Diffusion-Weighted MRI of the placenta in normal pregnancies and in pregnancies complicated by Fetal Growth Restriction

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STUDENT REPORT

Diffusion-Weighted MRI of the placenta in normal pregnancies and in pregnancies complicated by Fetal Growth Restriction

Master thesis

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Contents

Preface

This master thesis serves as a two-pieced product: the master thesis, with preface where methods and information have been further elucidated and the main scientific contribution to this semester; the article.

Study setting

This retrospective cohort-study was performed at Department of Obstetrics and Gynecology, Aalborg University Hospital, Aalborg, Denmark over a four months' period from September 1st to December 21st 2015. I have been a member of the research group, "Placentagruppen", established to create a supporting environment for current and future researchers with an interest in the human placenta. During weekly Friday meetings, we have been through topics such as statistical analysis, placental physiology and pathology, MRI physics, systematic literature search and review and publication strategy. The placental DWI MRIs were retrieved from the research Placental MRI protocol established by Marianne Sinding and Anne Sørensen who included the study participants and performed the placental MRIs.

Background

Fetal growth restriction (FGR), due to placental dysfunction, is a major challenge in modern obstetrics. In such pregnancies, the fetuses are at high risk of neonatal morbidity and mortality(1). Identification and surveillance of these high-risk pregnancies is based on ultrasound examination with fetal Doppler flow measurements and cardiotocography, serving the purpose to estimate fetal well-being(2). Increased resistance of the uterine arteries can be estimated using Doppler flow measurement, and therefore it can be used in the assessment of placental function. However, Doppler flow measurement of the uterine arteries remains inadequate to detect early placental

dysfunction. In clinical practice today, no other methods for *direct*, non-invasive assessment of placental function is available but diffusion-weighted MRI and ADC value might be an option.

Diffusion-weighted imaging makes use of microscopic and macroscopic motions of water intracellular, extracellular and intravascular, so called Brownian motions(3). There are no barriers to diffusion in fluids. Hence the molecules can move over great distance, i.e. high diffusion. In tissue, there are barriers to these random motions, i.e. low diffusion. The apparent diffusion coefficient (ADC) describes the "distance of diffusion"; an approximation of the minimum distance from start to stop, or the change in molecule position, of Brownian motion. In dense tissue, where the movement of the molecules are slower and more restrained, the diffusion will be limited. Signal intensity of the DWI decreases less and will therefore be more intense(4).

Purpose

The purpose of this study is to investigate the feasibility of placental DWI and placental apparent diffusion coefficient (ADC) value as a method of assessing placental diffusional properties (or placental function) in normal singleton pregnancies and in singleton pregnancies complicated by FGR.

Hypothesis

1. In normal singleton pregnancies, the placental ADC value is reduced with advancing gestational age.
2. In singleton pregnancies complicated by FGR, the ADC value is reduced

Ethical considerations

This study was conducted in accordance with the approval of Anne Nødgaard Sørensen's placental MRI-protocol, obtained from the local Danish Ethical Committees (journal number: M2009006 and N20090052).

MRI safety

The potential hazardous effects of MRI during pregnancies has been a subject of many scientific studies. Areas of concern are temperature elevation and the exposure to very loud noise during MRI. No studies have yet shown association between exposure to MRI and adverse fetal outcome(5). It is recommended that adults wear ear protection to reduce sound levels during MRI examination. The fetus is protected by the maternal abdomen and amniotic fluid.

In this study we've used 1.5 Tesla. No studies have reported adverse fetal outcome after exposure to magnetic fields at this strength(5).

Methods

At the time of writing this report, only 38 of the participating women had given birth to healthy neonates. 31 met the requirement of birth after week 37 and birth weight above the 2.3rd percentile and were included as normal material in this cohort study. The remaining seven resulted in birth weight under the 2.3rd percentile and were included as FGR cases. Only one of the histopathological examination of FGR-placentas were ready at time of writing and revealed signs of maternal hypoperfusion. The results of the remaining six cases will be added to the manuscript before submission. In all seven cases, Doppler ultrasound examinations of the umbilical arteries revealed increased resistance. Therefore, in the manuscript draft, we assume that the placental histological examination revealed abnormal placental histology in all cases.

The placenta database

During a period of six weeks, a fellow medical student and I created a so-called "Placenta-database" serving the purpose to accumulate all information on the participants included in the MRI studies. We have learned to set up and program the database using the software EpiData Manager. Maternal, neonatal, US, MRI and publication information accounted for 145 variables, were

discussed and agreed upon by "Placenta-gruppen" (Appendix 1). We have used double entry and specified entry fields to prevent entry errors and thereby minimizing potential bias in our statistical analysis. Sources of information, used to cover all variables, were Clinical Suite, AS400, Astraia and RoiTools.

The use of patient information in the master thesis, is approved by the Danish Data Protection agency and covered by "Region Nordjyllands paraplyanmeldelse ved Datatilsynet – Sundhedvidenskabelig forskning I Region Nordjylland" (2008-58-0028), September 14th 2015.

Statistical analysis

All statistical analysis was conducted using the commercial software Statistical Package for the Social Sciences (SPSS, Version 23.0, released 2015. Armonk, N.Y: IBM Corp). A few commands were not available in SPSS. In these cases, the statistical software package Stata®13 (StataCorp LP, College Station, TX, USA) was used instead. SPSS-syntax and STATA-do-file is attached (Appendix 2 and 3).

Literature

The objective of this project is still very new and there has only been a few previous studies conducted. Hence there is not much information to be found. A systematic literature search was conducted to generate relevant academic knowledge and insight and to ensure that the project is founded on a scientific basis. The literature research strategy and review of used literature is attached (appendix 4 and 5).

Publication strategy

I pursue a publication of the article in Prenatal Diagnosis in 2016. This journal was chosen in collaboration with my supervisors as it communicates research in prenatal and preimplantation diagnosis and all aspects of fetal imaging, including in vivo magnetic resonance imaging(6). The

scientific product of this project, the article, is therefor based on Prenatal Diagnosis' *Author Guidelines* for abstract and manuscript at maximum 200 and 3.500 words, respectively (http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1097-0223/homepage/ForAuthors.html).

Resumé

Baggrund

En optimalt fungerende placenta er nødvendig for at opretholde en levedygtig graviditet. I graviditeter kompliceret af væksthæmning (FGR) fungerer placenta insufficient og har en høj morbiditets- og mortalitetsrate(1). I klinikken er identifikationen og monitoreringen af disse høj-risiko graviditeter en stor udfordring. Ultralydsundersøgelse og cardiotocografi (CTG) bruges til at identificere og monitorere den føtale trivsel og risikograviditeter(2). Øget modstand i arteria uterina kan måles ved hjælp af Doppler flow og kan benyttes som eneste direkte mål for placentas funktion. Dog er dette mål utilstrækkelig til at detektere tidlig placental dysfunktion. Ingen anden direkte og non-invasiv metode for evaluering af placentas funktion er tilgængelig, men diffusionsvægtet MR-skanning (DWI) og placental *apparent diffusion coefficient* (ADC)-værdi kan være et alternativ. Signalet ved DWI skanninger skabes af Brownske bevægelser, som er intracellulære, ekstracellulære og intravaskulære mikroskopiske bevægelser af vandmolekyler(3). Størrelsen af disse tilfældige bevægelser er afhængig af vævstype og densitet. Det vil sige, at diffusionen er større i væskefyldte hulrum uden barrierer end i tæt væv, som i fx muskler. ADC-værdien er et udtryk for diffusionsafstanden; et cirka-mål for den mindste ændring i molekyleposition ved de Brownske bevægelser. I et review om MR-skanning af placenta fra 2015, foreslås teorien om, at de fysiologiske strukturelle ændringer som sker i placenta ved progredierende gestationsalder, kan påvirke diffusionen og dermed undersøges ved hjælp af DWI. Der foreslås også, at den svigtende placenta, kan give anledning til nedsatte diffusionsegenskaber og dermed en reduceret ADC værdi(7).

I dette studiet har vi derfor valgt at beskrive placentas ADC-værdi i normale graviditeter og associationen til progredierende gestationsalder. Yderligere vil vi vurdere ADC-værdien i syv cases med FGR.

Metode

I denne retrospektive kohorte-studie blev der inkluderet 38 singleton graviditeter uden misdannelser og med normal karyotype. 31 resulterede i raske mature børn født efter uge 37 med en fødselsvægt over 2,3 percentilen. De resterende syv havde en fødselsvægt under 2,3 percentilen og er inkluderet som FGR-cases. Ved alle MR-skanninger blev der anvendt et 1.5 Tesla system (GE Discovery MR450) og under undersøgelsen blev kvinderne placeret i en venstresidig lateral position for at forhindre eventuel kompression af vena cava. En DWI sekvens med 10 b-værdier (fra 0 til 1000 s/mm2) blev optaget som en del af en eksisterende MR-protokol. Total tid for MR-scanning var cirka 30 minutter. Efterfølgende blev der tegnet *Regions of Interests* (ROIs) på DWI-skanningerne i fem snitflader, som dækkede hele placenta. På baggrund af b-værdierne 200, 400 og 100 s/mm2 blev der beregnet en gennemsnits ADC-værdi for de fem snitflader. I normale graviditeter blev relationen mellem placental ADC-værdi og gestationsalder på MR-tidspunktet estimeret ved hjælp af lineær regression. I de syv cases med vaksthæmning blev der udregnet z-scores.

Resultater

I de 31 normale graviditeter varierede ADC-værdien fra 1,33 til 1,76 x 10^{-3} mm^2/s med en signifikant negativ korrelation mellem ADC-værdi og gestationsalder ($p = 0.001$). I de syv vaksthæmmede graviditeter varierede den placentale ADC z-score fra 1,10 og -2,80. I tre ud af syv cases med vaksthæmning var ADC-værdien betydelig nedsat, men i de resterende tre cases var de inden for normalområdet.

Konklusion

I den normale graviditet falder placental ADC-værdi med progredierende gestationsalder. Blandt cases med væksthæmning var ADC-værdien hovedsagelig inden for normalområdet og derfor synes den ikke at være en egnet markør til detektering af placenta dysfunktion.

Article manuscript

Diffusion-Weighted MRI of the placenta in normal pregnancies and in pregnancies complicated by Fetal Growth Restriction

Abstract

Objectives

The aim of this study was to evaluate placental apparent diffusion coefficient (ADC) values, obtained by diffusion-weighted imaging (DWI) in uncomplicated pregnancies and pregnancies complicated by Fetal Growth Restriction (FGR).

Methods

We retrospectively evaluated 1.5T placental magnetic resonance imaging (MRI) from 38 singleton pregnancies. In the DWI sequence, (bvalue 200, 400 and 1000 s/mm^2) regions of interest (ROIs) were drawn, covering the entire placenta in five placental slices and mean ADC values were calculated. In normal pregnancies delivering neonates ≥ 2.3rd percentile, the relation between ADC value and gestational age at time of MRI was estimated using ordinary linear regression. In FGR pregnancies, ADC z-scores were calculated.

Results

31 pregnancies (20 to 37 weeks of gestation) resulted in the delivery of neonates ≥ 2.3th percentile. In these pregnancies, placental ADC ranged from 1.33 to 1.76 x 10^{-3} mm^2/s, with significant inverse correlation between ADC values and gestational age (p=0.001). In seven pregnancies (27 to 37 weeks of gestation), resulting in neonates < 2.3th percentile, the placental ADC z-scores were

between 1,10 and -2,80. In three FGR cases, ADC value were significant reduced. However, in the remaining four FGR cases, it was within the normal range.

Conclusion

In normal pregnancy, placental ADC value, is reduced with advancing gestational age. However, the pathological abnormalities of the failing placenta in FGR, seems not to affect the ADC-value.

Introduction

Fetal Growth Restriction (FGR) due to placental dysfunction is associated with high rates of perinatal morbidity and mortality (1). In modern obstetrics, identifying and monitoring these high-risk pregnancies is a major challenge.

Ultrasound with Doppler flow has been the golden standard of in vivo placental and fetal examination for several decades. It is widely available, and a safe and inexpensive non-invasive method of estimating fetal well-being (4,8). However, the use of US and Doppler flow of maternofetal circulation is an indirect tool to asses placental function (7). Significant clinical and US-changes becomes apparent first when the placenta is severely impaired, delaying diagnosis and management, causing a significant clinical challenge in management of FGR pregnancies (9). US with Doppler flow of the uterine artery is inadequate to detect early placental dysfunction and there is a need for a method to directly assess placental function (3).

Placental Magnetic resonance imaging (MRI) is increasingly used as a complementary tool to the traditional ultrasound. Diffusion-weighted imaging (DWI) provides previously unavailable in vivo information on the diffusion and perfusion properties of the placenta. DWI may therefor serve as a direct assessment of placental function (7). The random motion of water molecules within tissue, know as Brownian motion, provides qualitative information on the placental diffusion phenomena. In dense tissue where the movement of the molecules are slower, the diffusion will be limited. Signal intensity decreases less and will therefore be more intense (4). The apparent diffusion coefficient (ADC) can be obtained identifying and quantifying areas of the placenta with restricted or accelerated diffusion (10).

Andescavage et al (7) stated that maturational changes in the normal placenta associated with advancing gestational age, such as microstructural changes resulting in increased villous surface

area, may have an influence on diffusion and therefore be detectable by DWI. They also suggests that structural changes in the failing placenta, such as necrosis and fibrosis, causes altered diffusion and therefor may be detected by decreasing ADC on DWI (7).

In this study, we describe the placental ADC value in normal singleton pregnancies and the association with advancing gestational age. Furthermore, we assess the ADC value in seven cases of FGR.

Methods and materials

Diffusion-weighted MRI data were retrieved from our Placenta MR-database, which include different MRI-sequences designed for placental examination. Oral and written consents were obtained from all participating women before all procedures. No contrasts or sedation were administered to mothers during the examinations. The study was approved by the Regional Committees on Biomedical Research Ethics (Journal number M-20090006 and N-20090052).

Population

In this retrospective cohort study, we included 31 normal pregnancies where neonatal outcomes were birth after 37 weeks, healthy without congenital anomalies or syndromes and birth weight above the 2.3rd percentile (Table 1). Gestational age at time of MRI examination ranged from 20 to 37 weeks (mean 28.7) confirmed by US-estimated crown-rump-length at 12 weeks of gestation. Furthermore, we included seven FGR cases with birth weight below the 2.3rd percentile without congenital anomalies or syndromes. The data is collected from the *Placenta database*.

MRI

The MRI examinations were conducted using a 1.5 Tesla MRI system (GE Discovery MR450). The pregnant women were placed in a left lateral position during the examination to avoid aortocaval compression and an eight channel receiver coil was placed over the abdomen, covering the uterus.

A T2 weighted localizing scan was initially performed to obtain and secure the most optimal anatomic orientation of the placenta. An echo-planar imaging DWI sequence with 10 b values in the range of 0 to 1000 was obtained perpendicular to the placenta. Depending on the size of the placenta, seven to fifteen slices (eight mm thickness) were collected. Acquisition time for DWI sequence was typically 4 minutes and 45 seconds. Following the DWI sequence, other MRI sequences were conducted as part of the placental MRI protocol. Total MRI examination time was approximately 30 minutes.

MRI analysis

An in-house developed program written in MATLAB (The MathWorks Inc., Natick, MA, USA) was used to process the images. Regions of interest (ROIs) were drawn covering the entire placenta in five placental slices equally distributed throughout the placenta (Figure 1). The same ROI on one slice were used for the consecutive ten frames, only repositioned and adjusted if the placental borders were affected by maternal or fetal movements. The mean signal intensity according to the three highest b-values (200, 400 and 1000) in the five slices was used to calculate the ADC values using a linear fitting algorithm (Figure 2).

Statistical analysis

In the normal pregnancies, the relation between the placental ADC value and gestational age at the time of the MRI was estimated using an ordinary linear regression. Pearson's correlation, 95% confidence and prediction intervals were calculated. In the FGR cases, the standardized variables (Z-scores) of the placental ADC value were estimated.

The data analysis was generated using the commercial software Statistical Package for the Social Sciences (SPSS, Version 23.0, released 2015. Armonk, N.Y: IBM Corp) and the statistical software package Stata®13 (StataCorp LP, College Station, TX, USA).

Results

In the group of normal pregnancies (n = 31) the placental ADC values decreased by 0.010 x $10^{-3}$$mm^2$/sec per gestational week (Figure 3); with a statistically significant correlation between ADC values and GA (R^2 = 0.340, p = 0.001). The ADC values ranged from 1.33 to 1.76 x 10^{-3} mm^2/sec (mean 1.57±0.11 SD).

In three out of the seven FGR cases, placental ADC values were significantly reduced (z-score < -2) (Table 2). However in the remaining four cases, the placental ADC value was within the normal range (Figure 4). In every FGR case, the placental histological examination revealed histological signs of maternal hypoperfusion.

Discussion

In this study, we demonstrated that in normal pregnancies the placental ADC value decreases as gestational age advances. In three of our FGR cases, we found a significant reduction in ADC value. Though, in the remaining four cases, there was no reduction compared to the ADC values to the ADC values in the normal pregnancies. These findings might indicate that placental ADC value reflects changes in placental maturation however; it is not a useful marker of placental dysfunction.

The association between placental ADC values and gestational age/placental aging has been investigated in a few studies. Manganaro et al(10) investigated in 2010 the possible association between ADC value and placental aging in a retrospective and prospective study. Respectively, 102 and 50 women were included and underwent MRI examination for suspected disorders identified by US, using b values of respectively 0, 200 and 700 s/mm^2 and 50, 200 and 700 s/mm^2. The retrospective study showed a statistical significant correlation between ADC and GA, but the latter prospective study did not. Based on the conflicting statistical results of the varying b values, Manganaro et al concluded that perfusional and circulatory motion influences the DWI and is

therefore not useful as indicators of placental maturation. We demonstrated a reduction in ADC value as gestational age advances using only high b-values specifically to avoid these macroscopic motion effects.

Using a similar fetal MR acquisition protocol, Sivrioğlu et al (11) included 52 fetuses analyzed in three different trimester groups, DW-images obtained in the axial plane using b-values of 0, 500 and 1000 s/mm^2. Three ROIs per slice were manually positioned to avoid morphological changes as calcifications and necrotic parts. They did not find any significant difference in the normalized placental ADC value (rADC) in the different groups of gestational age and concluded that the stable rADC values, despite morphological placental maturation, reflects a stable extracellular water diffusion. In our study, the ROIs covered the entire placenta including morphological structures as septae, calcifications, fibrosus and other connecting tissue. This may be explaining why our results shows a significant correlation, whilst Sivrioğlu et al (11) did not.

Changes in placental diffusional properties, as a part of the physiological maturational changes, might be what affects the placenta with advancing gestational age. In contrast to Manganaro et al and Sivrioğlu et al, we chose higher b-values to to target the microscopic Brownian motions of diffusion and avoid perfusional and circulatory motion effects and positioned one ROI which covered the whole placenta in each of the five slices to include all placental structures and found a statistical significant decrease in placental ADC value with advancing gestational age.

To our knowledge, only one previous study has investigated placental ADC values in FGR pregnancies. In 2010, Bonel et al(9) investigated placental ADC value in pregnancies with and without IUGR suspected of having placental insufficiency. Retrospectively, 102 fetuses with abnormal findings at US had underwent MRI examinations and were included in the study. The fetuses were classified in groups of fetuses with or without placental insufficiency, respectively 33

and 69 fetuses. Using b values 0-1000 s/mm2 they found significant reduction of placental ADC value in pregnancies complicated by placental dysfunction diagnosed by clinical and US findings. This significant reduction in ADC value of FGR placentas might be a consequence of using lower b-values (0 s/mm^2) and therefore reflecting perfusional changes rather than the diffusional properties.

In our study, the placental ADC value were significantly reduced in three of our FGR cases contra the ADC values estimated in the normal pregnancies. Though, in the remaining four cases, the placental ADC value were not reduced. This could be explained by a theory of placental dysfunction in FGR not being caused by loss of diffusional properties. Pathological examination with placental histology were conducted and one case showed maternal hypoperfusion, whilst the pathological examination of the six remaining cases, in writing, remains unfinished.

Our study had limitations. A pathological examination with histological reference to ensure no placental abnormalities, was not available for the uncomplicated pregnancies included in our study. The effects of fetal and maternal movement and contractions during MRI examination represented a great challenge when positioning the ROIs. ROI drawings were conducted by one single observer, who was blinded to the study groups. Therefore, inter-observer agreements should be investigated in future studies.

Conclusion

In conclusion, the placental ADC value in normal pregnancies decreases with advancing gestational age. In pregnancies complicated by FGR, the ADC value is not affected by the pathological abnormalities. Therefore, we conclude that placental ADC value is not a suitable marker for detecting cases of placental dysfunction.

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Tables and figures

Characteristics	Normal (n=31)	FGR (n=7)
Maternal age at nuchal scan	28 (19-37)	25 (22 to 40)
Maternal BMI	22,5 (19-30,5)	22,3 (16,7 to 30,8)
Nulliparous (%)	51,6	57,1
Gestational age at MRI	31,3 (20,6-37,3)	33,6 (27,7-37,0)
Gestational age at birth	39,9 (32,4-41,9)	37,0 (28,0-37,6)*
Birth weight, z-score	-0,233 (-1,675 to 1,837)	-2,333 (-2,511 to -2,000) *

*Table 1: Maternal and neonatal characteristics. Data presented as median (IQR) or n (%). Comparison of characteristics between groups by Independent t-test or Mann-Whitney U test for continuous variables and Fisher's exact test for categorical (dicotome) variable; * P < 0.05*

Placental ADC value	GA at MRI	Z-score
1.49	33.6	-0.3244526
1.61	35.3	1.099672
1.27	35.9	-2.299299
1.32	27.6	-2.795479
1.30	32.6	-2.40766
1.38	37.0	-1.045657
1.63	28.0	0.4766805

Table 2: ADC z-score for FGR cases

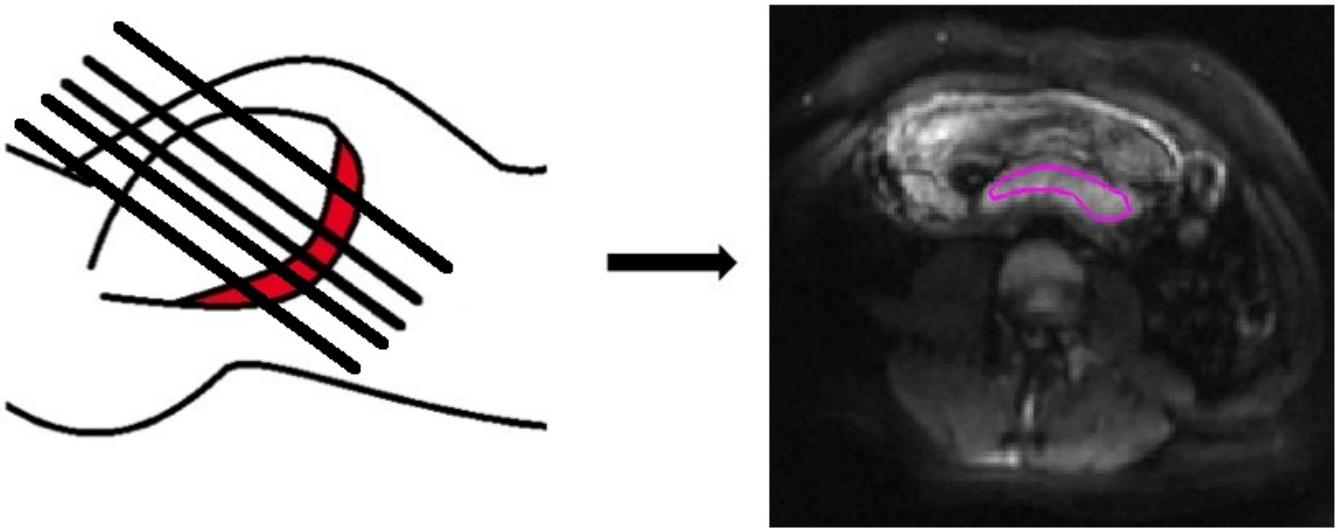

Figure 1: Schematic drawing of five slices covering the placenta and screenshot of RoiTools with ROI (pink) covering the placenta

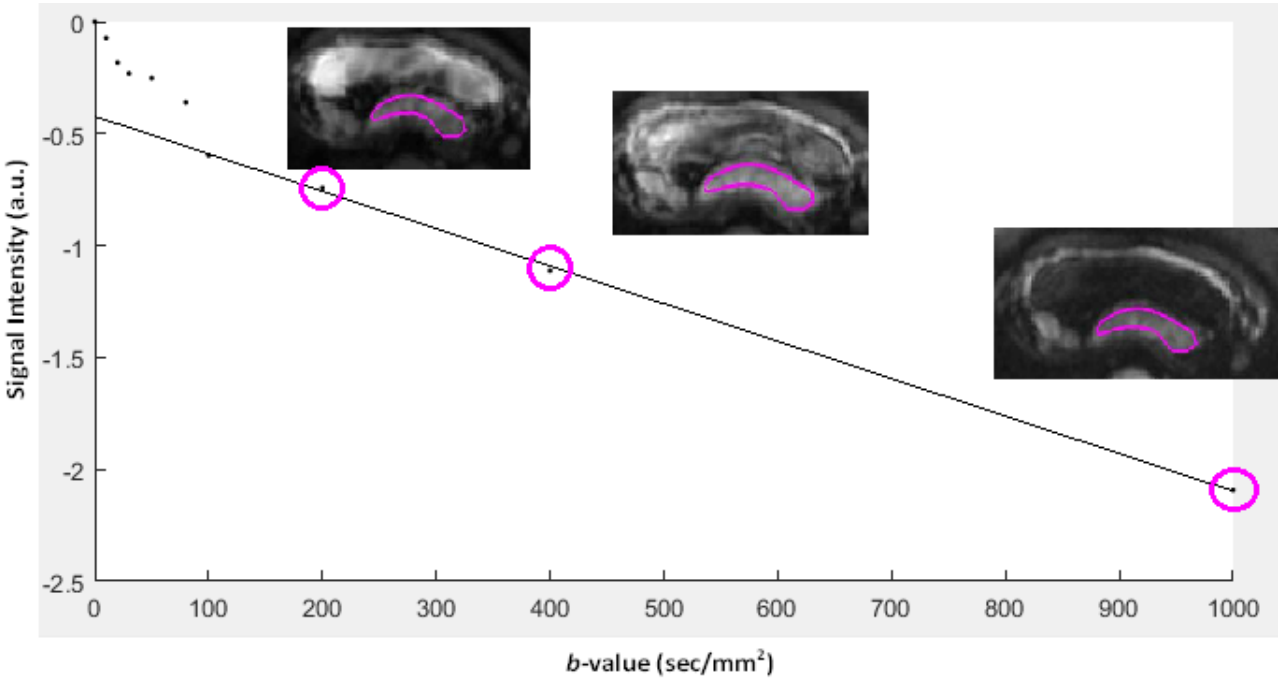

Figure 2: Linear fitting algorithm for ADC value using b-values 200, 400 and 1000 s/mm^2 from MATLAB software "ROItools". The best fitted line calculates placental ADC value based on signal intensity in the three b-values mentioned. a.u. = arbitrary unit.

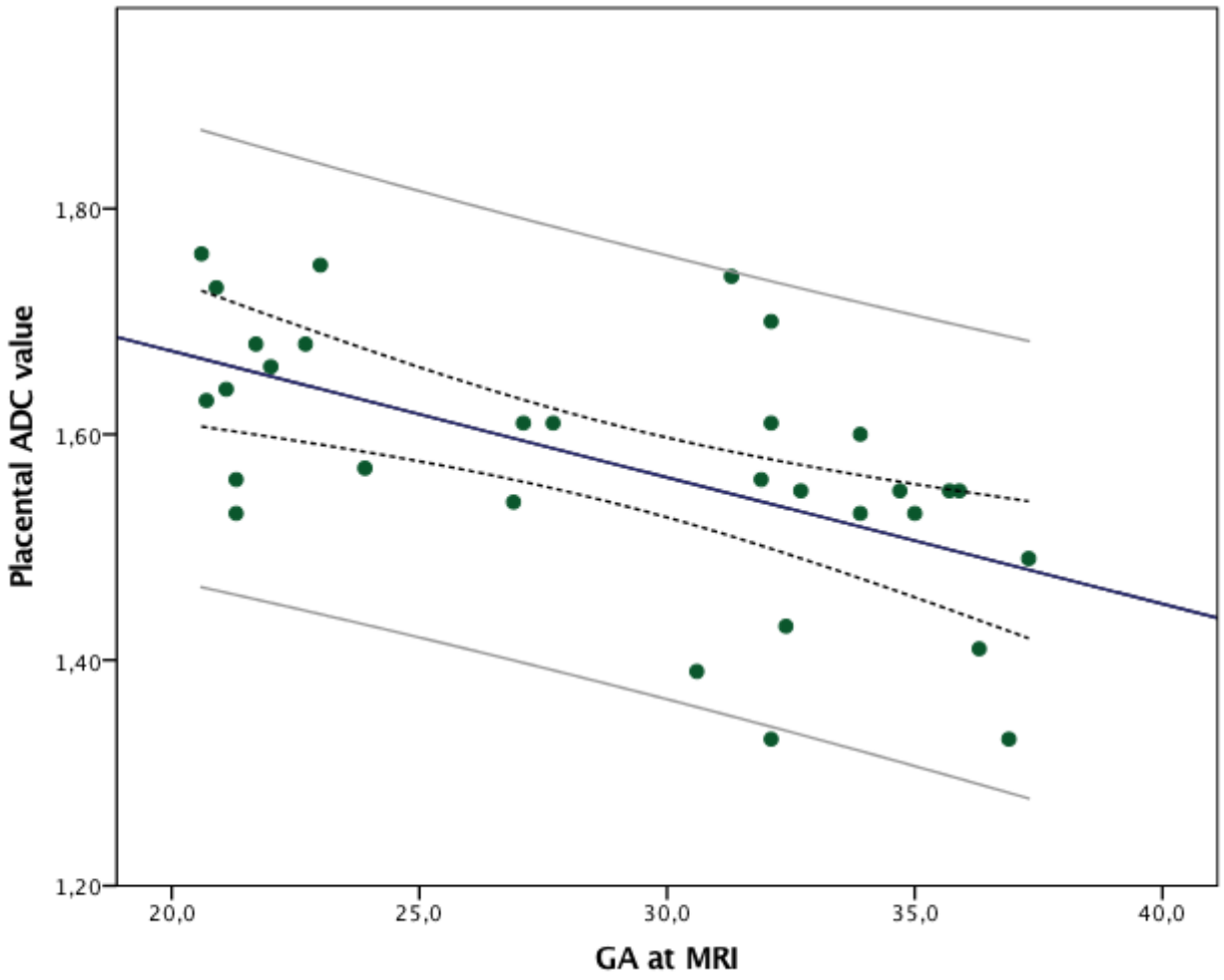

Figure 3: Relations between ADC value and GA in normal pregnancies

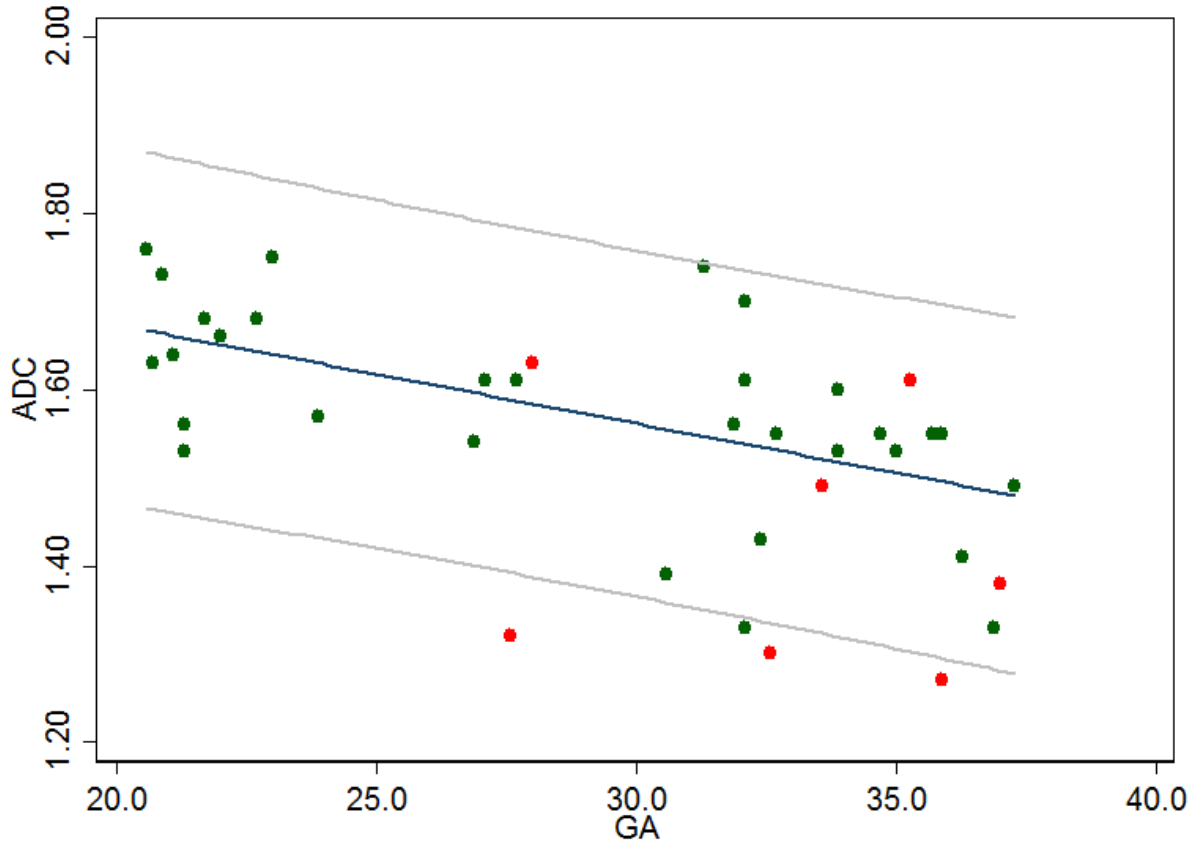

Figure 4: Relations between ADC and GA, with the seven FGR cases (red)

Appendix

1. EpiData – Overview of "Placenta-databasen"

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Report:  Extended list of questions/fields.
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------------------------------------------------------------------------

File 1: /Users/ca/Dropbox/DWI/EpiData/Database/Placentadatabase.epx
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Created     09/14/15 08:47:28 AM
Last Edited 12/09/15 09:06:48 AM
Version     1
Cycle       83
--------------------------------
Backup on shutdown: yes
Encrypted data: no

Dataforms:
------------------------------------------------------------------------------------------------------------------------
Caption          Created              Structure Edited     Data Edited          Sections Fields Records Deleted
------------------------------------------------------------------------------------------------------------------------
Placentadatabase 09/14/15 08:47:28 AM 11/18/15 11:36:53 AM 12/09/15 09:06:48 AM        1    155     123       0
------------------------------------------------------------------------------------------------------------------------

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Caption          Fields in key
--------------------------------
Placentadatabase
--------------------------------


Field extended view: Placentadatabase
------------------------------------------------------------------------------------------------------------------------
------------------------------------------------------------
Name                    Type    Length Question                                ValueLabel
Def.Values Visual Entry Mode Range Compare Jumps Calculate Notes
------------------------------------------------------------------------------------------------------------------------
------------------------------------------------------------
ID                      Integer      4 ID-number
x        x        x
Singleton               Integer      1 Singleton                              no_yes
x        x        x           x
DCvsMC                  Integer      1 Gemelli                                DC_MC
x                 x
P_BOLD_rask             Integer      1 Placenta BOLD, raske                   no_yes
x                 x
P_BOLD_FGR              Integer      1 Placenta BOLD, FGR                     no_yes
x                 x
T2star_article          Integer      1 T2* artikel                            no_yes
x                 x
Contraction_article     Integer      1 Kontraktionsartikel                    no_yes
x                 x
T2star_BW               Integer      1 T2* vs. BW                             no_yes
x                 x
```

```
DWI_singleton           Integer      1 DWI singleton                          no_yes
x                 x
DWI_gemelli             Integer      1 DWI gemelli                            no_yes
x                 x
Age                     Integer      2 Age, at NF-UL
x        x        x
Ethnicity               Integer      1 Ethnicity                              Caucasian_Asian_African
x        x        x
Smoking                 Integer      1 Smoking                                No_Yes_Former
x        x        x
Alcohol                 Integer      1 Alcohol                                No_Yes_missing
x        x        x
Drugs                   Integer      1 Drugs                                  No_Yes_missing
x        x        x
BMI                     Float      2.1 BMI
x        x        x
Conception              Integer      1 Conception                             Spon_ovind_IVF_ICSI_IUID_IUIH
x        x        x
Pregest_med             Integer      1 Pregestational medication              no_yes
x        x        x             x
Pregest_med_type        String     100 Pregestational medication, type
x
Prenat_med              Integer      1 Prenatal medication                    no_yes
x        x        x             x
Prenat_med_type         String     150 Prenatal medication, type
x
BP_pretreat_syst        Integer      3 Blood pressure before treatment, systolic
x                 x
BP_pretreat_dia         Integer      3 Blood pressure before treatment, diastolic
x                 x
Prenat_adm              Integer      1 Prenatal admission                     no_yes
x        x        x             x
Prenat_adm_diagn        String     100 Prenatal admission, diagnosis
x
Para                    Integer      2 Para, without the current birth
x        x        x
Diabetes                Integer      1 Diabetes                               No_IDDM_NIDDM_GDM
x        x        x
Proteinuria             Integer      1 Proteinuria                            no_yes
x        x        x             x
Proteinuria_g           Float      2.1 Proteinuria, g
x                 x
Birth                   Integer      1 Given birth                            no_yes
x        x        x             x
Birth_BP_syst           Integer      3 Birth blood pressure, systolic
x                 x
Birth_BP_dia            Integer      3 Birth blood pressure, diastolic
x                 x
AB_birth                Integer      1 Antibiotics in vaginal labour          No_Yes_missing
x                 x
MgSO4                   Integer      1 Magnesium sulfate                      No_Yes_missing
x                 x
Steroids_prebirth       Integer      1 Antinatal steroids                     No_Yes_missing
x                 x
PPmed                   Integer      1 PPmed                                  No_Yes_missing
x                 x             x
PPmed_type              Integer      1 PPmed, type                            prosta_oxy_balloon_HSP
```

x	x					
PPmed_indication		String	100	PPmed, indication		
x						
GA_birth		Float	2.1	Gestational age at birth		
x	x					
Delivery_mode_F1		Integer	1	Delivery mode		vag_elec_acute_vacuum
x	x					
Anesthesia_labour_F1		Integer	1	Anesthesia in labour		none_epi_other
x	x					
Apgar_F1		Integer	1	Apgar score 6 and under, 5 min.		no_yes
x	x					
Sex_F1		Integer	1	Sex		male_female
x	x					
BW_g_F1		Integer	4	Birth weight, g		
x	x					
BW_zscore_F1		Float	2.3	Birth weight, z-score		
x	x					
HC_cm_F1		Integer	2	Head circumference, cm		
x	x					
Length_cm_F1		Integer	2	Length, cm		
x	x					
UmbA_F1		Float	2.2	Umbilical cord blood gas, arterial		
x	x					
UmbV_F1		Float	2.2	Umbilical cord blood gas, venous		
x	x					
PW_g_F1		Integer	4	Placental weight, g		
x	x					
P_histo_F1		Integer	1	Placental histology		no_yes_unfinished
x	x	x				
P_histo_result_F1		Integer	1	Result, Placental histology		normal_abnormal
x	x					
Foetus_2		Integer	1	Foetus 2		no_yes
x	x	x				
Delivery_mode_F2		Integer	1	Delivery mode		vag_elec_acute_vacuum
x	x					
Anesthesia_labour_F2		Integer	1	Anesthesia in labour		none_epi_other
x	x					
Apgar_F2		Integer	1	Apgar score 6 and under, 5. min		no_yes
x	x					
Sex_F2		Integer	1	Sex		male_female
x	x					
BW_g_F2		Integer	4	Birth weight, g		
x	x					
BW_zscore_F2		Float	2.3	Birth weight, z-score		
x	x					
HC_cm_F2		Integer	2	Head circumference, cm		
x	x					
Length_cm_F2		Integer	2	Length, cm		
x	x					
UmbA_F2		Float	2.2	Umbilical cord blood gas, arterial		
x	x					
UmbV_F2		Float	2.2	Umbilical cord blood gas, venous		
x	x					
PW_g_F2		Integer	4	Placental weight, g		
x	x					
P_histo_F2		Integer	1	Placental histology		no_yes_unfinished
x	x	x				

P_histo_result_F2			Integer	1	Result, Placental histology		normal_abnormal
x		x					
PAPP_A_MoM			Float	1.3	PAPP-A, MoM		
x	x	x					
hCG_MoM			Float	1.3	beta-hCG, MoM		
x	x	x					
NT_mm_F1			Float	1.2	Nuchal translucency, mm		
x	x	x					
F2_NS			Integer	1	Foetus 2, nuchal scan		no_yes
x	x	x		x			
NT_mm_F2			Float	1.2	Nuchal translucency, foetus 2, mm		
x		x					
GA_UL_S1F1			Float	2.1	Gestational age at UL		
x		x					
EFW_g_S1F1			Integer	4	Estimated fetal weight, g		
x	x	x					
EFW_procent_S1F1			Float	3.1	Estimated fetal weight, procent		
x		x					
UA_PI_zscore_S1F1			Float	2.3	a. umbicalis, PI, z-score		
x		x					
MCA_PI_zscore_S1F1			Float	2.3	a. cerebri media, PI, z-score		
x		x					
UtA_meanPI_zscore_S1F1			Float	2.3	a. uterina, mean PI, z-score		
x		x					
CPR_zscore_S1F1			Float	2.3	Cerebro placental ratio (CPR), z-score		
x		x					
DV_PIV_zscore_S1F1			Float	2.3	Ductus venosus, PIV, z-score		
x		x					
GA_MRI_S1F1			Float	2.1	Gestational age at MRI		
x	x	x					
P_T2star_S1F1			Float	3.6	T2*		
x		x					
P_delta_T2star_S1F1			Float	3.6	Delta T2*		
x		x					
P_delta_BOLD_S1F1			Float	3.4	Delta BOLD		
x		x					
P_vol_S1F1			Integer	3	Placentalvolumen		
x		x					
P_pf_b0_S1F1			Integer	3	Perfusionsfraction, med b0		
x		x					
P_medianpf_b0_S1F1			Integer	3	Median, perfusionsfraction, med b0		
x		x					
P_pf_udenb0_S1F1			Integer	3	Perfusionsfraction, uden b0		
x		x					
P_medianpf_udenb0_S1F1			Integer	3	Median, perfusionsfraction, uden b0		
x		x					
P_diffcoeff_medb0_S1F1			Float	1.2	Diffusionscoefficient_med b0		
x		x					
P_ADC_S1F1			Float	1.2	Apparent Diffusion Coefficient (ADC)		
x		x					
P_diffcoeff_udenb0_S1F1			Float	1.2	Diffusionscoefficient_uden b0		
x		x					
F2_S1			Integer	1	Foetus 2, scan 1		no_yes
x	x	x		x			
GA_UL_S1F2			Float	2.1	Gestational age at UL		
x		x					
EFW_g_S1F2			Integer	4	Estimated fetal weight, g		

x		x					
EFW_procent_S1F2			Float		3.1	Estimated fetal weight, procent	
x		x					
UA_PI_zscore_S1F2			Float		2.3	a. umbicalis, PI, z-score	
x		x					
MCA_PI_zscore_S1F2			Float		2.3	a. cerebri media, PI, z-score	
x		x					
UtA_meanPI_zscore_S1F2			Float		2.3	a. uterina, mean PI, z-score	
x		x					
CPR_zscore_S1F2			Float		2.3	Cerebro placental ratio (CPR), z-score	
x		x					
DV_PIV_zscore_S1F2			Float		2.3	Ductus venosus, PIV, z-score	
x		x					
GA_MRI_S1F2			Float		2.1	Gestational age at MRI	
x		x					
P_T2star_S1F2			Float		3.6	T2*	
x		x					
P_delta_T2star_S1F2			Float		3.6	Delta T2*	
x		x					
P_delta_BOLD_S1F2			Float		3.4	Delta BOLD	
x		x					
P_vol_S1F2			Integer		3	Placentavolumen	
x		x					
P_pf_b0_S1F2			Integer		3	Perfusionsfraction, med b0	
x		x					
P_medianpf_b0_S1F2			Integer		3	Median, perfusionsfraction, med b0	
x		x					
P_pf_udenb0_S1F2			Integer		3	Perfusionsfraction, uden b0	
x		x					
P_medianpf_udenb0_S1F2			Integer		3	Median, perfusionsfraction, uden b0	
x		x					
P_diffcoeff_medb0_S1F2			Float		1.2	Diffusionscoefficient_med b0	
x		x					
P_ADC_S1F2			Float		1.2	Apparent Diffusion Coefficient (ADC)	
x		x					
P_diffcoeff_udenb0_S1F2			Float		1.2	Diffusionscoefficient	
x		x					
S2			Integer		1	Second scan	no_yes
x	x	x		x			
ID2			Integer		3	ID 2	
x		x					
GA_UL_S2F1			Float		2.1	Gestational age at UL	
x		x					
EFW_g_S2F1			Integer		4	Estimated fetal weight, g	
x		x					
EFW_procent_S2F1			Float		3.1	Estimated fetal weight, procent	
x		x					
UA_PI_zscore_S2F1			Float		2.3	a. umbicalis, PI, z-score	
x		x					
MCA_PI_zscore_S2F1			Float		2.3	a. cerebri media, PI, z-score	
x		x					
UtA_meanPI_zscore_S2F1			Float		2.3	a. uterina, mean PI, z-score	
x		x					
CPR_zscore_S2F1			Float		2.3	Cerebro placental ratio (CPR), z-score	
x		x					
DV_PIV_zscore_S2F1			Float		2.3	Ductus venosus, PIV, z-score	
x		x					
GA_MRI_S2F1			Float		2.1	Gestational age at MRI	

x	x					
P_T2star_S2F1		Float	3.6	T2*		
x	x					
P_delta_T2star_S2F1		Float	3.6	Delta T2*		
x	x					
P_delta_BOLD_S2F1		Float	3.4	Delta BOLD		
x	x					
P_vol_S2F1		Integer	3	Placentavolumen		
x	x					
P_pf_b0_S2F1		Integer	3	Perfusionsfraction, med b0		
x	x					
P_medianpf_b0_S2F1		Integer	3	Median, perfusionsfraction, med b0		
x	x					
P_pf_udenb0_S2F1		Integer	3	Perfusionsfraction, uden b0		
x	x					
P_medianpf_udenb0_S2F1		Integer	3	Median, perfusionsfraction, uden b0		
x	x					
P_diffcoeff_medb0_S2F1		Float	1.2	Diffusionscoefficient_med b0		
x	x					
P_ADC_S2F1		Float	1.2	Apparent Diffusion Coefficient (ADC)		
x	x					
P_diffcoeff_udenb0_S2F1		Float	1.2	Diffusionscoefficient_uden b0		
x	x					
F2_S2		Integer	1	Foetus 2, scan 2		no_yes
x	x	x				
GA_UL_S2F2		Float	2.1	Gestational age at UL		
x	x					
EFW_g_S2F2		Integer	4	Estimated fetal weight, g		
x	x					
EFW_procent_S2F2		Float	3.1	Estimated fetal weight, procent		
x	x					
UA_PI_zscore_S2F2		Float	2.3	a. umbicalis, PI, z-score		
x	x					
MCA_PI_zscore_S2F2		Float	2.3	a. cerebri media, PI, z-score		
x	x					
UtA_meanPI_zscore_S2F2		Float	2.3	a. uterina, mean PI, z-score		
x	x					
CPR_zscore_S2F2		Float	2.3	Cerebro placental ratio (CPR), z-score		
x	x					
DV_PIV_zscore_S2F2		Float	2.3	Ductus venosus, PIV, z-score		
x	x					
GA_MRI_S2F2		Float	2.1	Gestational age at MRI		
x	x					
P_T2star_S2F2		Float	3.6	T2*		
x	x					
P_delta_T2star_S2F2		Float	3.6	Delta T2*		
x	x					
P_delta_BOLD_S2F2		Float	3.4	Delta BOLD		
x	x					
P_vol_S2F2		Integer	3	Placentavolumen		
x	x					
P_pf_b0_S2F2		Integer	3	Perfusionsfraction, med b0		
x	x					
P_medianpf_b0_S2F2		Integer	3	Median, perfusionsfraction, med b0		
x	x					
P_pf_udenb0_S2F2		Integer	3	Perfusionsfraction, uden b0		
x	x					

```
P_medianpf_udenb0_S2F2  Integer      3 Median, perfusionsfraction, uden b0
x                   x
P_diffcoeff_medb0_S2F2  Float      1.2 Diffusionscoefficient_med b0
x                   x
P_ADC_S2F2              Float      1.2 Apparent Diffusion Coefficient (ADC)
x                   x
P_diffcoeff_udenb0_S2F2 Float      1.2 Diffusionscoefficient_uden b0
x                   x
-------------------------------------------------------------------------------------------------
-------------------------------------------------------------
An x in a column indicate one or more of these specifications:
Def.Values:    Repeat, Default Value
Visual:        Show Picklist, show Category text from Value Label
Entry-Mode :   Mustenter, Noenter, confirm
Range:         Range is specified
Compare:       Compare with another field
Jumps:         Jump specified
Calculate:     Calculation, copy from category text to other field
Notes:         Note text defined
Scrip:         Script defined
```

2. SPSS syntax

Syntax for data in IBM SPSS Statistics, version 23.0 for MAC

```
GET DATA /TYPE=XLSX
  /FILE='/Users/ca/Dropbox/Forskningssemester/EpiData/Placentadatabase.xlsx'
  /SHEET=name 'Placentadatabase'
  /CELLRANGE=full
  /READNAMES=on
  /ASSUMEDSTRWIDTH=32767.
EXECUTE.
DATASET NAME DataSet1 WINDOW=FRONT.

/* Fjern ikke-inkluderede ID-numre

SELECT IF NOT (SYSMIS(DWI_singleton)).
EXECUTE.

/* Fjern cases der ikke har født

FILTER OFF.
USE ALL.
SELECT IF (Birth = 1).
EXECUTE.

/* compute new varable: Para -> nulliparous and case -> dicotome varable

DATASET ACTIVATE Dataset1.
COMPUTE Nulliparous=Para > 0 = 1.
EXECUTE.
```

```
DATASET ACTIVATE DataSet1.
COMPUTE Case=BW_zscore_F1 <=  - 2.
EXECUTE.

/*Select cases - Normal og FGR

DATASET ACTIVATE DataSet1.
DATASET COPY  Normal.
DATASET ACTIVATE  Normal.
FILTER OFF.
USE ALL.
SELECT IF (BW_zscore_F1 >  - 2).
EXECUTE.
DATASET ACTIVATE  DataSet1.

DATASET COPY  FGR.
DATASET ACTIVATE  FGR.
FILTER OFF.
USE ALL.
SELECT IF (BW_zscore_F1  <=   - 2).
EXECUTE.
DATASET ACTIVATE  DataSet1.

/* Scarretplot og lineær regression for normalmaterialet

DATASET ACTIVATE Normal.
* Chart Builder.
GGRAPH
  /GRAPHDATASET NAME="graphdataset" VARIABLES=GA_MRI_S1F1 P_ADC_S1F1
MISSING=LISTWISE
```

```
    REPORTMISSING=NO
  /GRAPHSPEC SOURCE=INLINE.
BEGIN GPL
  SOURCE: s=userSource(id("graphdataset"))
  DATA: GA_MRI_S1F1=col(source(s), name("GA_MRI_S1F1"))
  DATA: P_ADC_S1F1=col(source(s), name("P_ADC_S1F1"))
  GUIDE: axis(dim(1), label("GA at MRI"))
  GUIDE: axis(dim(2), label("Placental ADC value"))
  ELEMENT: point(position(GA_MRI_S1F1*P_ADC_S1F1))
END GPL.

REGRESSION
  /DESCRIPTIVES MEAN STDDEV CORR SIG N
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS CI(95) R ANOVA CHANGE
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT P_ADC_S1F1
  /METHOD=ENTER GA_MRI_S1F1
  /SCATTERPLOT=(*ZRESID ,*ZPRED)
  /RESIDUALS HISTOGRAM(ZRESID) NORMPROB(ZRESID).

/* Normalfordeling Normalmateriale

DATASET ACTIVATE Normal.
EXAMINE VARIABLES=Age
  /PLOT BOXPLOT HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /STATISTICS DESCRIPTIVES
  /CINTERVAL 95
```

```
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=BMI
  /PLOT BOXPLOT HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /STATISTICS DESCRIPTIVES
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=GA_MRI_S1F1
  /PLOT BOXPLOT HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /STATISTICS DESCRIPTIVES
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.


EXAMINE VARIABLES=GA_birth
  /PLOT BOXPLOT HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /STATISTICS DESCRIPTIVES
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=BW_zscore_F1
  /PLOT BOXPLOT HISTOGRAM NPPLOT
```

```
  /COMPARE GROUPS
  /STATISTICS DESCRIPTIVES
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

/* Normalfordeling FGR

DATASET ACTIVATE FGR.
EXAMINE VARIABLES=Age
  /PLOT BOXPLOT HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /STATISTICS DESCRIPTIVES
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=BMI
  /PLOT BOXPLOT HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /STATISTICS DESCRIPTIVES
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

EXAMINE VARIABLES=GA_MRI_S1F1
  /PLOT BOXPLOT HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /STATISTICS DESCRIPTIVES
  /CINTERVAL 95
```

```
  /MISSING LISTWISE
  /NOTOTAL.


EXAMINE VARIABLES=GA_birth
  /PLOT BOXPLOT HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /STATISTICS DESCRIPTIVES
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.

 EXAMINE VARIABLES=BW_zscore_F1
  /PLOT BOXPLOT HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /STATISTICS DESCRIPTIVES
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.


/* Normalfordeling dikotome variabler Nullipara

DATASET ACTIVATE DataSet1.
CROSSTABS
  /TABLES=Case BY Nulliparous
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT EXPECTED
  /COUNT ROUND CELL.
```

```
/* Comparison of characteristics between groups

DATASET ACTIVATE DataSet1.
T-TEST GROUPS=Case(0 1)
  /MISSING=ANALYSIS
  /VARIABLES=Age
  /CRITERIA=CI(.95).

DATASET ACTIVATE DataSet1.
T-TEST GROUPS=Case(0 1)
  /MISSING=ANALYSIS
  /VARIABLES=BMI
  /CRITERIA=CI(.95).

DATASET ACTIVATE DataSet1.
NPAR TESTS
  /M-W= GA_MRI_S1F1 BY Case(0 1)
  /STATISTICS=DESCRIPTIVES QUARTILES
  /MISSING ANALYSIS.

DATASET ACTIVATE DataSet1.
NPAR TESTS
  /M-W= GA_birth BY Case(0 1)
  /STATISTICS=DESCRIPTIVES QUARTILES
  /MISSING ANALYSIS.

DATASET ACTIVATE DataSet1.
NPAR TESTS
  /M-W= BW_zscore_F1 BY Case(0 1)
```

```
/STATISTICS=DESCRIPTIVES QUARTILES
/MISSING ANALYSIS.
```

3. STATA Do-file

```
-------------------------------------------------------------------------------------------------------------------------
----------------
      name:  <unnamed>
       log:  C:\Users\Admin\Documents\DWI singletons 2015 Marianne Sinding.log
  log type:  text
 opened on:   9 Dec 2015, 10:00:13

. codebook, compact

Variable      Obs Unique      Mean     Min    Max  Label
-------------------------------------------------------------------------------------------------------------------------
----------------
ID            123    123   97.07317      18    174  ID-number
Singleton     123      2   .7886179       0      1  Singleton
DWI_single~n   56      1          1       1      1  DWI singleton
Age           123     22   29.50407      19     40  Age, at NF-UL
Ethnicity     123      2   .0325203       0      2  Ethnicity
Smoking       123      3   .2926829       0      2  Smoking
BMI           123     77   22.98293    16.7   32.7  BMI
Para          123      5   .6504065       0      4  Para, without the current birth
GA_birth       97     51   38.26289    26.4     42  Gestational age at birth
BW_zscore_F1   97     95  -.3990722  -3.798  1.837  Birth weight, z-score
EFW_g_S1F1    123    117    1223.78     170   3559  Estimated fetal weight, g
UA_PI_zsco~1   82     81   .2160488  -2.693  4.588  a. umbicalis, PI, z-score
MCA_PI_zsc~1   65     65  -.1982154  -4.057  1.968  a. cerebri media, PI, z-score
UtA_meanPI~1   68     67  -.2653235  -2.388  3.428  a. uterina, mean PI, z-score
CPR_zscore~1   63     62  -.3918254  -4.258  2.948  Cerebro placental ratio (CPR), z-score
GA_MRI_S1F1   123     80   28.06504    18.3   39.9  Gestational age at MRI
P_ADC_S1F1     80     42    1.57275    1.27   2.04  Apparent Diffusion Coefficient (ADC)
-------------------------------------------------------------------------------------------------------------------------
----------------

. set more off
```

```
.
.
. **udeluk gemelli**
. drop if Singleton==0
(26 observations deleted)

. drop Singleton

. keep if DWI_singleton==1
(41 observations deleted)

. drop if BW_zscore_F1==.
(18 observations deleted)

. replace P_ADC_S1F1 = 1.49 in 1
(1 real change made)

. **(ID 78 ikke indtastet)
.
. **lave bw-z-score-grupper**
. recode BW_zscore_F1 (min/-2=1 "sga")(-2/max=0 "normal"), generate(bw_group)
(38 differences between BW_zscore_F1 and bw_group)

.
. **regres GA og ADC i raske singletons***
. scatter P_ADC_S1F1 GA_MRI_S1F1 if bw_group==0

. regres P_ADC_S1F1 GA_MRI_S1F1 if bw_group==0

      Source |       SS       df       MS              Number of obs =      31
-------------+------------------------------           F(  1,    29) =   14.93
       Model |  .133424808     1  .133424808           Prob > F      =  0.0006
```

```
   Residual |  .259130031    29  .008935518          R-squared     =  0.3399
-------------+------------------------------          Adj R-squared =  0.3171
       Total |  .392554839    30  .013085161          Root MSE      =  .09453

------------------------------------------------------------------------------
  P_ADC_S1F1 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 GA_MRI_S1F1 |  -.0112017   .0028988    -3.86   0.001    -.0171305   -.0052729
       _cons |   1.897849   .0854611    22.21   0.000     1.723062    2.072637
------------------------------------------------------------------------------

. twoway (scatter P_ADC_S1F1 GA_MRI_S1F1 if bw_group==0) (lfit P_ADC_S1F1
GA_MRI_S1F1 if bw_group==0)

. ***signifikant sammenhæng
. **tjekker assumptions
.  predict fit if e(sample), xb
(7 missing values generated)

. predict res if e(sample), resid
(7 missing values generated)

. scatter res fit

. scatter res GA_MRI_S1F1

.
. **gør klar til z-scores
. regress P_ADC_S1F1 GA_MRI_S1F1 if bw_group==0

      Source |       SS       df       MS              Number of obs =      31
-------------+------------------------------           F(  1,    29) =   14.93
       Model |  .133424808     1  .133424808           Prob > F      =  0.0006
```

```
   Residual |  .259130031    29  .008935518          R-squared     =  0.3399
-------------+------------------------------          Adj R-squared =  0.3171
       Total |  .392554839    30  .013085161          Root MSE      =  .09453

------------------------------------------------------------------------------
  P_ADC_S1F1 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 GA_MRI_S1F1 |  -.0112017   .0028988    -3.86   0.001    -.0171305   -.0052729
       _cons |   1.897849   .0854611    22.21   0.000     1.723062    2.072637
------------------------------------------------------------------------------

. predict yhat
(option xb assumed; fitted values)

. predict sea , stdp

. predict sef , stdf

. display invttail(22, .025)
2.0738731

.
. generate lci = yhat-2.07387*sea

. generate uci = yhat+2.07387*sea

. generate lpi = yhat-2.07387*sef

. generate upi = yhat+2.07387*sef

.
. // Z-score
. gen Zscore=(P_ADC_S1F1-yhat)/sef
```

```
. list P_ADC_S1F1 GA_MRI_S1F1 Zscore if bw_group==1

     +---------------------------------+
     | P_ADC_~1   GA_MRI~1      Zscore |
     |---------------------------------|
  1. |     1.49       33.6   -.3244526 |
  3. |     1.61       35.3    1.099672 |
  4. |     1.27       35.9   -2.299299 |
  8. |     1.32       27.6   -2.795479 |
 30. |     1.30       32.6    -2.40766 |
     |---------------------------------|
 33. |     1.38       37.0   -1.045657 |
 34. |     1.63       28.0    .4766805 |
     +---------------------------------+

.
.
. **2 slags plots for ADC vs GA**
. set scheme s1color

. twoway (scatter P_ADC_S1F1 GA_MRI_S1F1 if bw_group==0) (line yhat GA_MRI_S1F1 if
bw_group==0, lcolor(black) lwidth(medthick)) ///
>       (line lci GA_MRI_S1F1 if bw_group==0, lcolor(black) lpattern(dot)) (line uci
GA_MRI_S1F1 if bw_group==0, lcolor(black) ///
>       lpattern(dot)) (line lpi GA_MRI_S1F1, lcolor(black) lpattern(dash)) ///
>       (line upi GA_MRI_S1F1 if bw_group==0, lcolor(black) lpattern(dash)), ytitle(adc) ///
>       xtitle(Gestational week) xmtick(##5) legend(off)

. graph export "ADC vs GA.wmf", replace
(file C:\Users\Admin\Documents\ADC vs GA.wmf written in Windows Metafile format)

.
. twoway (scatter P_ADC_S1F1 GA_MRI_S1F1 if bw_group==0) ///
```

```
>           (lfitci P_ADC_S1F1 GA_MRI_S1F1 if bw_group==0, stdf ciplot(rline) name(Zscore,
replace)) ///
>            , ytitle("ADC") legend(off) xtitle("GA")

. graph export "ADC vs GA1.wmf", replace
(file C:\Users\Admin\Documents\ADC vs GA1.wmf written in Windows Metafile format)


.
. **1 plot for ADC vs GA inkl. prediktionsinterval og cases:
. twoway (scatter P_ADC_S1F1 GA_MRI_S1F1 if bw_group==0) ///
>       (scatter P_ADC_S1F1 GA_MRI_S1F1 if bw_group==1, msy(O) mco(red)) ///
>           (lfitci P_ADC_S1F1 GA_MRI_S1F1 if bw_group==0, stdf ciplot(rline) name(Zscore,
replace)) ///
>            , ytitle("ADC") legend(off) xtitle("GA")

. graph export "ADC vs GA inkl. cases.png", replace
(file ADC vs GA inkl. cases.png written in PNG format)


.
.
.
. log close
      name:  <unnamed>
       log:  C:\Users\Admin\Documents\DWI singletons 2015 Marianne Sinding.log
  log type:  text
 closed on:   9 Dec 2015, 10:00:16
-------------------------------------------------------------------------------------------------------------
-----------------
```

4. Literature research strategy

Hypothesis:

1. In normal singleton pregnancies, the placental ADC value is reduced with advancing gestational age.
2. In singleton pregnancies complicated by FGR, the ADC value is reduced.

Block search:

Block 1:

- Placenta

Block 2:

- Diffusion Weighted Magnetic Resonance Imaging (DWI)

Block 3:

- Gestational age

Block 4:

- Fetal growth restriction (FGR)

Block search schema:

PubMed

AND

	Block 1: Placenta	Block 2: Diffusion weighted magnetic resonance imaging	Block 3: Gestational age	Block 4: Fetal growth restriction
OR	Placenta [MeSH] (58.046)	Diffusion Magnetic Resonance Imaging [MeSH] (12.223) DWI [tiab]	Gestational age [MeSH] (68.585) GA [tiab] (28.013)	Fetal Growth Retardation [MeSH] (13.483) FGR [tiab] (1.116)

	(5.621) Diffusion weighted imaging [tiab] (6.089) Apparent diffusion coefficient [tiab] (5.811) ADC [tiab] (7.677)		Intrauterine growth restriction [tiab] (4.080) Intrauterine growth retardation [tiab] (5.149) IUGR [tiab] (4.376) Placental insufficiency [MeSH] (1.441) Placental dysfunction [tiab] (566)

Embase

AND

	Block 1: Placenta	Block 2: Diffusion weighted magnetic resonance imaging	Block 3: Gestational age	Block 4: Fetal growth restriction
OR	'placenta'/exp (Emtree) (64.791)	"diffusion weighted imaging'/exp (Emtree) (23.739) 'dwi' (10.374) 'apparent diffusion coefficient' (7.740) 'ADC'	'gestational age'/exp (Emtree) (98.622)	'Intrauterine growth retardation'/exp (Emtree) (29.798) 'Fetal growth restriction' (3.880) 'FGR' (1.731)

	(25.397)		'Intrauterine growth restriction' (6.173) 'IUGR' (7.026) 'Placenta insufficiency'/exp (Emtree) (2.866)

Search delimitations:

There were no limitations used when searching PubMed or Embase. We included both human and murine models.

Sources of information:

Source of information	Reason for choice of source
Supervisors	Articles handed from supervisors at the start of the project. The aim of the project is still very innovative and new, so there is not that much information on the subject. My two principle supervisors are working on a subject in the same category, so key articles were already identified and handed to me, when I started my project in September.
PubMed	Systematic literature research in a medical database.
Embase (Ovid)	Systematic literature research in a medical database. Included this to ensure coverage of European publications.

Search results:

PubMed

Block and block combinations	Search combinations, based on blocks	Items found

Block 1	"Placenta"[Mesh]	58.046
Block 2	((((("Diffusion Magnetic Resonance Imaging"[Mesh]) OR DWI[tiab]) OR Diffusion weighted imaging[tiab]) OR Apparent diffusion coefficient[tiab]) OR ADC[tiab]	21.145
Block 3	("Gestational Age"[Mesh]) OR GA[tiab]	95.251
Block 4	((((((("Fetal Growth Retardation"[Mesh]) OR FGR[tiab]) OR intrauterine growth restriction[tiab]) OR intrauterine growth retardation[tiab]) OR IUGR[tiab]) OR Placental dysfunction[tiab]) OR "Placental Insufficiency"[Mesh]	19.995
Block 1 AND Block 2	("Placenta"[Mesh]) OR (((((("Diffusion Magnetic Resonance Imaging"[Mesh]) OR DWI[tiab]) OR Diffusion weighted imaging[tiab]) OR Apparent diffusion coefficient[tiab]) OR ADC[tiab])	13 (4)
Block 1 AND Block 2 AND Block 3	(("Placenta"[Mesh]) AND (((((("Diffusion Magnetic Resonance Imaging"[Mesh]) OR DWI[tiab]) OR Diffusion weighted imaging[tiab]) OR Apparent diffusion coefficient[tiab]) OR ADC[tiab])) AND (("Gestational Age"[Mesh]) OR GA[tiab])	5 (3)
Block 1 AND Block 2 AND Block 4	(("Placenta"[Mesh]) AND (((((("Diffusion Magnetic Resonance Imaging"[Mesh]) OR DWI[tiab]) OR Diffusion weighted imaging[tiab]) OR Apparent diffusion coefficient[tiab]) OR ADC[tiab])) AND (((((((("Fetal Growth Retardation"[Mesh]) OR FGR[tiab]) OR intrauterine growth restriction[tiab]) OR intrauterine growth retardation[tiab]) OR IUGR[tiab]) OR Placental dysfunction[tiab]) OR "Placental Insufficiency"[Mesh])	3 (1)
Block 1 AND Block 2 AND Block 3 AND Block 4	((((("Placenta"[Mesh]) AND (((((("Diffusion Magnetic Resonance Imaging"[Mesh]) OR DWI[tiab]) OR Diffusion weighted imaging[tiab]) OR Apparent diffusion	2 (1)

	coefficient[tiab]) OR ADC[tiab])) AND (("Gestational Age"[Mesh]) OR GA[tiab])) AND (((((("Fetal Growth Retardation"[Mesh]) OR FGR[tiab]) OR intrauterine growth restriction[tiab]) OR intrauterine growth retardation[tiab]) OR IUGR[tiab]) OR Placental dysfunction[tiab]) OR "Placental Insufficiency"[Mesh])	

History Download history Clear history

Search	Add to builder	Query	Items found	Time
#44	Add	Search ((("Placenta"[Mesh]) AND (((((("Diffusion Magnetic Resonance Imaging"[Mesh]) OR DWI[tiab]) OR Diffusion weighted imaging[tiab]) OR Apparent diffusion coefficient[tiab]) OR ADC[tiab])) AND (("Gestational Age"[Mesh]) OR GA[tiab]))) AND (((((("Fetal Growth Retardation"[Mesh]) OR FGR[tiab]) OR intrauterine growth restriction[tiab]) OR intrauterine growth retardation[tiab]) OR IUGR[tiab]) OR Placental dysfunction[tiab]) OR "Placental Insufficiency"[Mesh])	2	09:01:03
#43	Add	Search (("Placenta"[Mesh]) AND (((((("Diffusion Magnetic Resonance Imaging"[Mesh]) OR DWI[tiab]) OR Diffusion weighted imaging[tiab]) OR Apparent diffusion coefficient[tiab]) OR ADC[tiab])) AND (((((("Fetal Growth Retardation"[Mesh]) OR FGR[tiab]) OR intrauterine growth restriction[tiab]) OR intrauterine growth retardation[tiab]) OR IUGR[tiab]) OR Placental dysfunction[tiab]) OR "Placental Insufficiency"[Mesh])	3	08:56:09
#42	Add	Search (("Placenta"[Mesh]) AND (((((("Diffusion Magnetic Resonance Imaging"[Mesh]) OR DWI[tiab]) OR Diffusion weighted imaging[tiab]) OR Apparent diffusion coefficient[tiab]) OR ADC[tiab])) AND (("Gestational Age"[Mesh]) OR GA[tiab])	5	08:54:35
#40	Add	Search ("Placenta"[Mesh]) AND (((((("Diffusion Magnetic Resonance Imaging"[Mesh]) OR DWI[tiab]) OR Diffusion weighted imaging[tiab]) OR Apparent diffusion coefficient[tiab]) OR ADC[tiab])	13	08:49:43
#3	Add	Search "Placenta"[Mesh]	58046	07:27:37
#35	Add	Search ((((("Diffusion Magnetic Resonance Imaging"[Mesh]) OR DWI[tiab]) OR Diffusion weighted imaging[tiab]) OR Apparent diffusion coefficient[tiab]) OR ADC[tiab]	21145	08:32:11
#37	Add	Search ((((((("Fetal Growth Retardation"[Mesh]) OR FGR[tiab]) OR intrauterine growth restriction[tiab]) OR intrauterine growth retardation[tiab]) OR IUGR[tiab]) OR Placental dysfunction[tiab]) OR "Placental Insufficiency"[Mesh]	19995	08:34:30
#36	Add	Search ("Gestational Age"[Mesh]) OR GA[tiab]	95251	08:33:25
#35	Add	Search ((((("Diffusion Magnetic Resonance Imaging"[Mesh]) OR DWI[tiab]) OR Diffusion weighted imaging[tiab]) OR Apparent diffusion coefficient[tiab]) OR ADC[tiab]	21145	08:32:11

Embase

Block and block combinations	Search combinations, based on blocks	Items found
Block 1	'placenta'/exp	64.791

Block 2	‘diffusion weighted imaging'/exp OR ‘dwi’ OR ‘apparent diffusion coefficient’ OR ‘ADC’	48.562
Block 3	'gestational age'/exp	98.622
Block 4	‘Intrauterine growth retardation’/exp OR ‘Fetal growth restriction’ OR ‘FGR’ OR ‘Intrauterine growth restriction’ OR ‘IUGR’ OR ‘Placenta insufficiency’/exp	37.842
Block 1 AND Block 2	‘'placenta'/exp’ AND ‘’diffusion weighted imaging'/exp OR ‘dwi’ OR ‘apparent diffusion coefficient’ OR ‘ADC’’	89
Block 1 AND Block 2 AND Block 3	‘'placenta'/exp’ AND ‘’diffusion weighted imaging'/exp OR ‘dwi’ OR ‘apparent diffusion coefficient’ OR ‘ADC’’ AND ‘'gestational age'/exp’	19(2)
Block 1 AND Block 2 AND Block 4	‘'placenta'/exp’ AND ‘’diffusion weighted imaging'/exp OR ‘dwi’ OR ‘apparent diffusion coefficient’ OR ‘ADC’’ AND ‘‘Intrauterine growth retardation’/exp OR ‘Fetal growth restriction’ OR ‘FGR’ OR ‘Intrauterine growth restriction’ OR ‘IUGR’ OR ‘Placenta insufficiency’/exp’	23(3)
Block 1 AND Block 2 AND Block 3 AND Block 4	‘'placenta'/exp’ AND ‘’diffusion weighted imaging'/exp OR ‘dwi’ OR ‘apparent diffusion coefficient’ OR ‘ADC’’ AND ‘'gestational age'/exp’ AND ‘‘Intrauterine growth retardation’/exp OR ‘Fetal growth restriction’ OR ‘FGR’ OR ‘Intrauterine growth restriction’ OR ‘IUGR’ OR ‘Placenta insufficiency’/exp’	9(0)

Criteria for selection of relevant information:

- Relevant title and abstract, according to hypothesis.
- Access to full text
- Review
- Research article

Date and identification:

Literature search started September 2015 and final search completed December 16th 2015, by Caroline Frederike Haals, 11th semester medical student, Aalborg University, DK.

5. Review table

Author Year (reference)	Studied cases Number	MRI system	MRI sequence	B values	ADC-values	Conclusion
Sinding, Marianne **2015** (12)	24 normal cases 4 FGR cases	*GE Discovery MR450 1,5 MRI System*	T2 weighted loclizer → anatomic orientation of the placenta T2*-scan	-	-	Placental T2* measurements – potential as non-invasive test of placental dysfunction. In small fetus: placental T2* value below normal → strong indicator of placental dysfunction at the etiology of growth restriction.
Alison, Marianne **2013** (3)	Murine model: 10 pregnant rats	*Biospec 47/40 USR; Bruker, Ettlingen, Germany*	T2 weighted (SSPFP-2D True Fisp → 2 dimensional steady-state free	Fourteen (10, 25, 50, 75, 100, 125, 150, 200, 300, 400, 500, 600,	-	IVIM MRI can detect reduced placental perfusion at 4.7 T in a controlled murine model of vascular FGR. Perfusion fraction = sensitive marker of ⇓

			precession sequence)	700, 800 s/mm2)		placental perfusion. It could be of interest for the diagnosis of placental insufficiency in clinical practice as a noncontrast technique for assessing perfusion.
Bonel, Harald 2010 (9)	102 fetuses	*Magnetom Sonata Maestro Class; Siemens, Erlangen, Germany*	1.5T DW-MRI (3000/83; echo space, 0.58 msec) – performed as part of the local routine fetal MRI protocol	b values of 500, 700, and 1000 sec/mm 2	Ikke opgivet, dog: Without placental insufficiency – ADC did not show show significant correlation with gestational age. Normal pregnancy – ADCs were lower in IUGR fetuses.	Clinical and US-defined placental dysfunction is associated with decreased ADC.
Manganaro, Lucia 2006 (10)	Retrospective phase: 145 pregnant women	*Siemens Magnetom Avanto*, using a four-element phased array coil.	1.5T Single-shot EPI diffusion-sensitized sequences (TR	Retrospective phase: 0, 200, 700 Prospective phase: 0, 200,	Retrospective phase: from 1 to 2.4 mm2/s Prospective phase: with b0 ranged from 0.8 to 2.5 mm2/s, without b0 ranged	ADC using b values 0, 200 and 700 s/mm2 →significant statistical correlation. ADC using b values 50, 200 and 700 s/mm2 → no correlation with placental

	Prospective phase: 50 women		5800, TE 105, flip angle 90◦, FOV 420 mm × 300 mm, matrix 192×192, thickness 4 mm, total acquisition time 335 min for four measurements on each image, 30 slices)	700 and 50, 200, 700	from 1.5- 1.7 mm2/s.	aging → indicates: perfusional and circulatory motion plagues the DW images → do not believe that DWI and ADC maps can be used as indicators of placental aging.
Siauve, Nathalie 2015 (4)	-	-	-	The use of 2 different b-values, compared with reference image (i.e. b0)	Mean ADC in normal pregnancy: 1.77 +/- 0.19 x 10^{-3} mm^2/s - Variation with gestational age remains controversial	All reviewed functional MRI techniques demonstrate a potential for allowing timely recognition of placental insufficiency. Future placental fMRI should benefit from the use of well-defined sequences, consensual MRI

					A high ADC value = low restricted diffusion	protocols, and robust computational methods. - Necessary to standardize the parameters that are studied - Improvement of reproducibility of placental functional metrics.
Patenaude, Yves **2014** (5)	-	-	-	-	-	MRI: an expensive and limited resource, additional tool only to be done if US is inadequate. US: primary diagnostic tool for fetal imaging.
Andescavage, Nickie Nifratos **2015** (7)	-	DWI: potential to provide valuable information on the diffusion and	-	-	-	Advanced fetal MRI offers a promising non-invasive method to interrogate multiple fac-ets of placental development and function and is becoming a powerful obstetrical tool

		perfusion properties of the human placenta				to assess placental health and wellness in the living fetus.
Dekan, Sabine 2012 (8)	-	-	-	-	-	Fetal MRI → emerging and safe diagnostic tool in prenatal diagnostics. Providing additional important information on top of ultrasound of placental conditions → helping in clinical decisions of pregnancy management to minimize fetal and maternal perinatal complications
Sivrioğlu, Ali Kemal 2013 (11)	56 fetuses, grouped by GA; 1. 18-23, 2. 24-28, 3. 29-38	1.5 Tesla system → Magnetom Symphony, Siemens Healthcare, Erlangen, Germany	single-shot echo-planar sequence (TR, 3400 ms; TE, 94 ms; FOV, 23 cm; matrix, 128×128;	0, 500 and 1000 s/mm2	The median placental rADC value was 0.71 (min, max; 0.35, 1.31)	Placental rADC value was not significantly different between gestational age groups

			slice thickness, 4 mm; interslice gap, 10%; bandwidth, 1346 Hz/pixel; spatial resolution, 1.8×1.8×4.0 mm3			