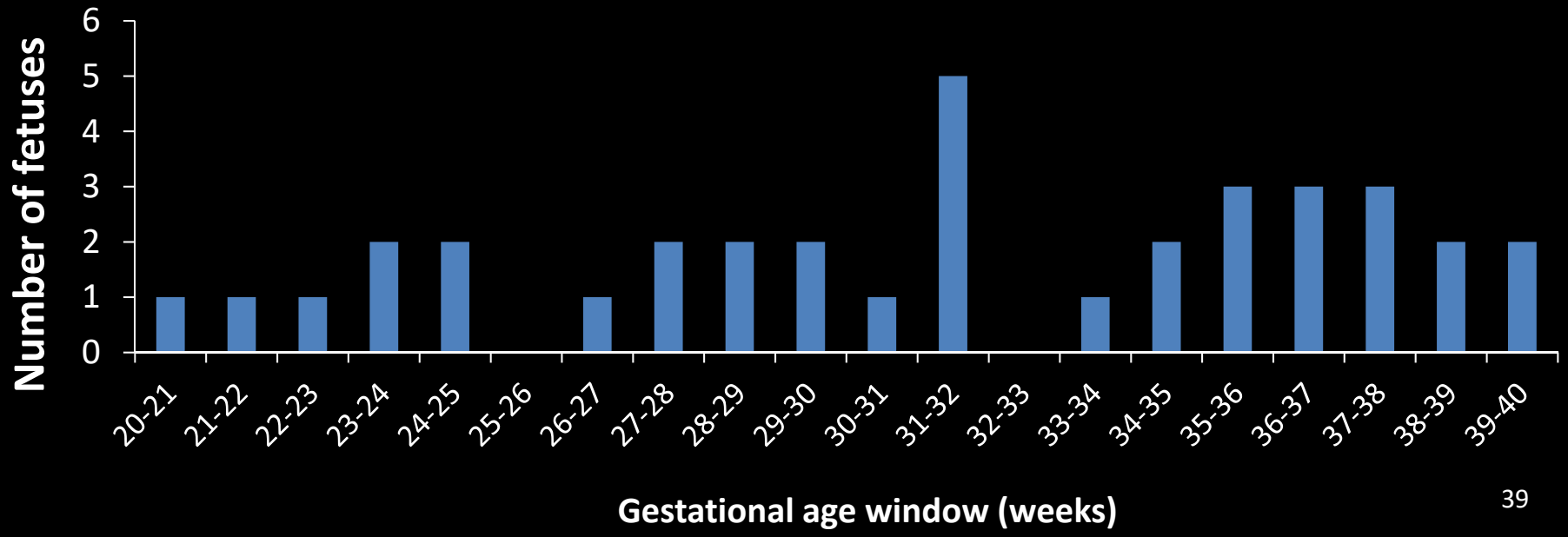
Fetal SWI:

Total number of healthy fetuses scanned = **196**

Measurements were made in **36** fetuses

8 in second trimester

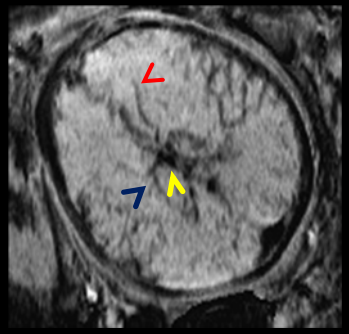
28 in third trimester

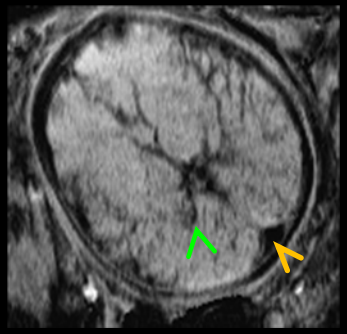


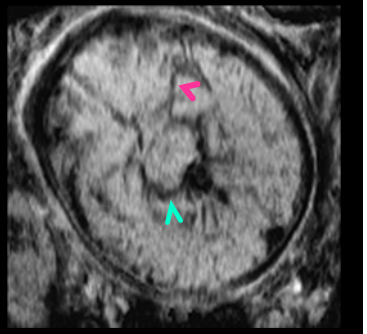
Fetal SWI: Fetal Brain

GA – 37 1/7 weeks

Fetal Brain







Thalamostriate vein

Septal vein

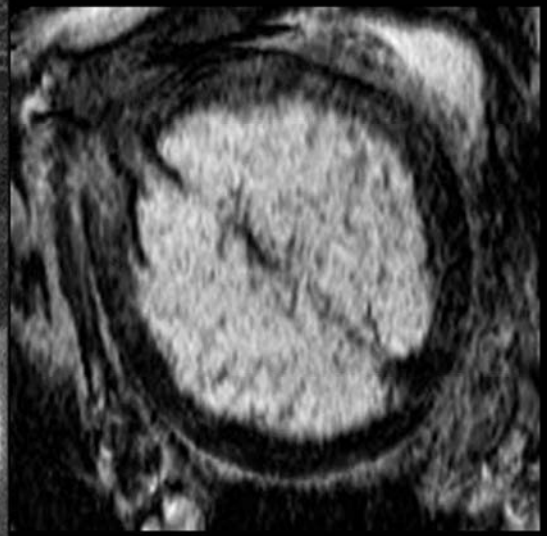
Medial Atrial vein

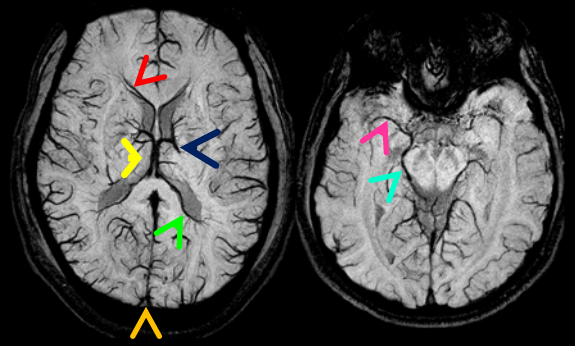
Internal Cerebral veins

deep Middle Cerebral Vein

Superior Sagittal Sinus

Basal vein of Rosenthal



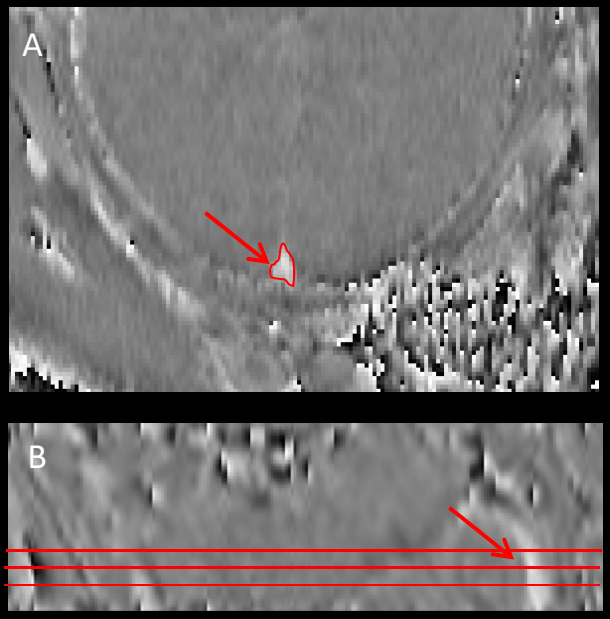


Adult Brain

Fetal SWI: Brain Oxygenation

- Free hand ROI is drawn in two or more consecutive slices to measure phase inside the vessel

Phase Image



Axial orientation

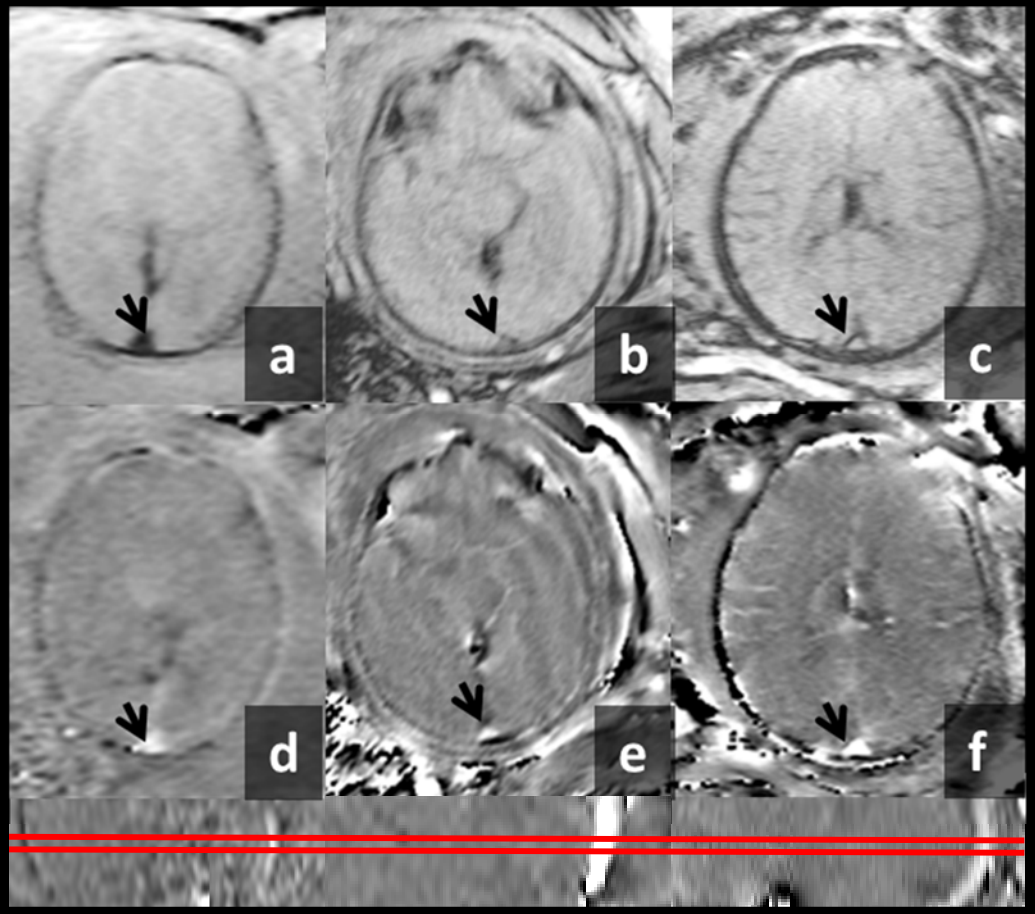
Sagittal orientation

Fetal SWI: Brain Oxygenation

Magnitude

Phase

Sagittal view

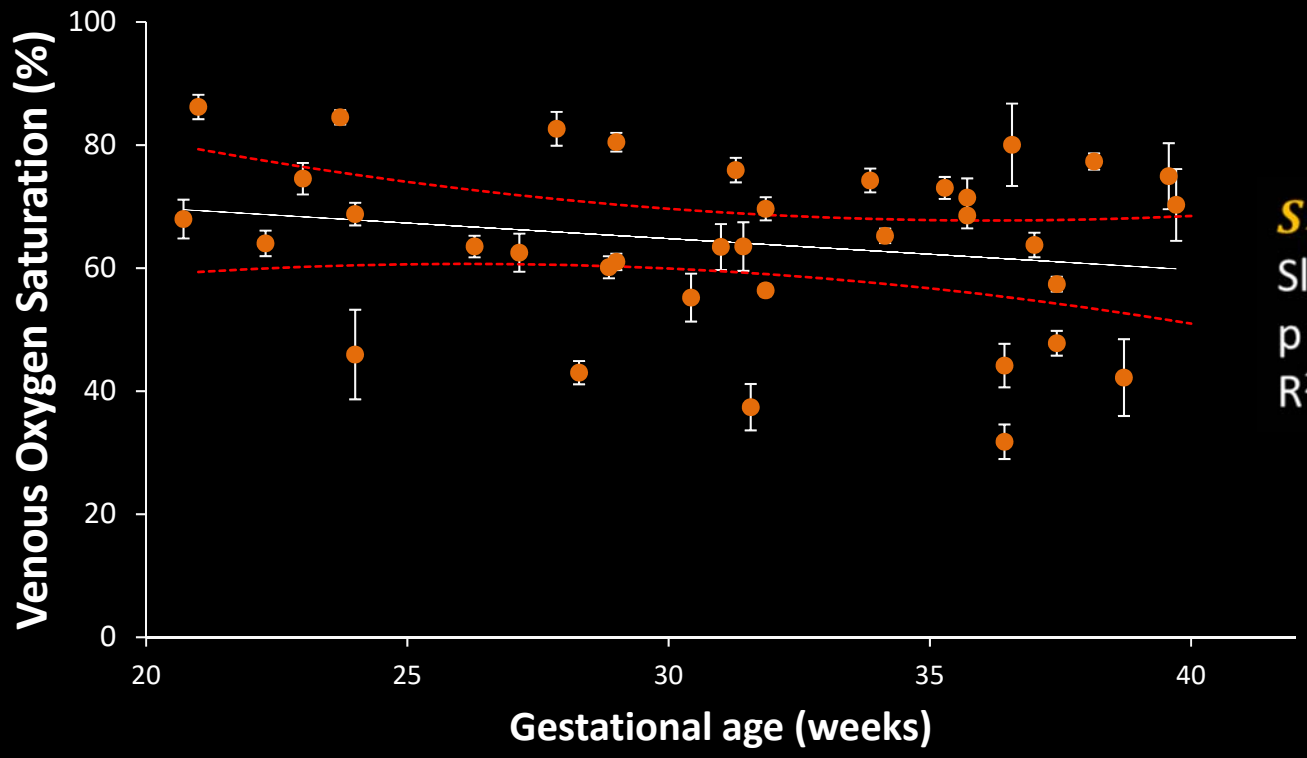


22 2/7 weeks 31 2/7 weeks 37 3/7 weeks

Fetal SWI: Brain Oxygenation

Normal fetuses: Mean oxygenation = 64.1 ± 3.3% (n=36)

Mean Susceptibility = 0.46 ± 0.06 ppm



S_vO_2

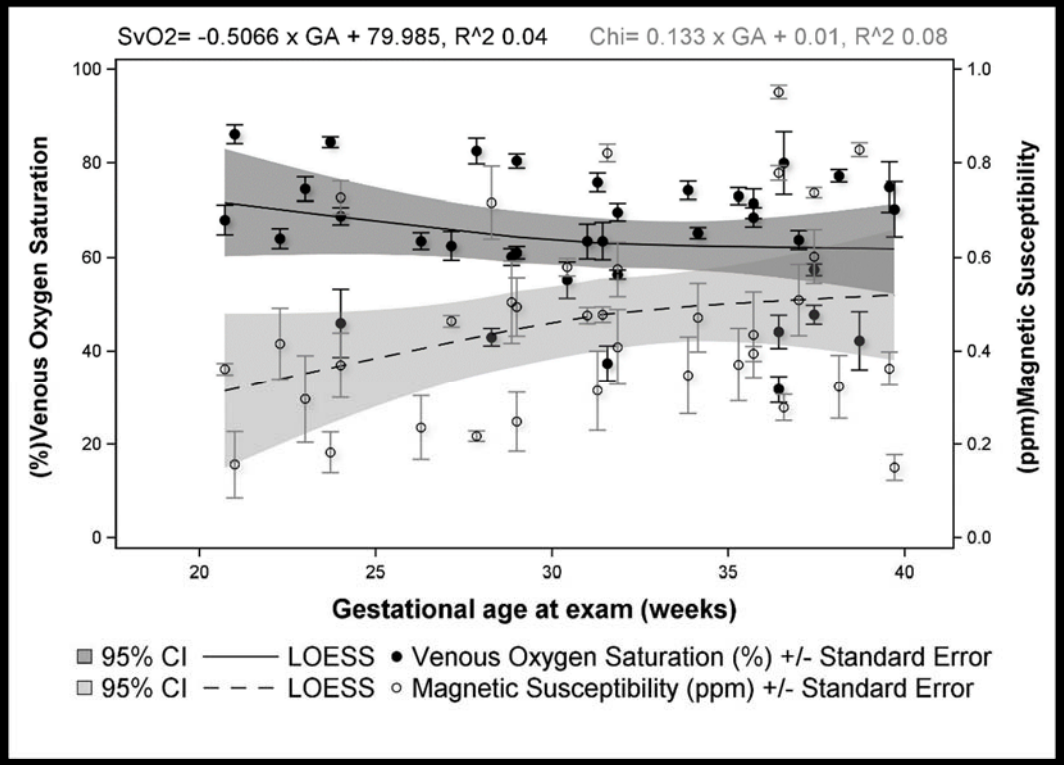
Slope= -0.5 ± 0.4

p = 0.22

R^2 = 0.04

Fetal SWI: Brain Oxygenation

$$\Delta\chi = \Delta\chi_{do} Hct(1-S_vO_2)$$



Fetal Cerebral Oxygenation

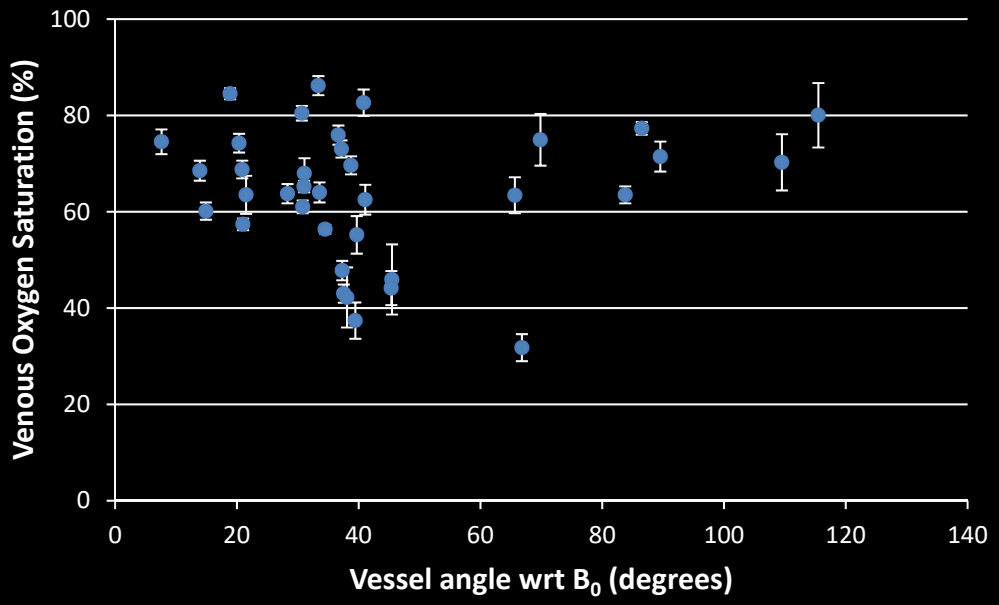
Limitations:

Oxygenation

- Vessel Curvature
- Unreliable phase near magic angle

Fetal SWI: Brain Oxygenation

$$\Delta\varphi = -\gamma \cdot \Delta\chi_{vein} \cdot B_0 \cdot (\cos^2\theta - 1/3) \cdot TE$$



The putative venous blood oxygen saturation, $SvO2$ (%) in normal human fetuses are plotted against the angle made by the superior sagittal sinus with respect to the main magnetic field, $B0$.

Fetal SWI: Brain Oxygenation

Primary finding:

- Results are in good agreement with neonatal studies (64%)[1,2]

- Although not statistically significant, a decreasing trend was found in oxygenation

[1] Liu, Peiying, et al. NMR in Biomedicine 27.3 (2014): 332-340. [2] Jain, Varsha, et al. JCBFM. 34.3 (2014): 380-388.

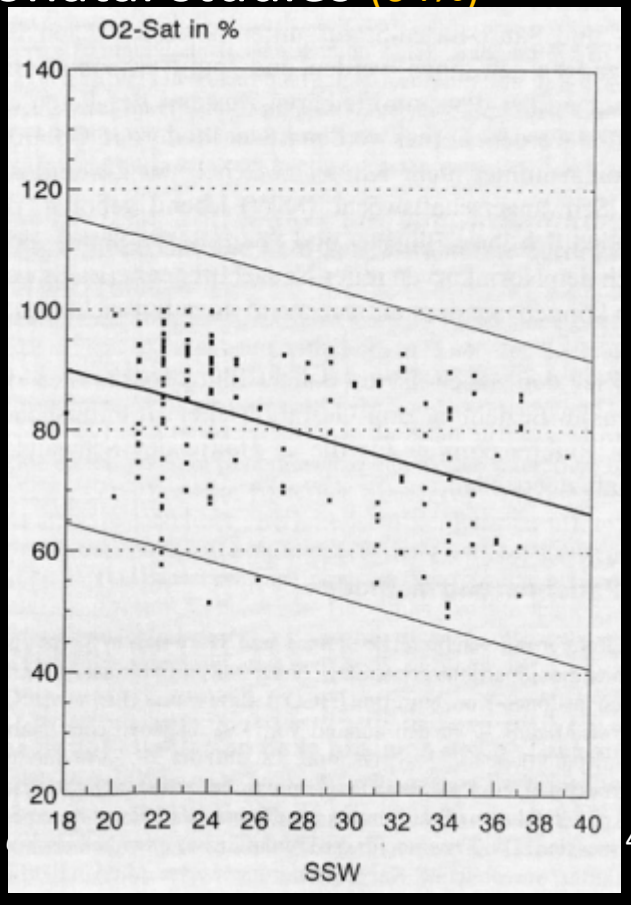
Fetal SWI: Brain Oxygenation

Primary finding:

- Results are in good agreement with neonatal studies (64%)[1,2]

- Although not statistically significant, a decreasing trend was found in oxygenation

N=150 healthy fetuses
GA: 18 to 40 weeks
Significant negative slope = -1.08
Method: cordocentesis



[1] Liu, Peiying, et al. NMR in Biomedicine 27.3 (2014): 332-340. [2] Jain, Varsha,
*[3] Schroter, B., et al.,. Gynakol Geburtshilfliche Rundsch, 1997. **37**(3): p. 130-5*

Topic 2

Multimodality Approach to Fetal Cerebral Hemodynamics: Oxygenation & Perfusion

Yadav, B.Y., et al. "*Multimodality Approach to Fetal Cerebral Hemodynamics: Perfusion and Oxygenation*" - To be submitted in Ultrasound in Obstetrics and Gynecology

Introduction:

- Low MCA-PI:
  - manifestation of brain sparing effect [1]
  - associated with abnormal neurological outcomes [2]

- Changes in MCA-PI is secondary to blood flow changes at the small vessels level [3,4]

- Blood perfusion could be more sensitive biomarker of early onset of change in blood flow in fetal brain

[1] Figueroa-Diesel, H., et al. Ultrasound in Obstetrics & Gynecology. 2007;30(3):297-302. [2] Cruz-Martínez, R., et al. Ultrasound in Obstetrics & Gynecology. 2011; 117(3):618-26. [3] Baschat, A., et al. Ultrasound in obstetrics & gynecology. 2001;18(6):571-7. [4] Roza, S.J., et al. American journal of epidemiology. 2008;168(10):1145-52.

Introduction:

Perfusion

- MRI- Limited spatial & temporal resolution, energy deposition, contraindication for contrast agent
- **FMBV**: US-based

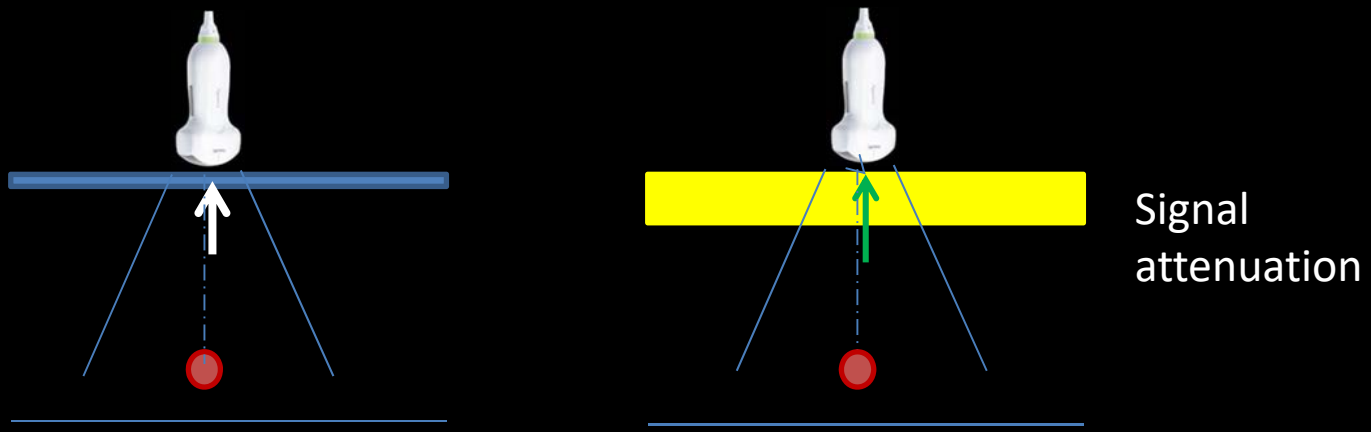
Oxygenation

- US does not provide oxygenation information
- **SWI**: MRI-based

Association between Perfusion and Oxygenation is not known

Fractional Moving Blood Volume (FMBV)

- 2D US technique based on Power Doppler (PDU)
- Performs normalization[1,2] of PDU signal within a region-of-interest (ROI)



[1] Rubin, J. M., et al. Radiology. 1995;197(1):183-90. *[2] Rubin, J. M., et al.* Radiology. 205.3 (1997): 757-765.

Fractional Moving Blood Volume (FMBV)

- 2D US technique based on Power Doppler (PDU)
- Performs normalization[1,2] of PDU signal within a region-of-interest (ROI): compensates for attenuation due to depth or tissue interphase

GA: 32 weeks

Power Doppler

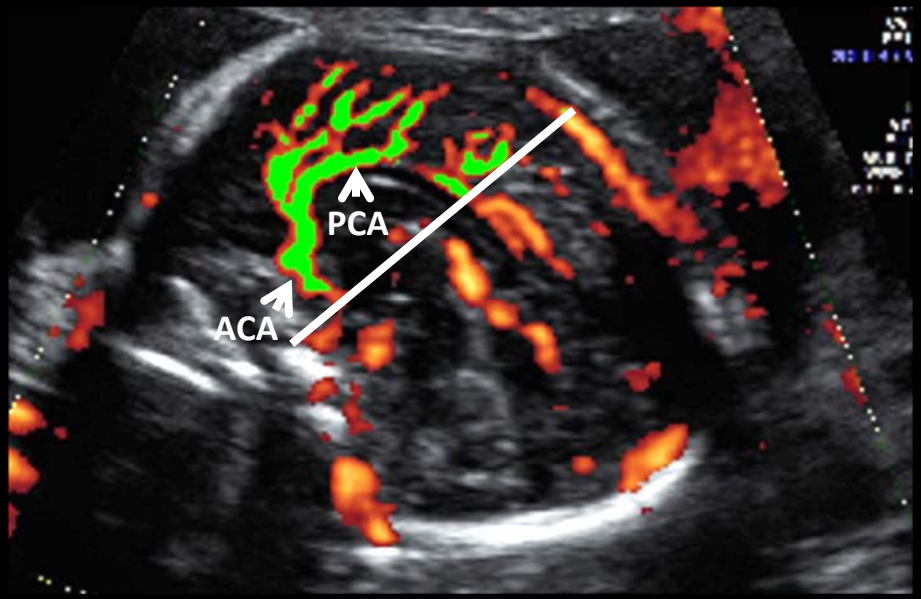
FMBV or Normalized power Doppler

[1] Rubin, J. M., et al. Radiology. 1995;197(1):183-90. *[2] Rubin, J. M., et al.* Radiology. 205.3 (1997): 757-765.

FMBV: Fetal Cerebral Perfusion

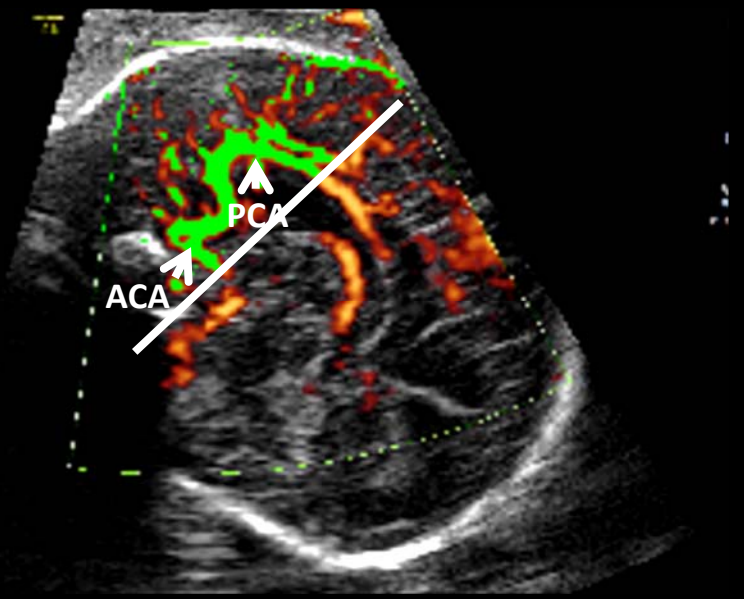
- Imaging was performed in **33** healthy fetuses

GA : 22 weeks



Perfusion = 24.2%

GA : 31 weeks



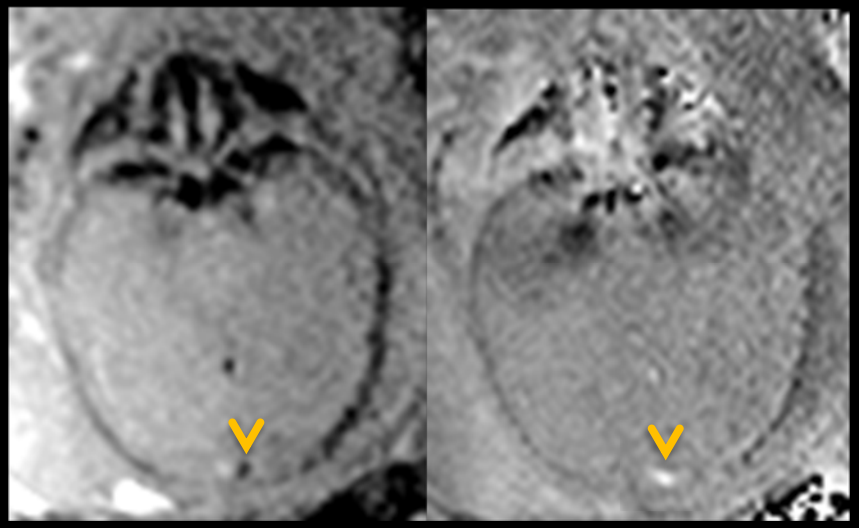
Perfusion = 35.6%

ACA: Anterior cerebral artery; PCA: Pericollosal artery

SWI: Fetal Cerebral Oxygenation

Model-based Oximetry

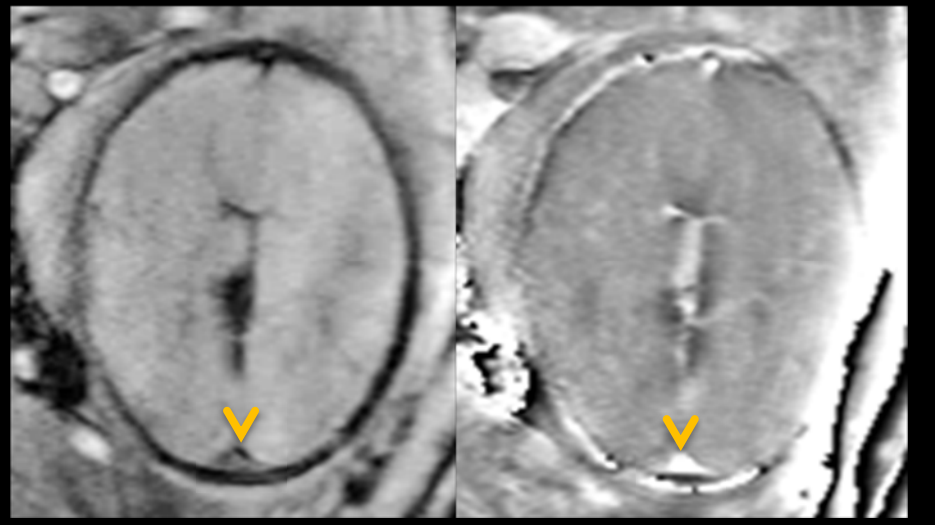
GA : 22 weeks



Magnitude Phase

S_vO_2 : 77.6%

GA : 31 weeks

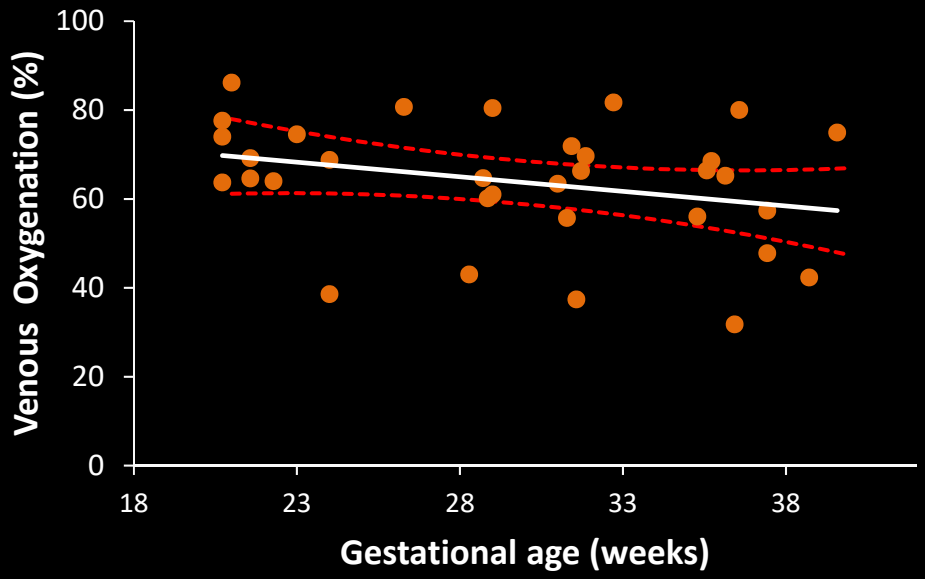


Magnitude Phase

S_vO_2 : 42.3%

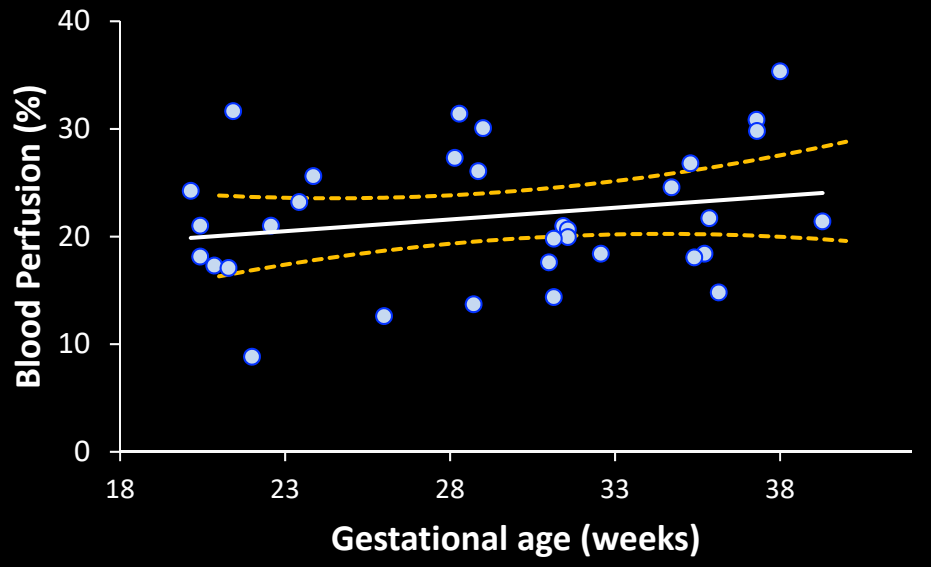
Fetal Cerebral Oxygenation & Perfusion

Oxygenation



Average S_vO_2 : 63.9±3.2%
(n=33)
Slope= -0.7 ± 0.4
p = 0.1
R^2 = 0.08

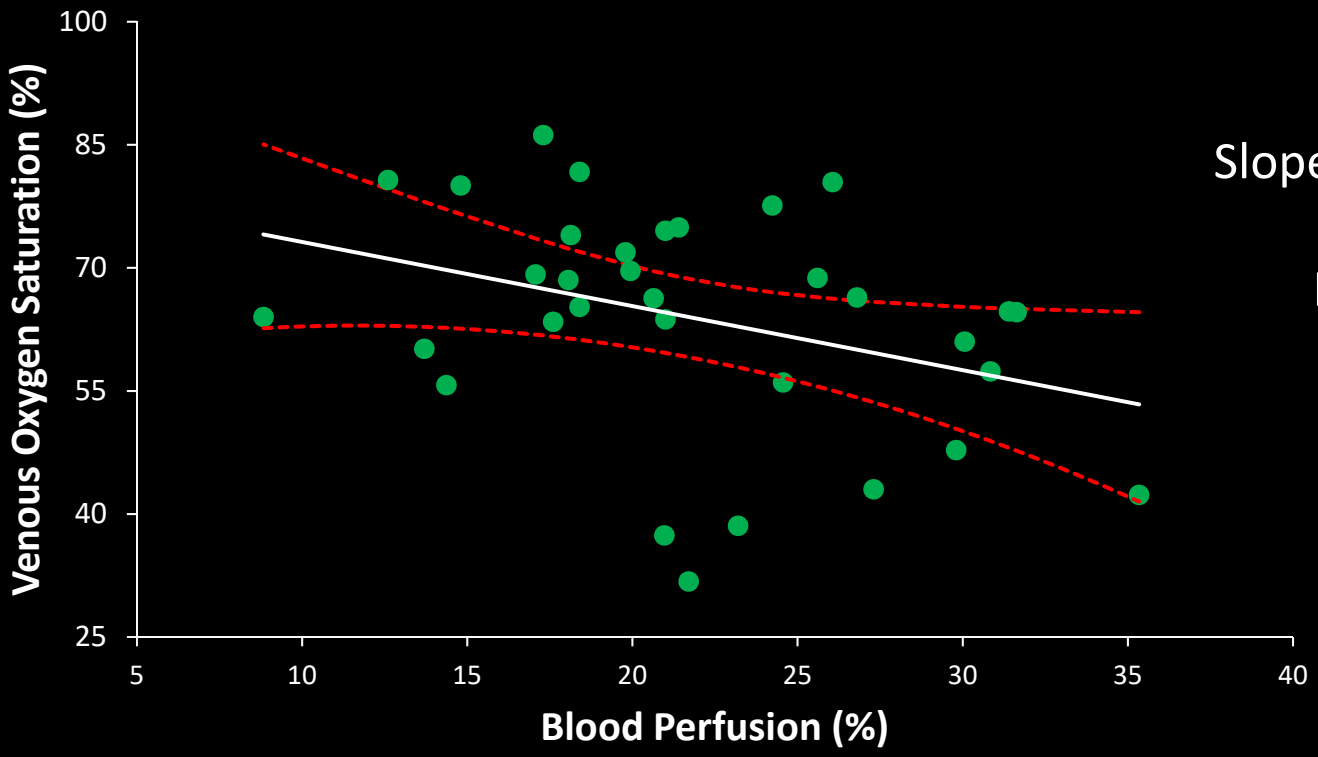
Perfusion



Average Perfusion : 21.9 ± 1.1%
(n=33)
Slope= 0.2 ± 0.2
p = 0.23
R^2 = 0.05

Fetal Cerebral Oxygenation & Perfusion

Association: Oxygenation vs. Perfusion (n = 33)



Slope= -0.78 ± 0.3

p = 0.04

R^2 = 0.12

Fetal Cerebral Perfusion & Oxygenation

Primary finding:

- Oxygenation and perfusion were found to be in normal physiological range [1,2]

Fetal Cerebral Perfusion & Oxygenation

Primary finding:

- Oxygenation and perfusion were found to be in normal physiological range [1,2]

FMBV [1]
N = 230 healthy fetuses
GA: 24-41 weeks
Method: FMBV

Frontal brain = 6% to 24%

Oxygen saturation [2]
N = 1281 healthy pregnancy
GA: 37-42 weeks
Method: Blood gas analyzer

Umbilical artery = 2.7% to 69%
Umbilical vein = 16.4% to 83.3%

[1] Cruz-Martinez, R., et al. UOG 37.2 (2011): 196-201.; [2] Arikan, G. M., et al. *BJOG* 107.8 (2000): 987-994.

Fetal Cerebral Perfusion & Oxygenation

Primary finding:

- Oxygenation and perfusion were found to be in normal physiological range [1,2]
- Significant negative association between blood oxygenation and blood perfusion in the healthy fetal brain
- Both biological parameters are well coupled in fetuses

Topic 3

Quantitative Susceptibility Mapping In The Human Fetus to Measure Blood Oxygenation In The Superior Sagittal Sinus

Yadav, B.Y., et al. "*Quantitative Susceptibility Mapping In The Human Fetus to Measure Blood Oxygenation In The Superior Sagittal Sinus*" - Under review in European Radiology

Quantitative susceptibility mapping (QSM)

– Not dependent on model and object orientation

– 3D phenomena

$$\Delta\varphi(r) = -\gamma \cdot \{\Delta\chi_v(r) * g(r)\} \cdot B_0 \cdot TE \qquad \chi << 1$$

$$\Delta\chi_v(r) = FT^{-1}\left(FT\left(\frac{\Delta\varphi(r)}{(\gamma . B_o . TE)}\right).\frac{1}{g(k)}\right)$$

where,

$$g(k) = \frac{1}{3} - \frac{k_z^2}{k_x^2 + k_y^2 + k_z^2}$$

$$\Delta\chi_v = \Delta\chi_{do}.(1 - S_v O_2).Hct$$

Haacke, E. Mark, et al. *Magnetic resonance imaging* 33.1 (2015): 1-25.

Quantitative susceptibility mapping (QSM)

– Not dependent on model and object orientation

– 3D phenomena

$$\Delta\varphi(r) = -\gamma \cdot \{\Delta\chi_v(r) * g(r)\} \cdot B_0 \cdot TE \qquad \chi << 1$$

$$\Delta\chi_v(r) = FT^{-1}\left(FT\left(\frac{\Delta\varphi(r)}{(\gamma . B_o . TE)}\right).\frac{1}{g(k)}\right)$$

where, $$g(k) = \frac{1}{3} - \frac{k_z^2}{k_x^2 + k_y^2 + k_z^2}$$ **Iterative SWIM**

$$\Delta\chi_v = \Delta\chi_{do}.(1 - S_vO_2).Hct$$

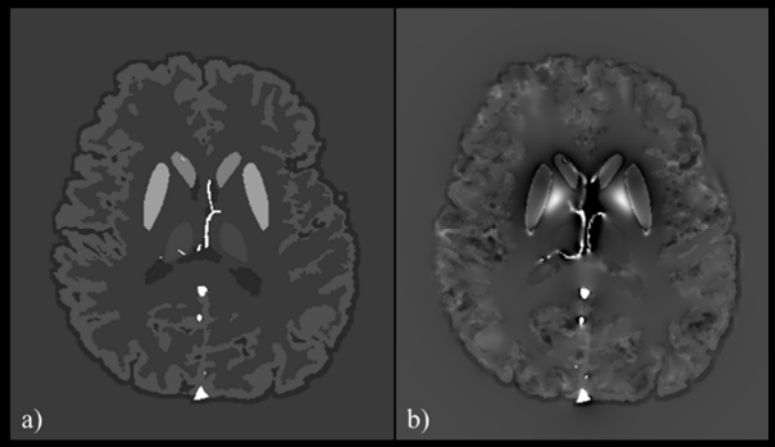
Haacke, E. Mark, et al. *Magnetic resonance imaging* 33.1 (2015): 1-25.

QSM: Practical Considerations

- Minimum 5 voxels around the superior sagittal sinus (SSS)
- Minimum 5 slices available

True $\Delta\chi_v$ = 0.45 ppm

True S_vO_2 = 70%



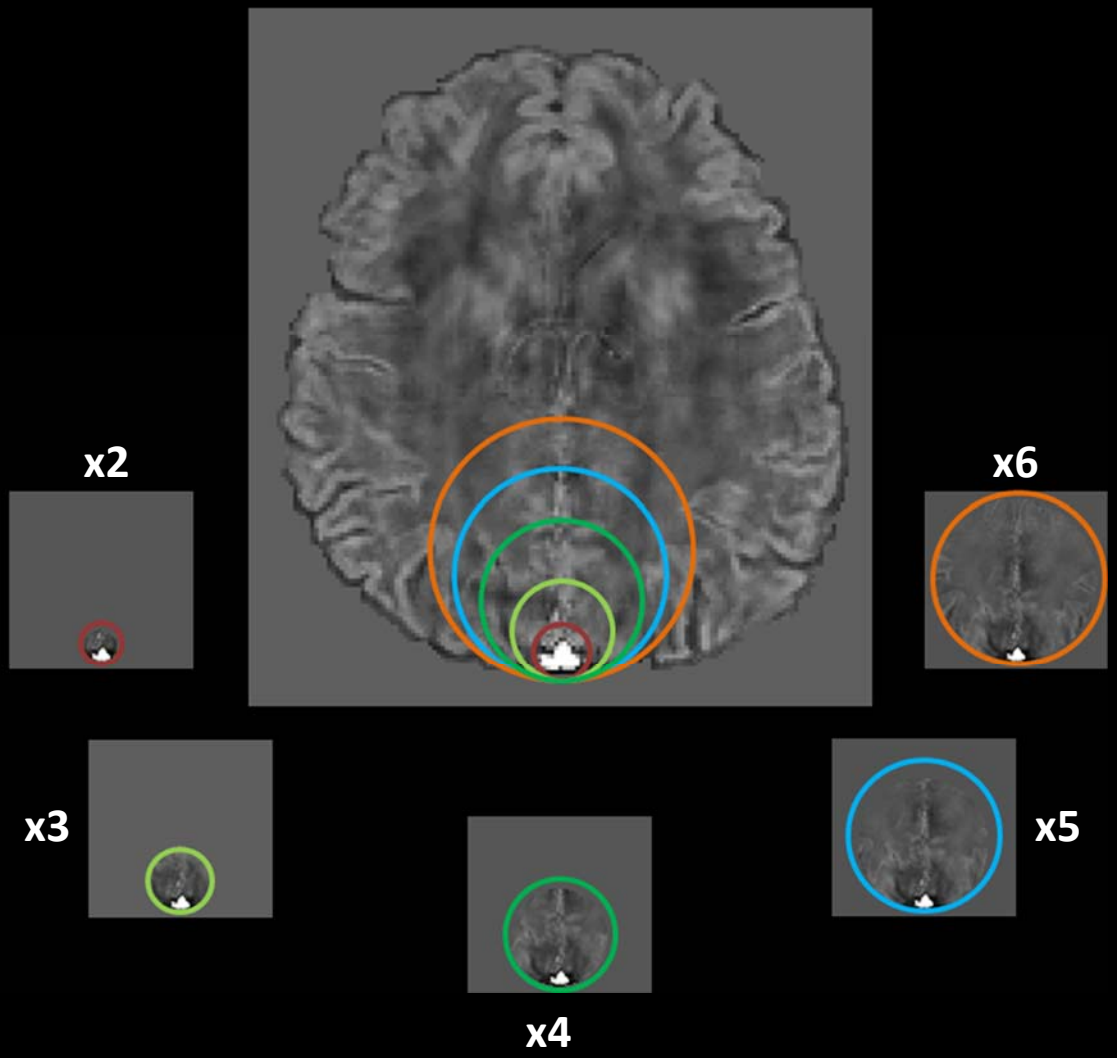
Original susceptibility model

Simulated phase

Haacke, E. Mark, et al. *Magnetic resonance imaging* 33.1 (2015): 1-25.

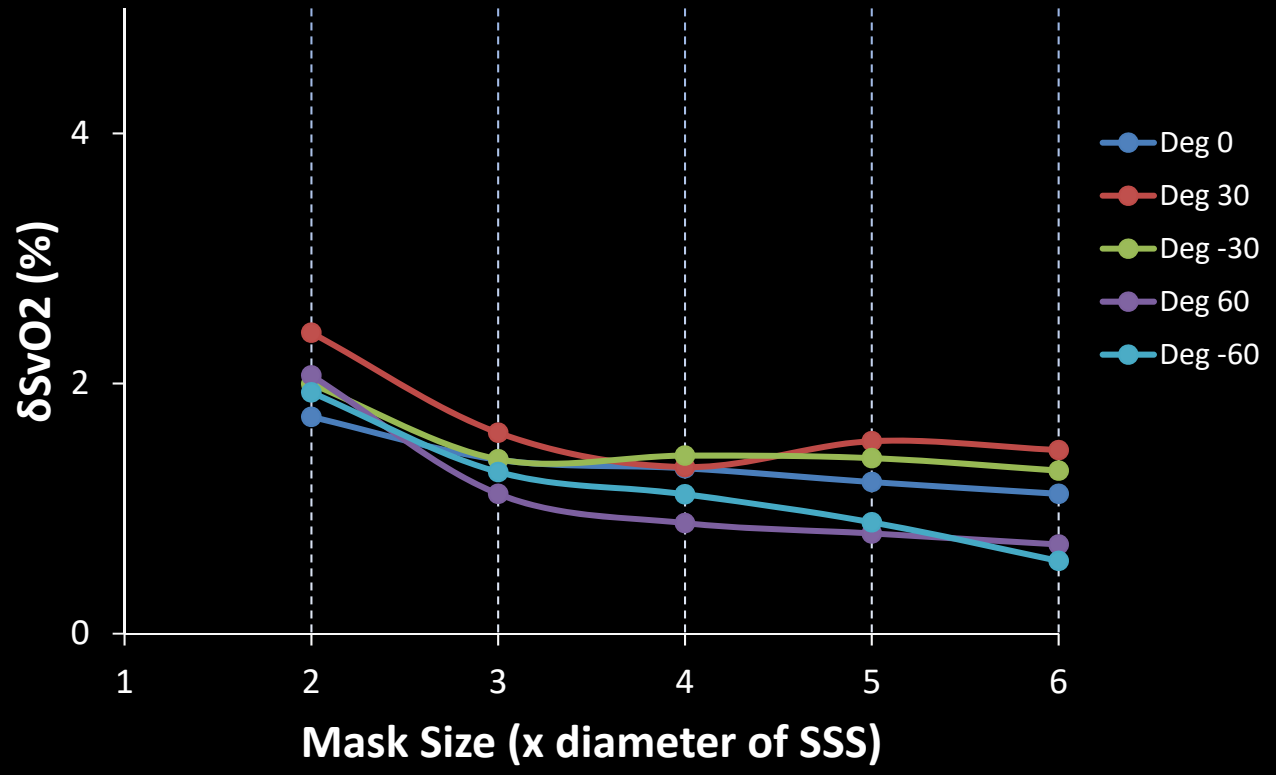
QSM: Simulations – Mask Formation

x2 -> 2 times the diameter of SSS



QSM: Simulations

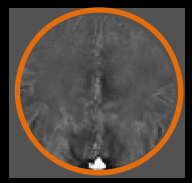
Relative error in $\delta S_vO_2 < 4\%$

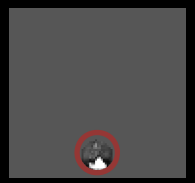


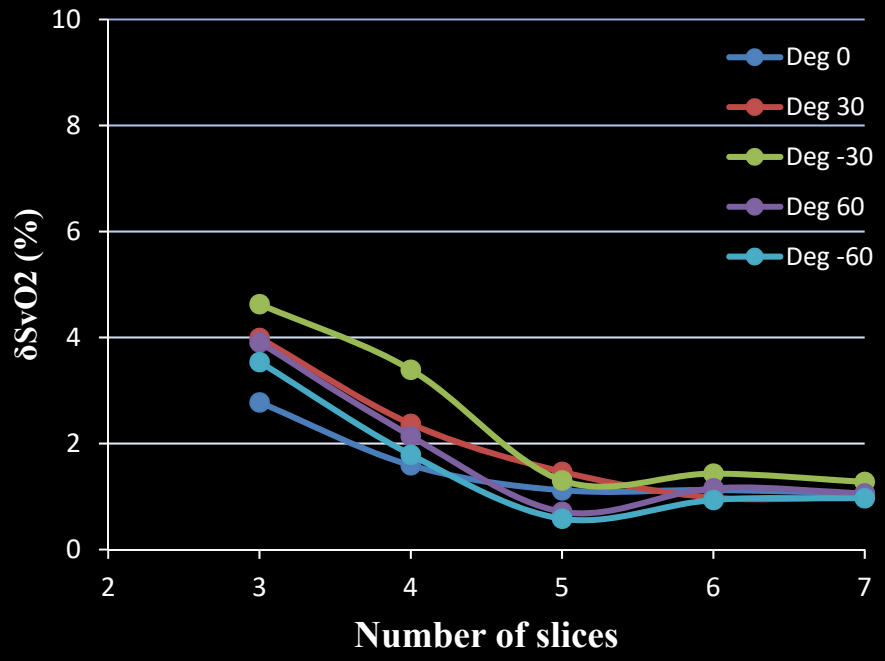
For 5 slices and 5 voxels around SSS

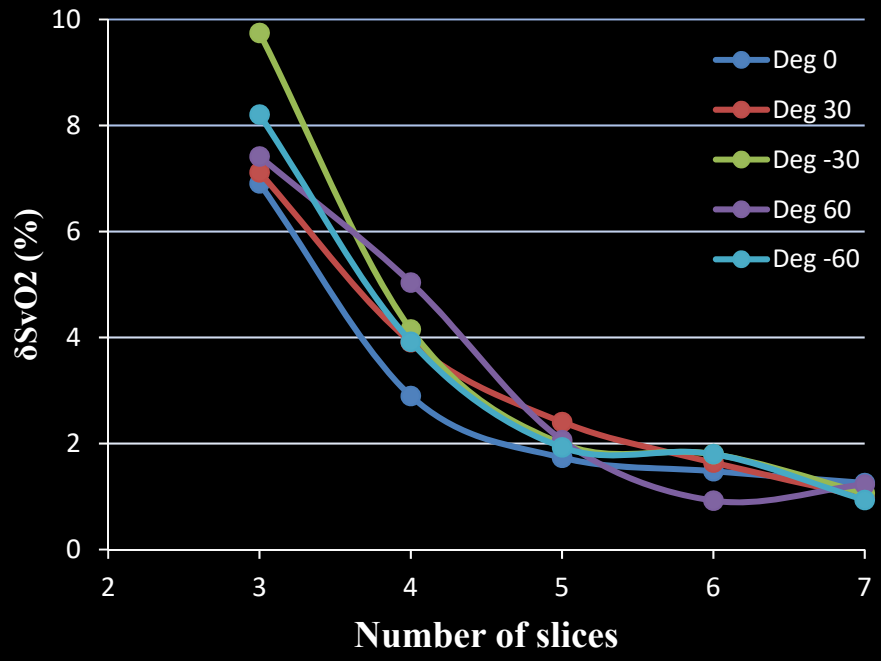
QSM: Simulations

Relative error for number of slices >=5, the $\delta S_vO_2 < 4\%$

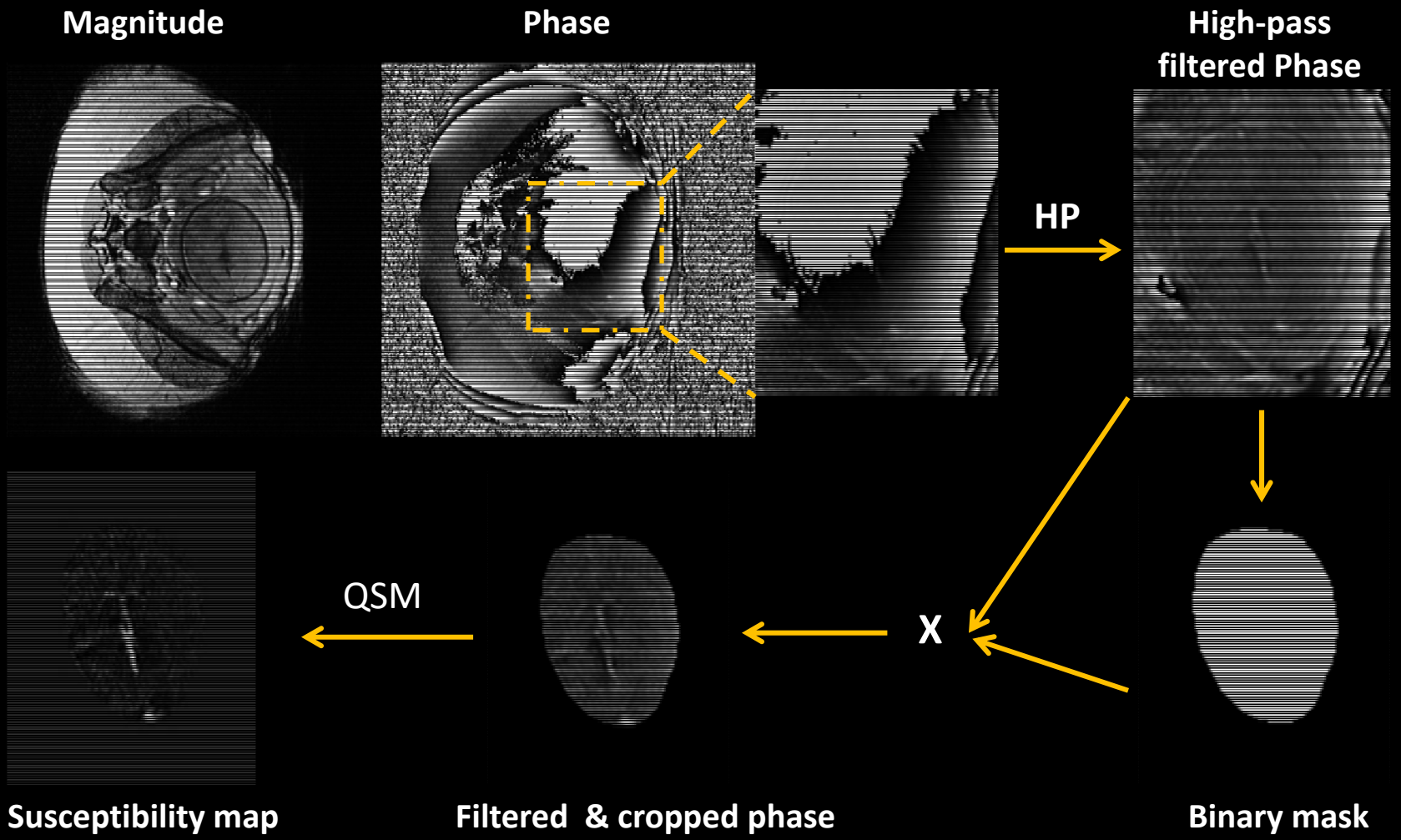
6x 

 2x

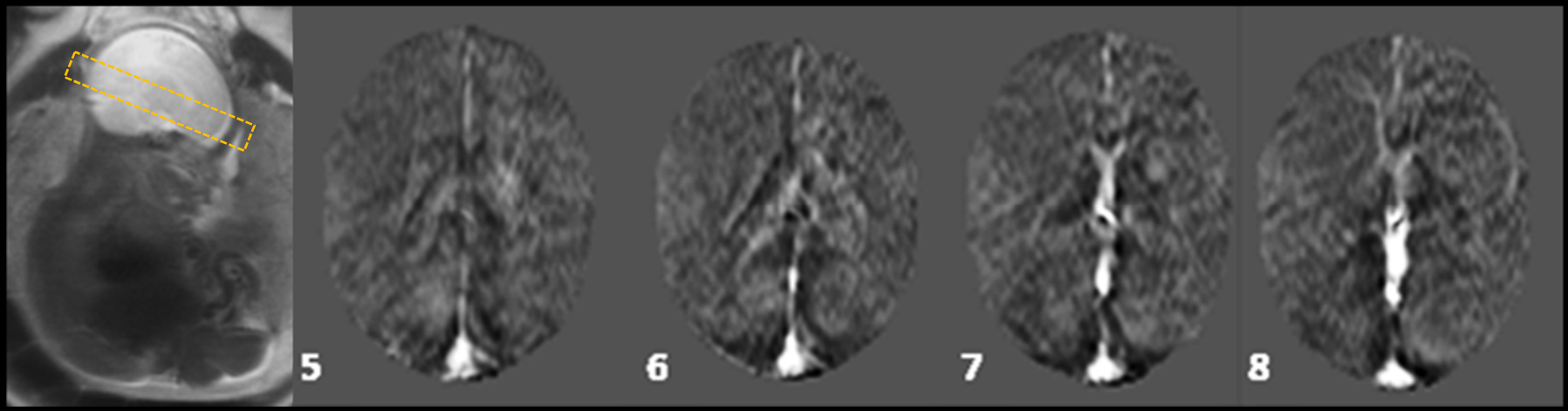




Fetal QSM: *in-vivo* Pipeline



Fetal QSM



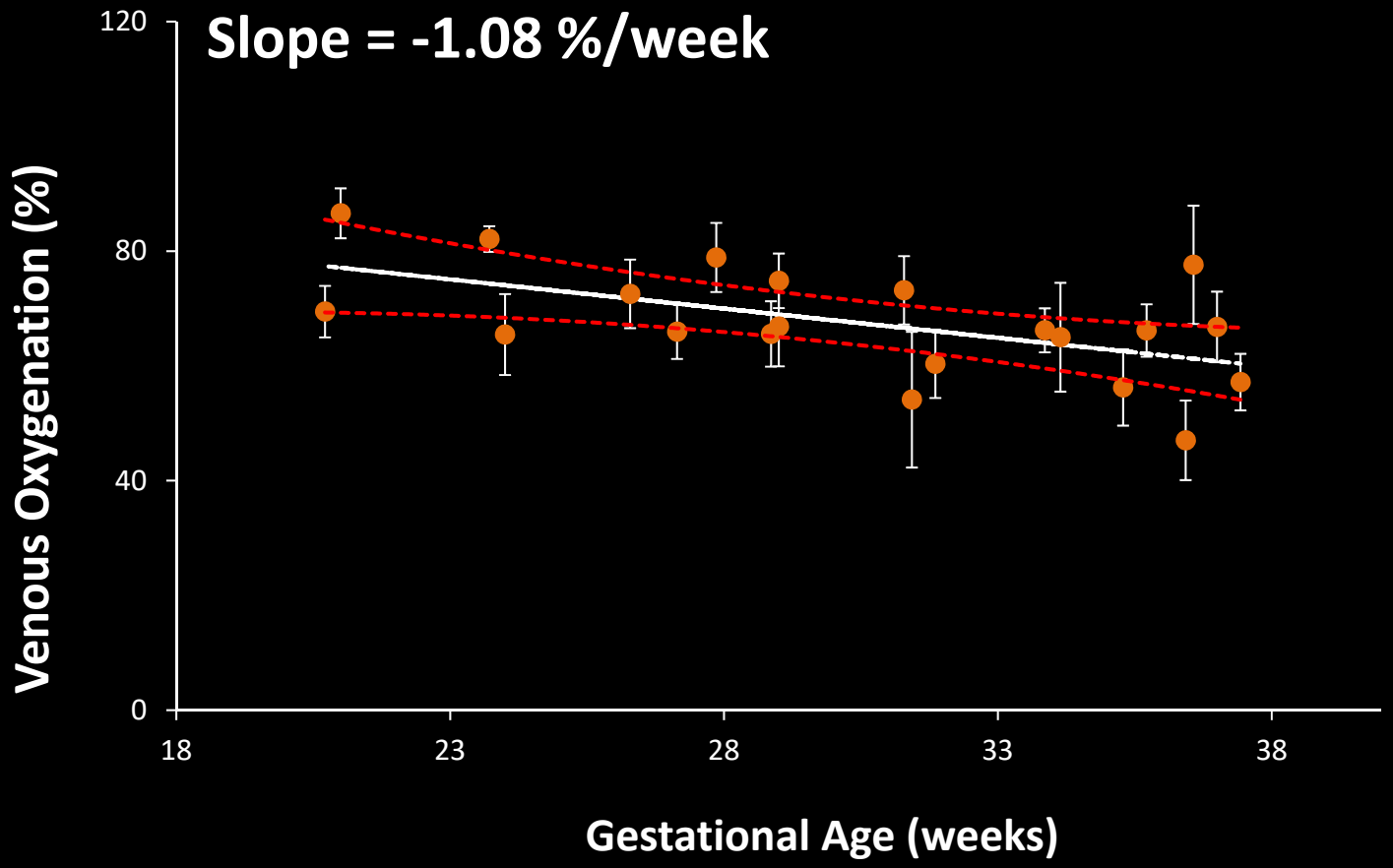
Localizer

GA: 29 weeks

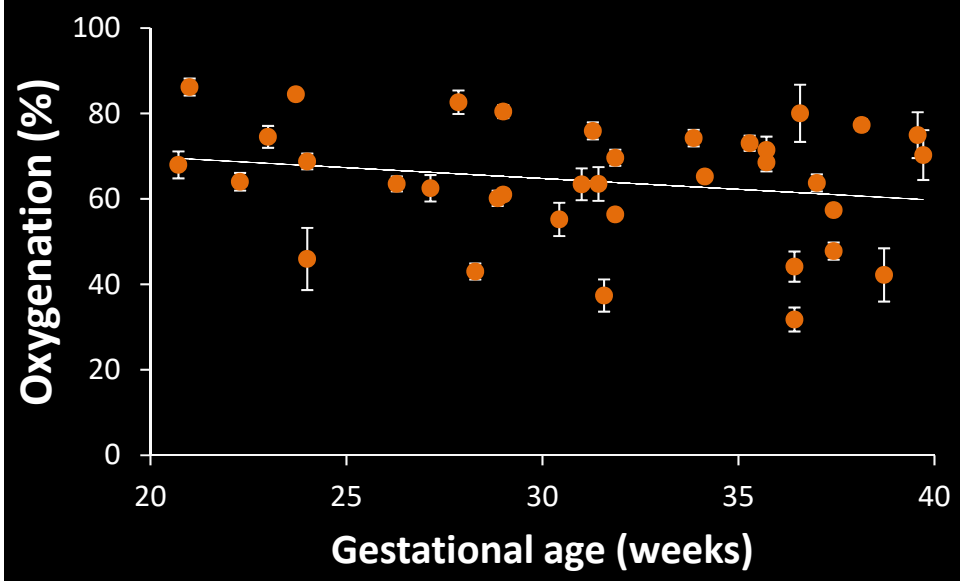
Slices of the Susceptibility maps of the fetal brain

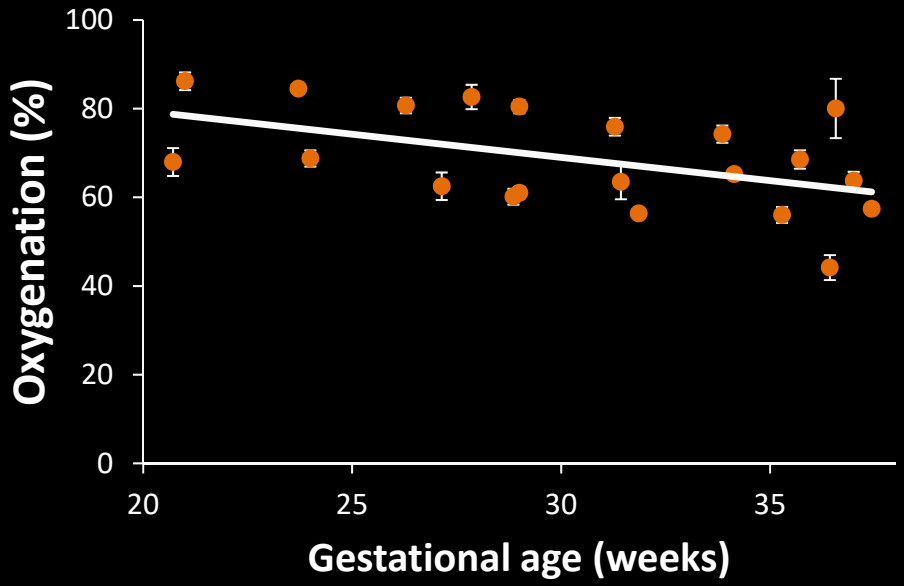
Fetal QSM: S_vO_2 across gestation

Healthy human fetuses, n = 21



Fetal SWI: Brain Oxygenation





S_vO_2 n=36
Slope= -0.5 ± 0.4
p = 0.22
R^2 = 0.04

S_vO_2 n=21
Slope= -1.05 ± 0.4
p = 0.02
R^2 = 0.24

Model based-oximetry as shown in Topic 1

Future Directions

- Extension of the presented methods to clinical cases
- Fetal as well as placental blood oximetry using QSM
- Radial SWI – motion insensitivity, higher resolution, large FOV

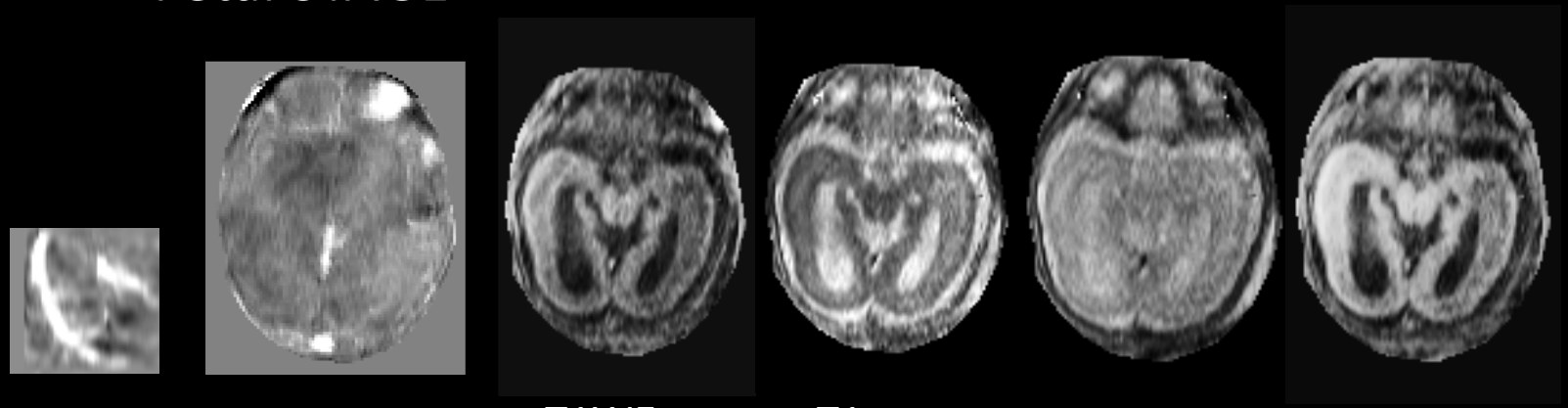
Biomedical Engineering & Imaging Sciences, KCL: https://www.youtube.com/watch?v=djJnsC_CddI

Future Directions

- Extension of the presented methods to clinical cases
- Fetal as well as placental blood oximetry using QSM
- Radial SWI – motion insensitivity, higher resolution, large FOV
- Validation of fetal oximetry: SWI vs. T2 vs. T2*

Future Directions

- Extension of the presented methods to clinical cases
- Fetal as well as placental blood oximetry using QSM
- Radial SWI – motion insensitivity, higher resolution, large FOV
- Validation of fetal oximetry: SWI vs. T2 vs. T2*
- Fetal STAGE



QSM T1WE T1 map PD map T1 FLAIR

Courtesy: Yongsheng Chen and Dr. Taotao Shun

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Mentors: Drs E.M. Haacke & J. Neelavalli

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