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Pregnancy in diabetes

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Rathcke, Sidsel Linneberg

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FETAL GROWTH AND PLACENTAL FUNCTION
IN PREGESTATIONAL DIABETES

BY
SIDSEL LINNEBERG RATHCKE

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FETAL GROWTH AND PLACENTAL FUNCTION IN PREGESTATIONAL DIABETES

PhD thesis

Sidsel Linneberg Rathcke

AALBORG UNIVERSITY
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ENGLISH SUMMARY

Pregnancies complicated by pregestational diabetes mellitus (PGDM) are associated with adverse obstetric outcomes, such as large-for-gestational-age (LGA) neonates, preeclampsia, fetal asphyxia and still birth, the majority of which are associated with placental dysfunction. Current antenatal care in PGDM pregnancies focus on close fetal monitoring and good maternal glycaemic control during pregnancy, as it has been demonstrated that maternal hyperglycaemia is directly related to adverse obstetric outcomes and compromised placental development. The combination of impaired oxygen supply due to placental dysfunction and an increased metabolic demand due to fetal overgrowth explains the increased risk of adverse neonatal outcomes due to chronic and acute fetal hypoxia. Early identification of placental dysfunction and fetal overgrowth provides an opportunity to predict and ultimately prevent adverse obstetric outcomes. Current methods used to identify placental dysfunction and fetal overgrowth include ultrasound assessment of fetal weight by measurement of fetal biometry, as well as Doppler flow measurements of fetal, uterine, and umbilical blood flow. Unfortunately, in PGDM pregnancies the performance of ultrasound in the prediction of fetal weight and placental dysfunction is inaccurate due to asymmetric fetal growth and unreliable Doppler flow measurements. T2* weighted placental magnetic resonance imaging (MRI) is a new method that in recent years has demonstrated the potential to assess placental function in non-diabetes pregnancies.

Therefore, the overall aim of this PhD project was to investigate fetal growth and placental function in PGDM pregnancies by use of fetal ultrasound, maternal glycaemic level, and placental MRI.

This PhD project demonstrates that pregnancies complicated by PGDM are associated with a general fetal overgrowth with increased z-scores of all fetal biometry. There is no significant difference in the predictive performance of EFW and AC regarding LGA at birth, and both perform significantly better than the HC/AC-ratio (*Study I*). In type 1 diabetes (T1DM) pregnancy birth weight is primarily associated with early glycaemic level, whereas in type 2 diabetes (T2DM) improved glycaemic control in late pregnancy reduces fetal overgrowth (*Study II*). Placental function as assessed by placental T2* is reduced in T1DM pregnancies compared to non-diabetes pregnancies. Mean birth weight deviation is correlated with maternal HbA$_{1c}$ level in T1DM pregnancies with normal placental T2*. However, this is not found in those with reduced placental T2* (*Study III*).

In conclusion, pregnancies complicated by PGDM are characterized by a general fetal overgrowth, partly caused by hyperglycaemia, but placental function may alter the effect of glucose on fetal growth.

DANSK RESUME

Gravide kvinder med prægestationel diabetes (PGDM) har en øget risiko for obstetriske komplikationer såsom høj fødselsvægt for gestationsalderen (LGA), svangerskabsforgiftning, iltmangel hos fostret og dødfødsel. Størstedelen af disse komplikationer er associeret med placentadysfunktion. I PGDM-graviditeter fokuserer den nuværende svangreomsorg på god glykæmisk kontrol hos den gravide, da tidligere studier har indikeret, at maternel hyperglykæmi er relateret til obstetriske komplikationer og kompromitteret placentaudvikling. Nedsat iltforsyning på grund af placentadysfunktion kombineret med et øget stofskiftebehov på grund af føtal overvækst, kan forklare den øgede risiko for neonatale komplikationer grundet hhv. kronisk og akut føtal hypoxi. Ved at identificere placentadysfunktion og overvækst hos fostret tidligt i graviditeten, kan obstetriske komplikationer potentielt forudsiges og forhindres. Overvågning af fostret og placentas funktion foregår for nuværende ved hjælp af en ultralydsundersøgelse, hvor fostrets vægt estimeres ud fra dets biometriske mål, og placentas funktion vurderes ud fra Doppler-målinger af føtale kar og kar i navlesnoren. Det er dog vist, at ultralydsundersøgelser er mindre præcise i PGDM-graviditeter i forhold til at vurdere fostrets størrelse og placentas funktion, formentlig grundet asymmetrisk vækst af fostret. Magnetisk resonans (MR) skanning af placenta hos gravide uden diabetes har vist potentiale til at vurdere placentas funktion.

Formålet med dette ph.d.-projekt var at undersøge fostervækst og placentafunktion i PGDM-graviditeter med ultralyd, det maternelle glykæmiske niveau og MR-skanning af placenta.

Dette ph.d.-projekt viser at PGDM-graviditeter er associeret med en generel overvækst af fostret med øgede z-scores af alle de føtale biometrier. Vedrørende prædiktion af LGA ved fødslen, er der ingen signifikant forskel mellem brug af estimeret fostervækst og abdominalomfang, og begge er signifikant bedre end ratioen af hovedomfang/abdominalomfang (*Studie I*). I graviditeter kompliceret af type 1 diabetes (T1DM) er fødselsvægten primært associeret med det glykæmiske niveau tidligt i graviditeten. Derimod ses det i graviditeter kompliceret af type 2 diabetes, at den føtale overvækst reduceres hvis den glykæmiske kontrol bedres i løbet af graviditeten (*Studie II*). Der ses nedsat placentafunktion i T1DM sammenlignet med ikke-diabetes graviditeter, når den vurderes ved placenta T2* MR-skanning af placenta. I T1DM graviditeter med en normal placenta T2* værdi, ses en sammenhæng mellem fødselsvægten og den maternelle glykæmiske kontrol, hvilket ikke ses i de graviditeter hvor der er en abnorm placenta T2* værdi (*Studie III*).

Afslutningsvist kan det konkluderes at PGDM-graviditeter er karakteriseret ved en generel føtal overvækst, delvist grundet maternel hyperglykæmi, men placentas funktion ændrer muligvis blodsukkerets effekt på fostervæksten.

ACKNOWLEDGEMENTS

FUNDING

LIST OF PAPERS

The PhD thesis is based on three studies presented in the following papers, which are referred to in the text by their Roman numerals:

Paper I

Rathcke SL, Sinding MM, Christensen TT, Uldbjerg N, Christiansen OB, Kornblad J, Søndergaard KH, Krogh S, Sørensen AN.

Prediction of large-for-gestational-age at birth using fetal biometry in type 1 and type 2 diabetes.

Submitted to International Journal of Gynecology and Obstetrics

Paper II

Rathcke SL, Sinding MM, Christensen TT, Uldbjerg N, Christiansen OB, Jepsen AH, Fricke CH, Beckmann H, Sørensen AN.

Birth weight and first trimester maternal glycaemic level in type 1 and type 2 diabetes: a retrospective cohort study.

Submitted to Obstetrics and Gynecology

Paper III

Rathcke SL, Sinding MM, Christensen TT, Uldbjerg N, Leenskjold S, Christiansen OB, Peters DA, Frøkjær JB, Sørensen AN.

T2* weighted placental MRI in type 1 diabetes pregnancies – a prospective study based on the FaPDi cohort.

Submitted to Ultrasound in Obstetrics and Gynecology

TABLE OF CONTENTS

CHAPTER 1. INTRODUCTION

The prevalence of pregestational diabetes mellitus (PGDM) has increased in recent decades and now complicates up to 1.3% of all pregnancies, being the most frequent medical disorder to complicate pregnancy (1,2). PGDM is associated with adverse obstetric outcomes, including preeclampsia, abnormal fetal growth, fetal asphyxia, still birth, Caesarean section, and preterm delivery, many of which are related to placenta dysfunction (3–5). Furthermore, PGDM is associated with adverse long term consequences in the offspring, such as increased risk of obesity, diabetes and cardiovascular diseases (6–8) that may be related to the suboptimal intrauterine environment in PGDM pregnancies.

Large-for-gestational-age (LGA) at birth is a frequent obstetric complication in both type 1 diabetes (T1DM) and type 2 diabetes (T2DM) pregnancies (4,9,10), and clinically it is both relevant and challenging to predict LGA accurately. Currently, ultrasound measurements of fetal biometry are used to determine the estimated fetal weight (EFW). However, the predictive performance of LGA at birth might not be as strong in PGDM compared to non-diabetes pregnancies (11). Thus, a more correct prediction of LGA could facilitate rational obstetric decisions.

It is well known that maternal hyperglycaemia is associated with an increased risk of LGA in PGDM pregnancies (12), and several studies have supported this hypothesis by the assessment of maternal glycated haemoglobin (HbA_{1c}) in the second and third trimester (13–17). However, the correlation between HbA_{1c} in the first trimester and birth weight show conflicting results (13–15,17–20), potentially because hyperglycaemia in early pregnancy has a negative effect on placentation, which may lead to placental dysfunction later in pregnancy (21–24).

In modern obstetrics it remains a major challenge to correctly diagnose placental dysfunction especially in PGDM pregnancies. Isolated low birth weight <3rd centile is regarded as a proxy for placental dysfunction in non-diabetes pregnancies (25). However, in PGDM pregnancies this may not be true as diabetes neonates are often LGA (17,18). T2* weighted placental magnetic resonance imaging (MRI) has demonstrated the ability to depict placental oxygenation and thereby assess placental function non-invasively in non-diabetes cohorts (26–30).

Therefore, the aim of this PhD project is to investigate fetal growth and placental function in PGDM pregnancies by use of fetal ultrasound, maternal glycaemic level, and placental MRI.

CHAPTER 2. BACKGROUND

This chapter contain five parts. The first part covers background information regarding fetal growth in PGDM pregnancies. The second part includes information about maternal glycaemic control in PGDM pregnancies and how it affects fetal growth. The third part presents information on placental development and structure as well as placental function in PGDM pregnancies. The fourth part is regarding fetal monitoring in PGDM pregnancies, and the last part contains information regarding placental MRI including clinical use of placental T2*.

2.1. FETAL GROWTH IN DIABETES PREGNANCIES

Neonates born LGA at birth is a common complication in PGDM pregnancies with a prevalence of 30-62% (4,9,10). This is an obstetric challenge as LGA at birth increases the risk of complications such as shoulder dystocia, Caesarean section and perinatal morbidity and mortality (31,32). It is therefore highly clinically relevant to predict LGA accurately. Identification of pregnancies with an increased risk of LGA in early pregnancy may facilitate the opportunity to improve the maternal glycaemic level and thereby potentially reduce the risk of LGA. Correct prediction of LGA in late pregnancy may facilitate relevant obstetric decisions in relation to the time and mode of delivery.

Current practice in the assessment of fetal size is by use of ultrasound measurements. Fetal biometry, such as head circumference (HC), abdominal circumference (AC) and femur length (FL), is commonly used to calculate estimated fetal weight (EFW). Several different equations have been proposed in order to give the most precise fetal weight estimate in PGDM pregnancies (33–35). The Hadlocks equation from 1985 (36) is still the one recommended to use in both non-diabetes and PGDM pregnancies in Denmark (37). However, the prediction of LGA in PGDM pregnancies is still challenging (33,35). A previous study found that the birth weight in PGDM neonates was underestimated by more than 15% in 26% of neonates >4000g compared to only 5.4% in non-diabetes pregnancies (11).

The inaccuracy in the assessment of EFW may be caused by an asymmetric fetal growth in PGDM pregnancies with a relatively large AC to HC ratio (10,38), as the formulas established to calculate EFW were based on well-proportionated non-diabetes fetuses (33,35,39,40). Several other ultrasound measurements, such as shoulder soft tissue width (41), anterior abdominal wall (42), fetal soft-tissue and liver

size (43), and 3D fractional thigh volume (44), have also been examined in order to improve the prediction of LGA at birth, none of which have proven superior.

The timing of ultrasound examination may also influence its predictive performance, as the prediction of LGA at birth is improved when ultrasound is performed at late gestation (42,45,46). One study investigated the performance of AC in the prediction of LGA at birth in a mixed PGDM cohort using area under the receiver operating characteristic curve (AUC). The predictive performance was higher in gestational week 36 (AUC=0.85) compared to gestational week 30 (AUC=0.76) (42). Moreover, the same study demonstrated that AC had a better predictive performance than EFW, which is similar to the findings in another study that found AC to be the best predictor of macrosomia, while the HC/AC-ratio had the lowest performance (41).

The correlation between the HC/AC-ratio and LGA at birth in PGDM neonates has only been described in a few studies with varying results (10,38,41). One could hypothesize that the HC/AC-ratio expresses the asymmetric growth to a higher extent than AC alone and by that the risk of LGA (10).

2.2. MATERNAL GLYCAEMIC CONTROL

Maternal hyperglycaemia is known to be associated with the increased risk of LGA in PGDM pregnancies. The association was described by Jørgen Pedersen in 1952 (12), as the hyperglycaemia-hyperinsulinemia hypothesis, which is now generally known as the Pedersen hypothesis: "Maternal hyperglycaemia results in foetal hyperglycaemia and, hence, in hypertrophy of foetal islet tissue with insulin-hypersecretion. This again means a greater foetal utilization of glucose. This phenomenon will explain several abnormal structures and changes found in the newborn." (47). At present the Pedersen hypothesis constitutes the basis of our understanding of the association between maternal hyperglycaemia and fetal overgrowth (Figure 2.2.1).
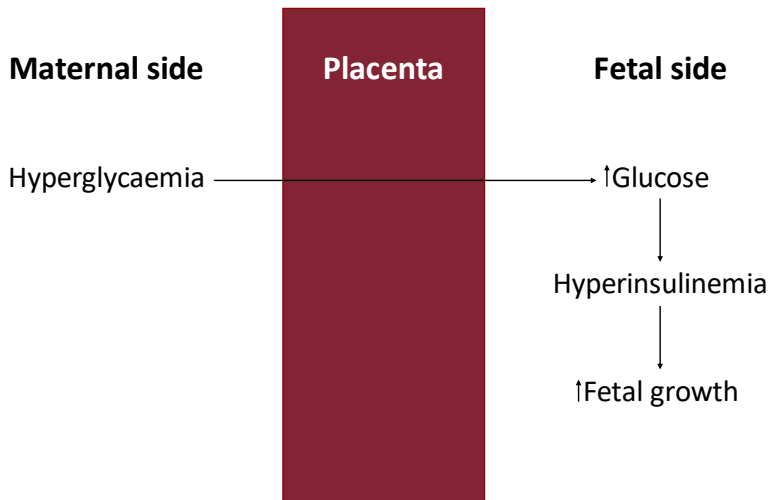
Figure 2.2.1 *Illustration of the Pedersen hypothesis.*

In the second and third trimester maternal hyperglycaemia stimulates fetal hyperinsulinemia which increases glucose utilization in insulin sensitive tissues, such as the liver, skeletal muscle, adipose tissue, and heart, and it also leads to the expansion of adipocytes and increased fat tissue deposition, which promotes excessive fetal weight gain (48). The principle of the Pedersen hypothesis was investigated in women with mild hyperglycaemia in the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study. This study demonstrated a dose-response correlation between HbA_{1c} and birth weight. Moreover, it showed a linear correlation between neonatal fat mass and fetal insulin levels measured by C-peptide concentrations in the umbilical cord (49,50).

In PGDM pregnancies several studies have supported the Pedersen hypothesis by a positive correlation between maternal HbA_{1c} in the second and third trimester and birth weight (13–17). However, even in large scale studies, the correlation is not as strong as anticipated, indicating that factors other than hyperglycaemia-hyperinsulinemia drive excess fetal growth (19,51). Some studies find no correlation between high maternal glycaemic level and LGA. Meanwhile other studies find LGA despite good glycaemic control (13,18,20,52,53). In particular one study has demonstrated that at very high glycaemic levels the correlation is unpredictable and even show an inverse U-shaped pattern (54). Moreover, the correlation between the first trimester HbA_{1c} and birth weight show conflicting results (13–15,17–20).

Originally the Pedersen hypothesis was formulated in relation to type 1 diabetes (T1DM) pregnancies. However, the majority of PGDM studies include a combination of T1DM and type 2 diabetes (T2DM) pregnancies as one single condition, which might partly explain the inconsistent findings in these studies (9,14,55). The underlying pathologies of the two diabetes types are different as T1DM is related to an autoimmune β-cell destruction causing insulin deficiency while T2DM is mainly caused by insulin resistance in the peripheral tissues leading to a non-autoimmune progressive loss of adequate β-cell insulin secretion (56). In addition, the two groups express differences in regards to glycaemic levels, maternal characteristics and obstetric outcomes (9,16,17,52).

2.3. PLACENTAL FUNCTION

The human placenta is a large circular discoidal endocrine organ with multiple functions. Besides playing a fundamental role in the transfer of oxygen and nutrients to the fetus, it also acts as an immunological barrier between the mother and fetus, and in early pregnancy it undertakes the function of several fetal organ systems (57–59).

Placentation starts around post-fertilization day 5-6 when the blastocyst attaches to the endometrial epithelium that the syncytiotrophoblast penetrates and grows into the decidual stroma (58,60). Within the syncytiotrophoblast, a fluid-filled lacunae emerges forming trabeculae, and the cytotrophoblast cells proliferate and migrate into the trabeculae forming the primary villi, which protrude into the intervillous space. Ultimately the cytotrophoblast penetrates through to the decidua forming cell columns that spread laterally, forming the cytotrophoblast shell which is the predecessor of the basal plate (60). From this primary basal plate, the trophoblasts go on to invade the endometrium and the walls of the spiral arteries replacing the arterial endothelium; this is called the vascular remodelling of the spiral arteries. Around 13-14 days post-fertilization, the extra embryonic mesodermal cells also migrate into the primary villi, transforming them into secondary villi. They further differentiate and about 20 days post-fertilization develop the first independent placental vessels and are now evolved into tertiary villi. Throughout pregnancy they further differentiate into different villous types from mesenchymal villi to terminal villi being the final branches of the villous trees (58).
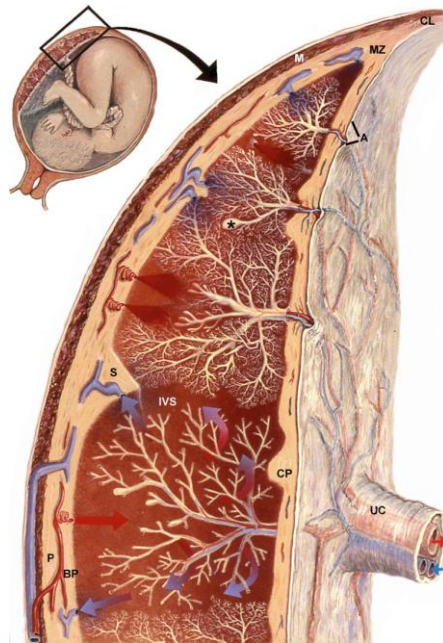
Figure 2.3.1. *The mature human placenta. CP chorionic plate; BP basal plate; IVS intervillous space; P placental bed; M myometrium; CL chorion leave; A amnion; MZ marginal zone between placenta and fetal membranes; S placental septum; UC umbilical cord. From Kaufmann and Scheffen* (61)*, with permission from publisher (Elsevier).*

The mature placenta consists of a maternal surface (the basal plate) and a fetal surface (the chorionic plate) divided by the intervillous space (Figure 2.3.1). The intervillous space is filled with maternal blood from the spiral arteries through an opening in the basal plate. The maternal blood filters between the fetal villous branches before exiting the placenta. In the villous tree the fetal capillary network in the terminal villi is locally thinned, reducing the diffusion distance between maternal and fetal circulation being the leading site of exchange (58,62). Oxygen transport from the maternal blood circulation to the fetal blood circulation occurs by simple diffusion, driven by the difference in partial pressure (57).

Glucose is the predominant substrate for placental and fetal metabolism, and almost all of the fetal glucose is received from the maternal circulation and crosses the placenta by facilitated diffusion via a family of glucose transporters (GLUTs) (62,63). In the first half of pregnancy the density of GLUT1 in the basal membrane is increased, while it subsequently reaches a plateau in the second half of pregnancy, suggesting that early pregnancy determines the fetal demands for glucose transfer (63,64). These findings indicate that transplacental glucose transport is regulated by

fetal glucose requirements rather than maternal blood glucose levels. Insulin does not cross the placental membrane, and the number of GLUTs is not directly affected by insulin (63).

2.3.1. PLACENTAL (DYS)FUNCTION IN DIABETES

PGDM is associated with a wide range of changes in the maternal metabolism that potentially can affect any of the complex and highly regulated steps in the early placentation (21,24). In PGDM pregnancies studies have shown an increase in GLUT1 expression in the basal membrane and thereby an increase in glucose transport capacity (65,66). Thus, metabolic abnormalities in early pregnancy may stimulate a further increase in GLUT1. However, the regulation of GLUTs is assumed to be multifactorial, indicating that fetal overgrowth is not simply due to maternal hyperglycaemia (63,65,67).

Another change in PGDM placental development is the trophoblast invasion that is affected by hyperglycaemia and hyperinsulinemia (21,68). An impairment in cytotrophoblast invasion has been reported in T1DM pregnancies, which causes an insufficient spiral artery remodelling, followed by impaired maternal perfusion and reduced oxygen supply to the fetoplacental unit, resulting in chronic fetal hypoxia (68,69). This is a well described histological finding known as maternal vascular malperfusion (MVM), commonly associated with placental dysfunction (70). Moreover, higher HbA_{1c} levels alter the maternal oxyhaemoglobin dissociation curve leading to an increased affinity for oxygen, which reduces the amount of oxygen delivered to the fetoplacental unit (68,71). (Hans Madsen)

Compensatory adaptive changes in the placenta attempt to increase the placental transport capacity to ensure adequate supply of oxygen for the diabetic fetus, which very often is macrosomic with increased metabolic demand (68,72). One adaptive mechanism is increased placental size and hypervascularisation of the fetal villous three, which is seen even in mild cases of maternal hyperglycaemia (68,73). In dysregulated PGDM pregnancies severe hyperglycaemia may lead to placental changes with negative effects on placental function such as MVM and chorangiosis (74,75). A collection of placental features including both gross and microscopic findings indicates MVM: reduced placental weight (<10th percentile), infarction (>5%), retroplacental hemorrhage, distal villous hypoplasia (long, thin villi), accelerated villous maturation (small, short hypermature villi for gestational age) and decidual arteriopathy including signs of abnormal spiral artery remodeling (76). Chorangiosis is characterized by extreme villous hypervascularity (>10 capillaries in more than 10 terminal chorionic villi in several areas of the placenta), and it is associated with a higher incidence of adverse obstetric outcomes, such as fetal growth

restriction, hypoxia, perinatal or neonatal mortality, and admission at a neonatal intensive care unit (77,78).

Several studies suggest that the timing of maternal hyperglycaemia in pregnancy may determine the effect on placental function and in particular fetal growth. Women with PGDM who are dysregulated in the first trimester may suffer from placental dysfunction, as placentation and in particular trophoblast invasion is negatively affected by hyperglycaemia (79,80). Hyperglycaemia in later pregnancy may lead to fetal overgrowth due to increased supply of glucose if placental function is normal, but in cases of placental dysfunction, fetal growth may be "normal". The hypothesis of placental dysfunction in PGDM pregnancies with "normal" fetal growth is supported by low levels of placental serum markers such as placental growth factor (PlGF), which is a serum marker of placental function (81–83).

Many of the dysfunctions in the PGDM placenta described above may explain the increase in placenta related adverse outcomes in PGDM pregnancies including preeclampsia, fetal asphyxia, still birth, Caesarean section, and preterm delivery (3–5), which highlights the need for accurate evaluation of placenta function. The inconsistent finding regarding fetal growth may be related to the fact that fetal growth is a result of several factors including placental function and the supply of oxygen and nutrients such as glucose, which is increased in PGDM pregnancies.

2.4. FETAL MONITORING IN DIABETES PREGNANCY

In non-diabetes pregnancies placental function is mostly evaluated using EFW and Doppler of measurements of UA (84). Isolated low birth weight <3rd centile or low birth weight <10th centile combined with increased resistance to blood flow in the UA (PI >95th centile) are regarded as proxies of placental dysfunction (25). However, in diabetes pregnancies the fetuses are rarely SGA (17). Therefore, their weight alone will not give the suspicion of placental dysfunction. Furthermore, studies have shown that Doppler flow measurements might not be as sensitive in diabetes pregnancies (85–87). In PGDM pregnancies macrosomic fetuses show a reduced UA PI compared to normal size fetuses (88).

Previous studies have investigated placental function in diabetes pregnancies by ultrasound (20,85–87,89,90), maternal serum markers of placental dysfunction(81), cordocentesis (91,92) or post-partum by histological examination (93–95). Current clinical practice in monitoring pregnancies complicated by diabetes is by use of EFW and UA and MCA Doppler flow (96). However, new methods to evaluate fetal growth and placental function are needed.

2.5. PLACENTAL MAGNETIC RESONANCE IMAGING

Nuclear magnetic resonance is the fundamental basis of MRI, and it is a character that atoms with uneven numbers of protons or neutrons possess. Hydrogen possess this ability is the most frequent atom in biological tissues, and it is therefore used to form the MRI signal. A proton has its own magnetic field, and its spins are normally oriented at random. When a person is placed in a magnetic field of an MRI scanner, the protons magnetic potential align either parallel or antiparallel to the longitudinal direction of the magnetic field. This results in a small net magnetic moment in parallel direction called longitudinal magnetisation which is used to form MR images. When applying a radiofrequency pulse, the net magnetisation can be displaced e.g. 90° into a transversal plane resulting in a transverse magnetisation. The recovery of the net longitudinal magnetisation after the radiofrequency pulse is called T1 relaxation, and more specifically T1 is the time of 63% of the recovery in milliseconds (ms). After the radiofrequency pulse, the process where protons dephase in the transverse plane resulting in a decreased net transverse magnetisation, is called T2 relaxation. The definition of T2 is the time of 37% decay of the transverse magnetisation in ms. T1 and T2 relaxations are parallel, independent processes (97,98).

2.5.1. T2* WEIGHTED MRI

T2* weighted MRI is a gradient-echo (GRE) sequences where the decay of transverse magnetization is referred to as transverse relaxation time or T2* relaxation given in ms (99). T2* relaxation is caused by a combination of relaxation caused by magnetic field inhomogeneities and "true" T2 relaxation (99). With the transverse relaxation time (T2*) depending on magnetic field inhomogeneities, T2* is shorter than T2. Inhomogeneity can be caused by deoxyhaemoglobin, air-tissue interfaces, blood products or iron deposits among others (99). Tissue morphology such as villus density and fibrin deposition in the placenta may also influence the T2* value (100,101). T2*-weighted MRI sequences are clinically applied to depict paramagnetic deoxyhaemoglobin, for example. When tissue oxygenation decreases, the T2* value will increase because of a larger amount of deoxyhaemoglobin (99).

2.5.2. PLACENTAL T2*

Placental T2* MRI has been performed in several studies since 2013 (26–29) where it has demonstrated the ability to depict placental oxygenation and thereby assess placental function non-invasively in non-diabetes cohorts (30). Placental T2* reference values have been established in uncomplicated pregnancies, and a negative correlation between T2* and gestational age is well described (28). The decreasing T2* value over gestation is caused by a decrease in oxygen amount in the placenta,

due to an increased metabolic demand of the fetus. In addition, the normal physiological placental maturation may also contribute to the decreasing T2*. The ability of placental T2* to non-invasively examine placental function is highly clinically relevant, as this modality can demonstrate placental dysfunction irrespective of the clinical manifestations (102). Placental T2* weighted MRI scanning takes about one minute and is considered safe in pregnancy (103).

2.5.3. CLINICAL USE AND SAFETY IN MRI

MRI has been used clinically since the early 1990s and is commonly used as a diagnostic tool in pregnancy (104). At present it is primarily used to diagnose fetal structural malformation in selected cases where ultrasound is insufficient (105). In addition, it has been used to diagnose abnormal placental invasion (106). MRI examination is considered safe in pregnancy (103). Several studies have investigated the association between MRI and adverse fetal outcomes, yet no such correlations have been demonstrated (107–109). Potential harmful effects of MRI are as follows:

- Acoustic noise: Noise generated by MRI ranges from 80-120 dB (110). During examination the maternal abdominal layer and the amniotic fluid reduces the noise exposure by a minimum of 30 dB (111). No studies have found hearing impairment in children that were exposed to 1.5T MRI in utero (112,113).
- Static magnetic fields: By magnetic induction the static magnetic field could interact with human tissue by moving electrolytes in the blood vessels creating electric currents (114). Studies have shown no effect on heart rate or blood pressure (115–117) even when exposed during one hour to 8T MRI examination. Also, exposure to static magnetic field possesses no effect on reproduction (118).
- Tissue heat: When generating images, the radiofrequency pulses may deposit heat in the tissue. Temperature elevation has previously been examined in relation to ultrasound examination, and a threshold at 1.5°C is considered safe for the fetus (119). A specific absorption rate (SAR value, Watt/kg) is calculated during the MRI. The SAR value is related to the heat deposited in the tissue. Using standard sequences in a 1.5T MRI system, the SAR value does not exceed the recommended maximum value (120).

CHAPTER 3. AIM OF THE THESIS

The overall aim of this PhD project was to investigate fetal growth and placental function in PGDM pregnancies by use of fetal ultrasound, maternal glycaemic level, and placental MRI.

The specific aims of the three studies in the PhD project were:

Study I:

- to compare the performance of fetal HC/AC-ratio, EFW and AC estimated by ultrasound in the prediction of LGA at birth when estimated in 16, 20, 28, and 34 weeks' gestation among pregnant women with T1DM and T2DM.

Study II:

- to investigate the association between first trimester HbA_{1c} and birth weight in both T1DM and T2DM pregnancies

Study III:

- to compare placental T2* obtained in the second and third trimester in non-diabetes pregnancies and pregnancies complicated by T1DM.
- to explore the correlations between placental T2*, birth weight deviation, and maternal glycaemic level in each trimester.

CHAPTER 4. MATERIAL AND METHODS

4.1. STUDY I & STUDY II

4.1.1. STUDY DESIGN AND POPULATION

All data for Study I and Study II came from the same retrospective cohort including all T1DM and T2DM singleton pregnancies giving birth at Aalborg University Hospital between January 2010 to December 2019. In the local Patient System, a total of 387 pregnancies were identified by the specific diagnostic codes of PGDM (DO240, DO241, DO242 and DO249)(121) and validated by review of the electronic patient records (Clinical Suite™ © 2021, Dedalus Healthcare Systems Group, Milano, Italy). The following exclusion criteria led to the exclusion of 47 pregnancies: multiple pregnancies, miscarriage before 22 weeks' gestation, relocation to another hospital before birth, or the T1DM or T2DM diagnosis could not be confirmed. Of the remaining 340 pregnancies in the cohort, there were 67 women with more than one pregnancy in the study period; one pregnancy was randomly selected to contribute to the final study cohort consisting of 180 women with T1DM and 87 women with T2DM pregnancies (Figure 4.1.1).
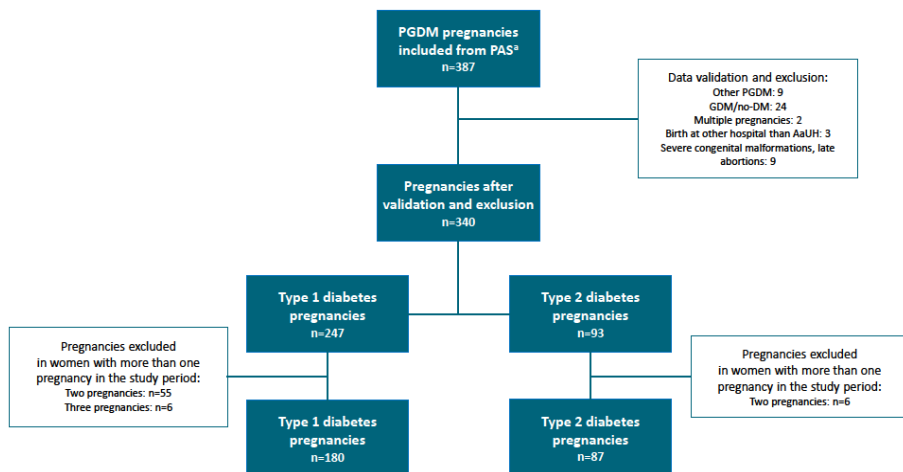
Figure 4.1.1 *Flowchart summarizing inclusion, validation, and exclusion of the study cohort. Aalborg University Hospital (AaUH), Gestational diabetes (GDM), Non-diabetes (no-DM), Patient system (PAS), Pregestational diabetes (PGDM).*

Data on maternal characteristics including maternal glycaemic control and perinatal outcomes were extracted from the electronic patient records. Data on fetal biometry were collected from the local Fetal Medicine database (Astraia software gmbh version 1.24.10, München, Germany). All data were collected and managed using REDCap electronic data capture tool hosted at The North Denmark Region (122).

4.1.2. OUTCOME MEASURES

Study I

All women with PGDM attended extensive routine antenatal care in an outpatient clinic at Aalborg University Hospital, Denmark. From these visits, fetal biometry was obtained by ultrasound scans at 16, 20, 28, and 34 weeks' gestation, including HC, AC, and FL using the reference by Verburg et.al. (123) and the reference by Snijders et.al. for the HC/AC-ratio (124). For all fetal biometry including the HC/AC-ratio, the corresponding z-score was used in the statistical analysis. EFW was calculated by Hadlock's formula (36), and the weight deviation (%) of the expected weight for gestational age was estimated using the Scandinavian reference by Maršál (125).
The primary outcome was LGA, which was defined by birth weight deviation $\geq 15\%$ of the expected for gestational age which corresponds with birth weight $\geq 90^{th}$ centile. A non-LGA group was defined by birth weight deviation $< 15\%$ of the expected for gestational age.

Study II

In PGDM pregnancies HbA_{1c} is measured every 4 weeks as part of the routine antenatal care. The HbA_{1c} was obtained from the electronic patient record, and one value was selected from each trimester for the study: first trimester, 8-12 weeks' gestation; second trimester, 18-22 weeks' gestation; and third trimester, 30-34 weeks' gestation. If more than one value was available in a time period, the earliest value in the specific time period was selected in each trimester.
Based on the first trimester glycaemic level, all T1DM and T2DM pregnancies were divided into two groups; Well-regulated pregnancies were defined by first trimester $HbA_{1c} < 53$ mmol/mol (7.0%) and dysregulated pregnancies were defined by first trimester $HbA_{1c} \geq 53$ mmol/mol (7.0%). This definition was in accordance with recommendations during the study period in clinical practice and international guidelines (126).
The primary outcome was birth weight deviation (%) from the expected for the gestational age using the Scandinavian reference by Marsal et al. (125).

Obstetric outcomes

Obstetric outcomes in Study I and Study II were defined as follows: maternal hypertensive disorders in pregnancy were defined as either gestational hypertension treated with antihypertensive medication or preeclampsia defined as hypertension and proteinuria and/or thrombocytopenia, impaired liver function, renal insufficiency, or subjective symptoms (127); preterm delivery was defined as giving birth before 37+0 and early preterm delivery as giving birth before 34+0 weeks of gestation; post-partum haemorrhage was defined as loss of blood volume $\geq$ 1000 ml; neonatal hypoglycaemia and severe hypoglycaemia were defined as neonatal blood glucose measurement below 2.5 mmol/l and 1.5 mmol/l respectively, within the two first hours after birth; neonatal asphyxia was defined as Apgar score < 7 at 5 minutes after birth and/or umbilical artery blood pH < 7.0.

4.2. STUDY III

4.2.1. STUDY DESIGN AND POPULATION

Study III was a prospective longitudinal cohort study including patients from the Fetal growth and Placental function in Diabetes pregnancies (FaPDi) cohort. The FaPDi cohort included T1DM, T2DM, and non-diabetes pregnancies giving birth at Aalborg University Hospital. The study was conducted from November 1, 2020 to April 12, 2023. All women with T1DM or T2DM were diagnosed before pregnancy according to international classification (ICD-10) (128). Inclusion criteria were age $\geq$ 18 years at inclusion and singleton pregnancy. Exclusion criteria were women who did not understand or read Danish, had fetal malformation or chromosomal abnormalities, and severe claustrophobia, or any other contraindications to MRI. All FaPDi participants were included at the routine first trimester screening by SLR. Each pregnancy was dated according to the ultrasound estimated crown-rump length from the first trimester scan using the reference by Robinson et al. (129). In the non-diabetes group, all participants underwent an oral glucose tolerance test around gestational week 28 to screen for gestational diabetes, and exclusion criteria was a two-hour value $\geq$ 9,0 mmol/l.

All participants in the FaPDi cohort were invited to three study visits: at 15-20, 26-30 and 34-38 weeks' gestation. At each visit they underwent an MRI examination, an ultrasound examination, a clinical evaluation, and they had a blood sample withdrawn. The clinical evaluation included blood pressure measurement and urine sample examination. At birth all participants had a venous blood sample withdrawn, a blood sample from the umbilical cord was taken, and information on outcomes was

registered. Clinical information was obtained from patient records (Figure 4.2.1). Of those included in the FaPDi cohort, all women with type 1 diabetes and those without diabetes constituted the study population in Study III.
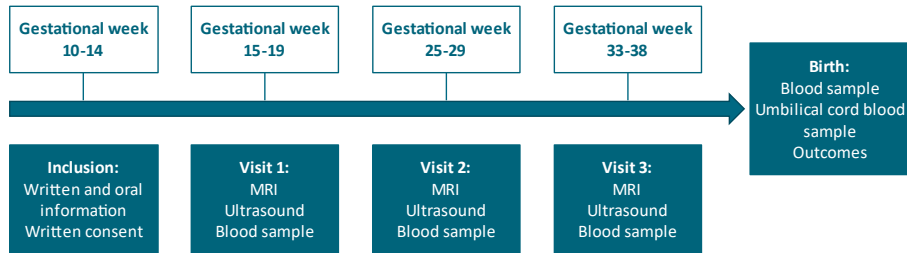
Figure 4.2.1 *Timeline of study protocol*

4.2.2. MAGNETIC RESONANCE IMAGING

At each study visit MRI examination was performed using a 1.5 Tesla wide bore 70 cm system, GE Optima 450W (GE Healthcare, Milwaukee, WI, USA) using the coil elements in the scan table and the anterior body array coil. During the MRI, participants were in left lateral position to avoid vena cava compression and hearing protection was provided. Total scan time in the FaPDi protocol was 30 minutes on the uterus and 15 minutes on the maternal heart with a short break between the two. Scan protocols were performed for fetal and placental volumetry and oxygenation (T2*) assessments; for Study III, only the placental T2* weighted MRI was used.

The T2* weighted placental MRI was acquired using 16 echoes in each slice and a total of five transversal placental slices. Each slice was obtained within a 12 second single breath hold. The MRI protocol for the T2* weighted MRI was: echo time [TE_{16}]: 3.0 msec - 67.5 msec in steps of 4.3 msec; repetition time [TR]: 71.2 msec; flip angle: 30°, spacing: 20.0 mm; slice thickness 8.0 mm; field of view [FOV]: 38.0 x 38.0 cm; frequency: 256; and phase: 160. Each of the five slices were critically review for artefacts, and three slices of high technical quality were selected (Figure 4.2.2). The MRI Dicom data were extracted anonymously and processed in an in-house developed software (RoiTool) written in MatLab (The MathWorks Inc. Natick, MA, USA) where placental regions of interest (ROIs) were drawn manually. Each ROI covered the entire placenta, and the T2* value was estimated from the mean signal intensity of the ROI in each slice. In each placenta the T2* value (ms) was calculated as an average of the three slices. T2* z-scores adjusted for gestational age at MRI was created at each visit using the non-diabetes pregnancies as a reference group.
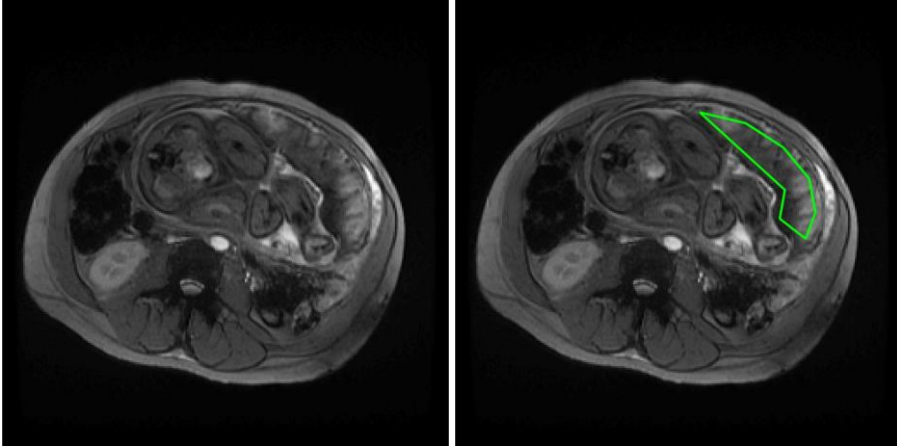
Figure 4.2.2 *Pictures of T2* weighted placental MRI without and with ROI (regions of interest) marked.*

4.2.3. ULTRASOUND

At each study visit an ultrasound examination was performed within a week of the MRI using a Voluson E10 ultrasound system (GE Healthcare, Kretz Ultrasound, Zipf. Austria). All ultrasound examinations were performed by trained sonographers, obstetricians or SLR, and data were entered into the local Fetal Medicine database (Astraia software gmbh version 1.24.10, München, Germany) from where they were extracted to the FaPDi research database managed in RedCap electronic data capture tool hosted at The North Denmark Region(122). Each examination followed the FaPDi protocol and included measurements of:

- Amniotic fluid index (AFI) or the deepest vertical pocket (DVP)
- Fetal biometry and the corresponding z-score (123):
    - head circumference (HC)
    - abdominal circumference (AC)
    - femur length (FL)
- Doppler flow pulsatility index (PI) and corresponding z-score:
    - Umbilical artery (UA) (84)
    - Middle cerebral artery (MCA) (84)
    - Ductus Venosus (DV) (130)
    - Uterine artery on both right and left side (UtA) (131)

The fetal biometry measurements were used to calculate EFW in grams by Hadlocks formula (36), and the deviation in percentage of the expected for gestational age was estimated using the Scandinavian reference by Maršál (125).

4.2.4. BLOOD SAMPLES

At each study visit a blood sample was drawn on the day of MRI. The blood sample was analysed immediately for maternal baseline physiology including HbA_{1c}, glucose, electrolytes, haematological parameters, and liver parameters. Part of the blood sample was stored in a biobank, at the Department of Clinical Biochemistry, Aalborg University Hospital, for later analyses of specific placental markers and for future research. For Study III only the HbA_{1c} was used for analyses. Further, for type 1 diabetes pregnancies it is clinical practice that an HbA_{1c} is obtained in the first trimester; this value was also used for analyses in Study III.

4.2.5. OUTCOME MEASURES

Outcomes in Study III were as follows: Placental T2* z-score was both analysed as a continuous variable and a binary variable using visit 2 to define normal (z-scores ≥ -1.0) and reduced (z-scores < -1.0) placental T2*. Using the Scandinavian reference by Marsal et al. (125), birth weight deviation given as a percentage of the expected birth weight for gestational age was analysed as a continuous variable and categorized in three birth weight groups; AGA: Birth weight >-15% and < +15%, LGA: Birth weight ≥ +15% (90th centile), and SGA: Birth weight ≤ -15% (10th centile).

Other obstetric outcomes were as follows: preterm delivery was defined as delivery before 37+0 weeks' gestation; neonatal asphyxia was defined as Apgar score < 7 at 5 minutes after birth or umbilical artery blood pH < 7.10; stillbirth was defined as intrauterine fetal demise after 21+6 weeks' gestation; preeclampsia was defined according to international consensus (127); and post-partum haemorrhage was defined as loss of blood volume ≥ 1000 ml within 24 hours after delivery.

4.3. ETHICS

Data collection and handling were approved by and registered at The North Denmark Region; Studies I-II were assigned case numbers 2021-092; Study III was assigned case numbers 2021-028. Data was handled in accordance with the Danish data protection law. All data were collected in and managed using REDCap electronic data

capture tool hosted by Aalborg University Hospital, The North Denmark Region (122).

For Studies I-II representative consent and data extraction permission was given by The North Denmark Region.

Study III was approved by The North Denmark Region Committee on Health Research Ethics, N-20200065 and all participants gave written informed consent. Furthermore, Study III was registered at ClinicalTrials.gov Identifier: NCT04801121.

4.4. STATISTICAL ANALYSIS

In all three studies, continuous data were tested for normality using histograms and q-q plots. In data that were normally distributed, groups were compared using student t-test. When data was not normally distributed Wilcoxon Rank Sum test was used. All binary data was compared between groups using the χ^2 test.

All statistical tests were performed in STATA version 16 (College Station, TX: StataCorp LLC.), and a p-value below 0.05 was considered statistically significant.

In Study I, LGA prediction was investigated by logistic regression, and area under the receiver operating characteristic curve (AUC) was used to investigate the performance of the fetal biometry z-score, HC/AC-ratio z-score and EFW (%) at each visit for each diabetes type. With AC as reference the predictive performance was compared with HC, FL, HC/AC-ratio and EFW (%) by the DeLong method (132). A multivariate analysis was performed, including BMI, age, smoking status, ethnicity, parity, conception mode and HbA_{1c} (first trimester HbA_{1c} against ultrasound at 16 weeks, second trimester HbA_{1c} against ultrasound at 20 weeks and third trimester HbA_{1c} against ultrasound at 28 and 34 weeks). The DeLong method (132) was used to compared the predictive performance of the univariate and the multivariate analysis.

In Study II the correlation between maternal first trimester HbA_{1c} and birth weight deviation (%) was investigated by Pearson's correlation (R^2) and linear regression analysis stratified on diabetes type and first trimester glycaemic level. The slope of the correlation was described by the linear regression coefficient (coef.) given as birth weight deviation per HbA_{1c} (%/(mmol/mol)). The slopes were tested for interaction, to compare the correlations according to first trimester maternal glycaemic level. The correlation between maternal first trimester HbA_{1c} and birth weight deviation (%) was also investigated using a spline analysis with multiple cutpoints. This analysis showed that statistically the most correct cutpoint for first trimester HbA_{1c} was 53 mmol/mol, which was also the clinically used reference point. The spline analysis did not add further knowledge to the study results and is therefore not shown. The statistical

decisions were made in collaboration with the Department of Research Data and Statistics at Aalborg University Hospital. The effect of first trimester glycaemic level on birth weight deviation was stratified on third trimester glycaemic level, and median birth weight deviation was compared by Wilcoxon Rank Sum test. Also, the risk of LGA was compared between all type 1 and type 2 diabetes and also when stratified on the maternal glycaemic level at first trimester. Multivariate analysis was performed by logistic regression adjusting for first trimester HbA$_{1c}$ and BMI.

In Study III the mean placental T2* z-score was compared between groups at each visit with students t-test. The correlation between birth weight deviation and placental T2* at visit 2 was examined using the Wilcoxon Rank Sum test. The correlation between maternal blood pressure (systolic and diastolic) at each visit and placental T2* at visit 2 was also examined using the Wilcoxon Rank Sum test. For type 1 diabetes pregnancies, we investigated the correlation between HbA$_{1c}$ at each visit and birth weight deviation using linear regression and Pearson's coefficient, stratified on placental T2* z-score at visit 2.

CHAPTER 5. RESULTS

5.1. STUDY I & II: BASELINE CHARACTERISTICS AND OBSTETRIC OUTCOMES

Maternal baseline characteristics were different between women with T1DM and T2DM. Those with T1DM were younger, had a lower BMI, were more often nulliparous, were non-smokers, were more likely diagnosed with hypothyroidism, had a longer duration of diabetes and more diabetic complications, and had a higher HbA_{1c} in each trimester (Table 5.1.1).

Maternal Characteristics	Type 1 diabetes (n=180)	Type 2 diabetes (n=87)	*p* value
BMI (kg/m^2)	26.4 ± 4.9	32.7 ± 7.3	**<0.01**
Age at first trimester ultrasound (years)	29.5 ± 4.8	32.8 ± 5.2	**<0.01**
Nullipara	92 (51.1)	32 (36.8)	**0.03**
Conception - spontaneous	167 (92.8)	78 (89.7)	0.38
Ethnicity - Caucasian	179 (99.4)	68 (78.2)	**<0.01**
Smoking	16 (8.9)	18 (20.7)	**0.01**
Pregestational hypertension [a]	21 (11.7)	12 (13.8)	0.62
Hypothyroidism	23 (12.8)	3 (3.5)	**0.02**
Aspirin [b]	37 (20.6)	22 (25.3)	0.38
Duration of diabetes (years)	14.3 ± 8.7	3.4 ± 3.3	**<0.01**
Diabetic complications [c]	57 (32.0)	7 (8.05)	**<0.01**
HbA_{1c} at first trimester (mmol/mol) (%)	60.7 ± 14.4 7.7 ± 3.47	51.0 ± 13.8 6.82 ± 1.49	**<0.01**
HbA_{1c} at second trimester (mmol/mol) (%)	50.5 ± 11.2 6.77 ± 3.18	40.0 ± 7.4 5.81 ± 2.82	**<0.01**
HbA_{1c} at third trimester (mmol/mol) (%)	52.8 ± 11.9 6.98 ± 3.24	42.9 ± 9.4 6.08 ± 3.01	**<0.01**

Table 5.1.1 *Maternal characteristics by diabetes type.*
Data are presented as n (%) or mean ± SD.
Body mass index (BMI).
[a] Defined as hypertension diagnosed and medicated before pregnancy.
[b] Treatment with 150 mg aspirin started before 16 weeks of gestation.
[c] Retinopathy, nephropathy, or neuropathy diagnosed before pregnancy.

Regarding obstetric outcomes there were also several differences. Pregnancies complicated by T1DM had higher birth weight and higher incidences of preterm delivery and neonatal hypoglycaemia, while post-partum haemorrhage occurred more often in T2DM pregnancies (Table 5.1.2). The risk of LGA in T1DM remained significantly increased even when adjusted for maternal BMI, parity, duration of diabetes, and first trimester HbA_{1c} (OR = 3.42, p < 0.01).

Obstetric outcomes	Type 1 diabetes (n=180)	Type 2 diabetes (n=87)	p value
Gender (girl)	90 (50.0)	46 (52.9)	0.66
Birth weight (g)	3564 ± 742	3332 ± 838	**0.02**
Birth weight deviation (%)	25.6 ± 21.3	11.3 ± 23.8	**<0.01**
Large-for-gestational-age [a]	118 (65.6)	36 (41.4)	**<0.01**
Appropriate-for-gestational-age [b]	58 (32.2)	41 (47.1)	**0.02**
Small-for-gestational-age [c]	4 (2.2)	10 (11.5)	**<0.01**

Hypertensive disorders
    Gestational hypertension
    Preeclampsia
	
	14 (7.8)
	15 (8.3)
		
		14 (16.1)
		9 (10.3)
			
			0.04
			0.59

Gestational week at birth	36+2 ± 2+0	36+6 ± 2+3	**0.01**
Preterm delivery < 37+0 weeks < 34+0 weeks	 95 (52.8) 21 (11.7)	 24 (27.6) 5 (5.8)	 **<0.01** 0.13
Caesarean section Elective	123(68.3) 67 (54.5)	54 (62.1) 28 (51.9)	0.31 0.75
Post-partum haemorrhage [d]	11 (8.7)	11 (23.9)	**0.01**
Neonatal hypoglycaemia [e] Severe	131(72.8) 61 (46.6)	46 (52.9) 10 (21.7)	**<0.01** **<0.01**
Apgar score < 7 at 5 minutes	3 (1.7)	2 (2.3)	0.72
Umbilical cord artery pH <7.0	5 (2.8)	3 (3.5)	0.76

Table 5.1.2 *Obstetric outcomes by diabetes type.*
Data are presented as n (%) or mean ± SD.
[a] Defined as birth weight deviation ≥ 15%
[b] Defined as birth weight deviation < 15% and > -15%
[c] Defined as birth weight deviation ≤ -15%
[c] Blood volume ≥ 1000 ml
[b] Defined as neonatal blood glucose < 2.5 mmol/l measured within two hours after birth. Severe neonatal hypoglycaemia < 1.5 mmol/l

5.2. STUDY I: FETAL GROWTH IN PGDM PREGNANCIES

5.2.1. TYPE 1 DIABETES

The prevalence of LGA at birth in T1DM was 66% (118/180). When stratified on birth weight groups (LGA versus non-LGA) there were no differences in maternal characteristics, except for a higher HbA_{1c} in the second and third trimesters in the LGA group (Table 5.2.1).

Type 1 diabetes Maternal Characteristics	Non-LGA (n=62)	LGA (n=118)	*p* value
BMI (kg/m²)	26.0 ± 4.8	26.6 ± 4.9	0.45
Age at first trimester ultrasound (years)	29.9 ± 5.2	29.2 ± 4.6	0.41
Nullipara	35 (56.5)	57 (48.3)	0.30
Conception - spontaneous	56 (90.3)	111 (94.1)	0.36
Ethnicity - Caucasian	61 (98.4)	118 (100)	0.17
Smoking	5 (8.1)	11 (9.3)	0.78
Pregestational hypertension [a]	11 (17.7)	10 (8.5)	0.07
Hypothyroidism	8 (12.9)	15 (12.7)	0.97
Aspirin [b]	10 (16.1)	27 (22.9)	0.29
Duration of diabetes (years)	14.3 ± 9.2	14.3 ± 8.4	0.99
Diabetic complications [c]	21 (34.4)	36 (30.8)	0.62
HbA_{1c} at first trimester (mmol/mol) (%)	59.0 ± 17.4 7.55 ± 3.74	61.6 ± 12.6 7.79 ± 3.30	0.25
HbA_{1c} at second trimester (mmol/mol) (%)	47.9 ± 12.4 6.53 ± 3.28	51.8 ± 10.3 6.89 ± 3.09	**0.02**
HbA_{1c} at third trimester (mmol/mol) (%)	49.2 ± 12.0 6.65 ± 3.25	54.7 ± 11.6 7.15 ± 3.21	**<0.01**

Table 5.2.1 *Maternal characteristics in type 1 diabetes divided in birth weight groups.*
Data are presented as n (%) or mean ± SD.
Body mass index (BMI).
[a] Defined as hypertension diagnosed and medicated before pregnancy.
[b] Treatment with 150 mg aspirin started before 16 weeks of gestation.
[c] Retinopathy, nephropathy, or neuropathy diagnosed before pregnancy.

Regarding obstetric outcomes, the two birth weight groups were comparable except for gender and preterm birth where the LGA group had a higher incidence of boys (56% vs. 39%) and preterm birth (59% vs. 40%) (Table 5.2.2).

Type 1 diabetes Obstetric outcomes	Non-LGA (n=62)	LGA (n=118)	*p* value
Gender (girl)	38 (61.3)	52 (44.1)	**0.03**
Birth weight (g)	2951 ± 660	3887 ± 556	**<0.01**
Birth weight deviation (%)	3.75 ± 9.95	37.1 ± 15.9	**<0.01**

Hypertensive disorders
    Gestational hypertension
    Preeclampsia
	
	4 (6.45)
	6 (9.68)
		
		10 (8.47)
		9 (7.63)
			
			0.63
			0.64

Gestational week at birth	36+1 ± 2+5	36+2 ± 1+4	0.77
Preterm delivery < 37+0 weeks < 34+0 weeks	 25 (40.3) 11 (17.7)	 70 (59.3) 10 (8.47)	 **0.02** 0.07
Caesarean section Elective	41 (66.1) 18 (43.9)	82 (69.5) 49 (59.8)	0.65 0.10
Post-partum haemorrhage [a]	5 (10.9)	6 (7.4)	0.51
Neonatal hypoglycaemia [b] Severe	40 (64.5) 19 (47.5)	91 (77.1) 42 (46.2)	0.07 0.89
Apgar score < 7 at 5 minutes	1 (1.6)	2 (1.7)	0.97
Umbilical cord artery pH <7.0	0 (0.0)	5 (4.2)	0.10

***Table 5.2.2** Obstetric outcomes in type 1 diabetes divided in birth weight groups.
Data are presented as n (%) or mean ± SD.
[a] Blood volume ≥ 1000 ml.
[b] Defined as neonatal blood glucose < 2.5 mmol/l measured within two hours after birth. Severe neonatal hypoglycaemia < 1.5 mmol/l.*

In T1DM pregnancies, LGA neonates were characterized by a general fetal overgrowth when compared to non-LGA neonates affecting all fetal biometry: increased AC (20-34 weeks), HC (20-34 weeks), and FL (28-34 weeks) and reduced HC/AC-ratio (28-34 weeks). (Figure 5.2.1, Table 5.2.3).
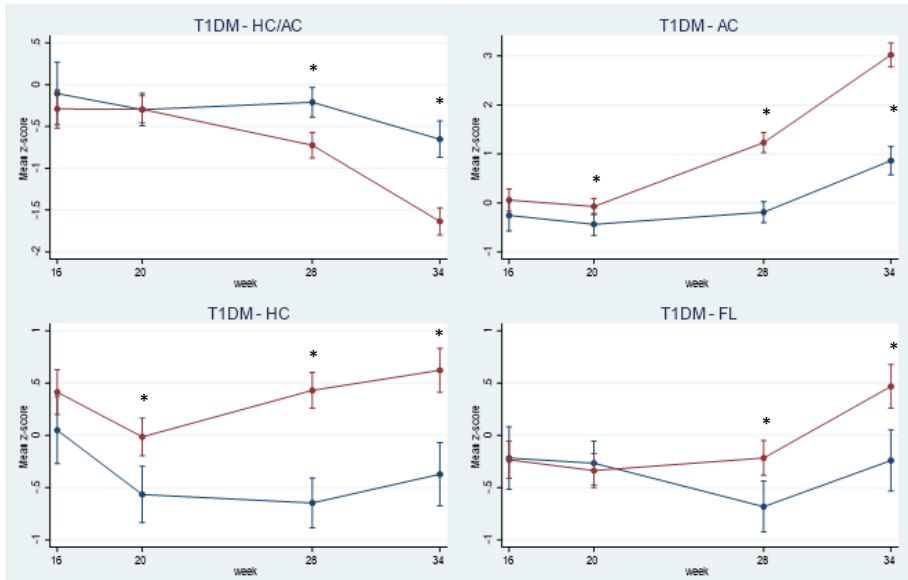
Figure 5.2.1 *Graphs comparing non-LGA neonates (Blue) and LGA neonates (Red) in type 1 diabetes (T1DM) pregnancies.*

The mean fetal biometry z-score is marked with error bars (95%CI) at each visit. Significant differences between groups (p-values <0.05) are marked with *.

Head circumference/ Abdominal circumference-ratio (HC/AC), Abdominal circumference (AC), Head circumference (HC), Femur Length (FL).

Type 1 diabetes	Non-LGA (n=62)	LGA (n=118)	*p* value
16w			
AC z-score (n = 127)	-0.25 ± 1.00	0.06 ± 1.07	0.12
HC/AC z-score (n = 127)	-0.10 ± 1.18	-0.29 ± 1.07	0.38
HC z-score (n = 152)	0.05 ± 1.14	0.41 ± 1.08	0.06
FL z-score (n = 148)	-0.22 ± 1.05	-0.23 ± 0.89	0.92
20w (n = 180)			
AC z-score	-0.44 ± 0.89	-0.07 ± 0.91	**0.01**
HC/AC z-score	-0.30 ± 0.77	-0.29 ± 0.88	0.98
HC z-score	-0.57 ± 1.06	-0.01 ± 0.98	**<0.01**
FL z-score	-0.27 ± 0.82	-0.34 ± 0.90	0.60
28w (n = 177)			
AC z-score	-0.19 ± 0.83	1.23 ± 1.11	**<0.01**
HC/AC z-score	-0.21 ± 0.69	-0.72 ± 0.82	**<0.01**
HC z-score	-0.65 ± 0.93	0.43 ± 0.94	**<0.01**
FL z-score	-0.68 ± 0.95	-0.22 ± 0.90	**<0.01**
34w (n = 157)			
AC z-score	0.86 ± 1.03	3.03 ± 1.26	**<0.01**
HC/AC z-score	-0.65 ± 0.79	-1.63 ± 0.84	**<0.01**
HC z-score	-0.37 ± 1.09	0.62 ± 1.09	**<0.01**
FL z-score	-0.24 ± 1.05	0.47 ± 1.08	**<0.01**

Table 5.2.3 *Mean fetal biometry z-score in type 1 diabetes divided in birth weight groups. Data are presented as mean ± SD.*

Abdominal Circumference (AC), Estimated Fetal Weight (EFW), Femur Length (FL), Head Circumference (HC), Head Circumference/Abdominal Circumference ratio (HC/AC), Large-for-Gestational-Age (LGA), Non-Large-for-Gestational-Age (Non-LGA).

The performance of AC, HC, HC/AC-ratio and FL, regarding the prediction of LGA at birth, is increased for each fetal biometry with increasing gestational age (Table 5.2.4). There was no difference in the predictive performance between AC and EFW, and both were better predictors of LGA than the HC/AC-ratio at 28 and 34 weeks' gestation ($p < 0.01$) (Figure 5.2.2, Table 5.2.4).

Type 1 diabetes	OR	*p* value	AUC
16w			
AC z-score (n = 127)	1.33	0.12	0.58
HC/AC z-score (n = 127)	0.86	0.38	0.55
HC z-score (n = 152)	1.35	0.06	0.59
FL z-score (n = 148)	0.98	0.92	0.48
20w (n = 180)			
AC z-score	1.58	**0.01**	0.61
HC/AC z-score	1.01	0.98	0.49
HC z-score	1.73	**<0.01**	0.64
FL z-score	0.91	0.60	0.54
28w (n = 177)			
AC z-score	5.13	**<0.01**	0.85
HC/AC z-score	0.42	**<0.01**	0.67*
HC z-score	3.58	**<0.01**	0.79
FL z-score	1.72	**<0.01**	0.65*
EFW (%)	1.21	**<0.01**	0.86†
34w (n = 157)			
AC z-score	8.41	**<0.01**	0.93
HC/AC z-score	0.23	**<0.01**	0.80*
HC z-score	2.46	**<0.01**	0.73*
FL z-score	1.88	**<0.01**	0.68*
EFW (%)	1.22	**<0.01**	0.92†

Table 5.2.4 *Univariate analysis of fetal biometry z-score predicting LGA in type 1 diabetes pregnancies.*

Abdominal Circumference (AC), Area Under the receiver operating characteristic Curve (AUC), Estimated Fetal Weight (EFW), Femur Length (FL), Head Circumference (HC), Head Circumference/Abdominal Circumference ratio (HC/AC), Odds Ratio (OR).

* The predictive performance of AC was significantly better (p < 0.05)

† The predictive performance was significantly better than HC/AC-ratio (p < 0.05)
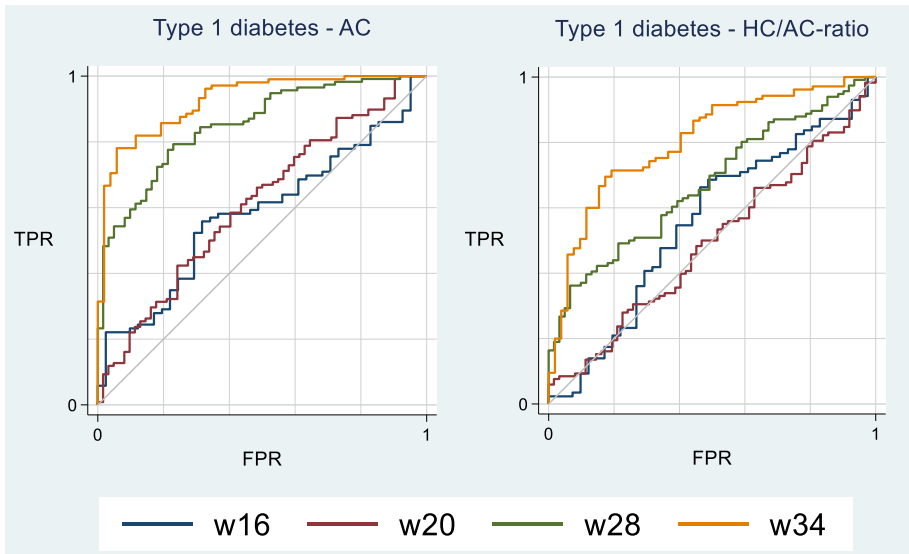
Figure 5.2.2 *Graphs comparing AUC for AC and HC/AC-ratio in T1DM pregnancies at each visit.*

The multivariate analysis including maternal characteristics and HbA_{1c} did not significantly improve the predictive performance when compared to the univariate analysis of AC or HC/AC-ratio (Table 5.2.5).

Type 1 diabetes		OR	*p* value	AUC	*p* value$_{DeLong}$
16w (n = 127)					
HC/AC z-score	Univariate	0.86	0.38	0.55	0.09
	Multivariate	0.94	0.74	0.66	
AC z-score	Univariate	1.33	0.12	0.58	0.09
	Multivariate	1.29	0.20	0.67	
20w (n = 180)					
HC/AC z-score	Univariate	1.01	0.98	0.50	**0.03**
	Multivariate	1.01	0.97	0.63	
AC z-score	Univariate	1.58	**0.01**	0.61	0.12
	Multivariate	1.66	**0.01**	0.67	
28w (n = 177)					
HC/AC z-score	Univariate	0.42	**<0.01**	0.67	0.10
	Multivariate	0.46	**<0.01**	0.72	
AC z-score	Univariate	5.13	**<0.01**	0.85	0.27
	Multivariate	5.16	**<0.01**	0.86	
34w (n = 157)					
HC/AC z-score	Univariate	0.23	**<0.01**	0.80	0.55
	Multivariate	0.24	**<0.01**	0.81	
AC z-score	Univariate	8.41	**<0.01**	0.93	0.33
	Multivariate	10.5	**<0.01**	0.93	

Table 5.2.5 *Comparison of univariate and multivariate analysis HC/AC-ratio z-score and AC z-score predicting LGA in type 1 diabetes.*

Adjusted for maternal age, BMI, smoking, ethnicity, parity, mode of conception and first trimester HbA1c (16 weeks), second trimester HbA1c (20 weeks) and third trimester HbA1c (28 and 34 weeks).

The AUC for the univariate HC/AC-ratio z-score and AC z-score is compared to the multivariate HC/AC-ratio z-score and AC z-score using the DeLong method and the p value for that comparison is p value$_{DeLong}$.

Abdominal Circumference (AC), Area Under the receiver operating characteristic Curve (AUC), Head Circumference (HC), Head Circumference/Abdominal Circumference ratio (HC/AC), Odds Ratio (OR).

5.2.2. TYPE 2 DIABETES

In type 2 diabetes pregnancies, the incidence of LGA at birth was 41% (36/87). When divided into birth weight groups, there were no differences in maternal characteristics, except for a higher incidence of hypothyroidism and a higher HbA$_{1c}$ in the second and third trimesters in the LGA group (Table 5.2.6).

Type 2 diabetes Maternal Characteristics	Non-LGA (n=51)	LGA (n=36)	*p* value
BMI (kg/m^2)	32.2 ± 7.7	33.4 ± 6.8	0.47
Age at first trimester ultrasound (years)	33.1 ± 5.3	32.4 ± 4.0	0.54
Nullipara	18 (35.3)	14 (38.9)	0.73
Conception - spontaneous	48 (94.1)	30 (83.3)	0.10
Ethnicity - Caucasian	39 (76.5)	29 (80.6)	0.65
Smoking	13 (25.5)	5 (13.9)	0.19
Pregestational hypertension [a]	5 (9.8)	7 (19.4)	0.20
Hypothyroidism	0 (0)	3 (8.3)	**0.04**
Aspirin [b]	16 (31.4)	6 (16.7)	0.12
Duration of diabetes (years)	3.19 ± 3.08	3.58 ± 3.60	0.58
Diabetic complications [c]	4 (7.8)	3 (8.3)	0.93
HbA$_{1c}$ at first trimester (mmol/mol) (%)	49.7 ± 12.0 6.70 ± 3.25	53.1 ± 16.2 7.01 ± 3.63	0.27
HbA$_{1c}$ at second trimester (mmol/mol) (%)	37.8 ± 6.11 5.61 ± 2.71	43.2 ± 7.96 6.10 ± 2.88	**<0.01**
HbA$_{1c}$ at third trimester (mmol/mol) (%)	38.8 ± 7.22 5.70 ± 2.81	48.7 ± 9.27 6.61 ± 3.00	**<0.01**

Table 5.2.6 *Maternal characteristics in type 2 diabetes divided in birth weight groups.*
Data are presented as n (%) or mean $\pm$ SD.
Body mass index (BMI).
[a] Defined as hypertension diagnosed and medicated before pregnancy.
[b] Treatment with 150 mg aspirin started before 16 weeks of gestation.
[c] Retinopathy, nephropathy, or neuropathy diagnosed before pregnancy.

Regarding obstetric outcomes, the two birth weight groups were comparable except for Caesarean section and umbilical cord artery pH < 7.0 where the LGA group had a higher incidence (Table 5.2.7).

Type 2 diabetes Obstetric outcomes	Non-LGA (n=51)	LGA (n=36)	*p* value
Gender (girl)	29 (56.9)	17 (47.2)	0.38
Birth weight (g)	2854 ± 700	4010 ± 466	**<0.01**
Birth weight deviation (%)	-4.6 ± 12.7	33.8 ± 16.5	**<0.01**

Hypertensive disorders
    Gestational hypertension
    Preeclampsia
	
	10 (19.6)
	6 (11.8)
		
		4 (11.1)
		3 (8.3)
			
			0.29
			0.61

Gestational week at birth	36+5 ± 2+6	37+1 ± 1+1	0.57
Preterm delivery < 37+0 weeks < 34+0 weeks	 13 (25.5) 5 (9.8)	 11 (30.6) 0 (0.0)	 0.60 0.05
Caesarean section Elective	27 (52.9) 9 (33.3)	27 (75.0) 19 (70.4)	**0.04** **0.01**
Post-partum haemorrhage [a]	4 (16.0)	7 (33.3)	0.17
Neonatal hypoglycaemia [b] Severe	23 (45.1) 5 (21.7)	23 (63.9) 5 (21.7)	0.08 1.00
Apgar score < 7 at 5 minutes	2 (3.9)	0 (0.0)	0.23
Umbilical cord artery pH <7.0	0 (0.0)	3 (8.3)	**0.04**

Table 5.2.7 *Obstetric outcomes in type 2 diabetes divided in birth weight groups.*
Data are presented as n (%) or mean ± SD.
[a] Blood volume ≥ 1000 ml
[b] Defined as neonatal blood glucose < 2.5 mmol/l measured within two hours after birth. Severe neonatal hypoglycaemia < 1.5 mmol/l.

In T2DM pregnancies, LGA neonates were characterized by a general fetal overgrowth affecting all fetal biometry when compared to non-LGA neonates; increased AC (all visits); increased HC (20-34 weeks); increased FL (28-34 weeks); and reduced HC/AC-ratio (28-34 weeks) (Figure 5.2.3, Table 5.2.8).
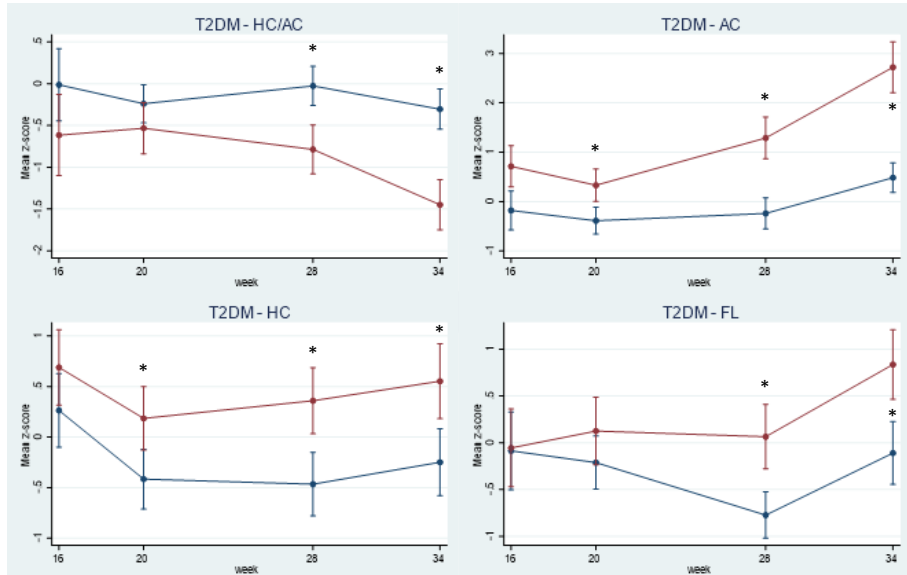
Figure 5.2.3 *Graphs comparing non-LGA neonates (Blue) and LGA neonates (Red) in type 2 diabetes (T2DM) pregnancies.*

*The mean fetal biometry z-score is marked with error bars (95%CI) at each visit. Significant differences between groups (p-values <0.05) are marked with *.*

Head circumference/ Abdominal circumference-ratio (HC/AC), Abdominal circumference (AC), Head circumference (HC), Femur Length (FL).

Type 2 diabetes	Non-LGA (n=51)	LGA (n=36)	*p* value
16w			
AC z-score (n = 58)	-0.18 ± 1.13	0.71 ± 0.99	**<0.01**
HC/AC z-score (n = 58)	-0.01 ± 1.24	-0.62 ± 1.15	0.07
HC z-score (n = 68)	0.26 ± 1.14	0.69 ± 0.96	0.11
FL z-score (n = 65)	-0.09 ± 1.25	-0.06 ± 1.07	0.92
20w (n = 81)			
AC z-score	-0.39 ± 0.92	0.33 ± 0.94	**<0.01**
HC/AC z-score	-0.24 ± 0.77	-0.53 ± 0.88	0.12
HC z-score	-0.42 ± 1.01	0.18 ± 0.90	**0.01**
FL z-score	-0.21 ± 0.96	0.13 ± 1.03	0.14
28w (n = 84)			
AC z-score	-0.24 ± 1.10	1.29 ± 1.24	**<0.01**
HC/AC z-score	-0.03 ± 0.81	-0.79 ± 0.85	**<0.01**
HC z-score	-0.47 ± 1.09	0.36 ± 0.95	**<0.01**
FL z-score	-0.77 ± 0.86	0.06 ± 1.00	**<0.01**
34w (n = 80)			
AC z-score	0.48 ± 1.00	2.72 ± 1.50	**<0.01**
HC/AC z-score	-0.30 ± 0.80	-1.45 ± 0.87	**<0.01**
HC z-score	-0.25 ± 1.10	0.55 ± 1.08	**<0.01**
FL z-score	-0.11 ± 1.11	0.84 ± 1.08	**<0.01**

***Table 5.2.8** Mean fetal biometry z-score in type 2 diabetes divided in birth weight groups. Data are presented as mean ± SD. Abdominal Circumference (AC), Estimated Fetal Weight (EFW), Femur Length (FL), Head Circumference (HC), Head Circumference/Abdominal Circumference ratio (HC/AC), Large-for-Gestational-Age (LGA), Non-Large-for-Gestational-Age (Non-LGA).*

Regarding the prediction of LGA at birth, the performance of AC, HC, HC/AC-ratio and FL is presented in Table 5.1.11. We found no difference in the predictive performance between AC and EFW, and both were a better predictor of LGA than HC/AC ration at 28 and 34 weeks' gestation (p < 0.01) (Figure 5.2.4, Table 5.2.9).

Type 2 diabetes	OR	p	AUC
16w			
AC z-score (n = 58)	2.19	**0.01**	0.72
HC/AC z-score (n = 58)	0.64	0.07	0.65
HC z-score (n = 68)	1.47	0.11	0.63
FL z-score (n = 65)	1.02	0.91	0.50
20w (n = 81)			
AC z-score	2.30	**<0.01**	0.70
HC/AC z-score	0.64	0.12	0.60*
HC z-score	1.92	**0.01**	0.67
FL z-score	1.42	0.14	0.59
28w (n = 84)			
AC z-score	3.45	**<0.01**	0.83
HC/AC z-score	0.32	**<0.01**	0.73*
HC z-score	2.21	**<0.01**	0.72*
FL z-score	2.67	**<0.01**	0.73
EFW (%)	1.18	**<0.01**	0.87†
34w (n = 80)			
AC z-score	4.99	**<0.01**	0.90
HC/AC z-score	0.17	**<0.01**	0.84
HC z-score	1.98	**<0.01**	0.71*
FL z-score	2.18	**<0.01**	0.72*
EFW (%)	1.15	**<0.01**	0.90

Figure 5.2.9 *Univariate analysis of fetal biometry z-score predicting LGA in type 2 diabetes.*

Abdominal Circumference (AC), Area Under the receiver operating characteristic Curve (AUC), Estimated Fetal Weight (EFW), Femur Length (FL), Head Circumference (HC), Head Circumference/Abdominal Circumference ratio (HC/AC), Odds Ratio (OR).

* The predictive performance of AC was significantly better (p < 0.05)

† The predictive performance was significantly better than HC/AC-ratio (p < 0.05)
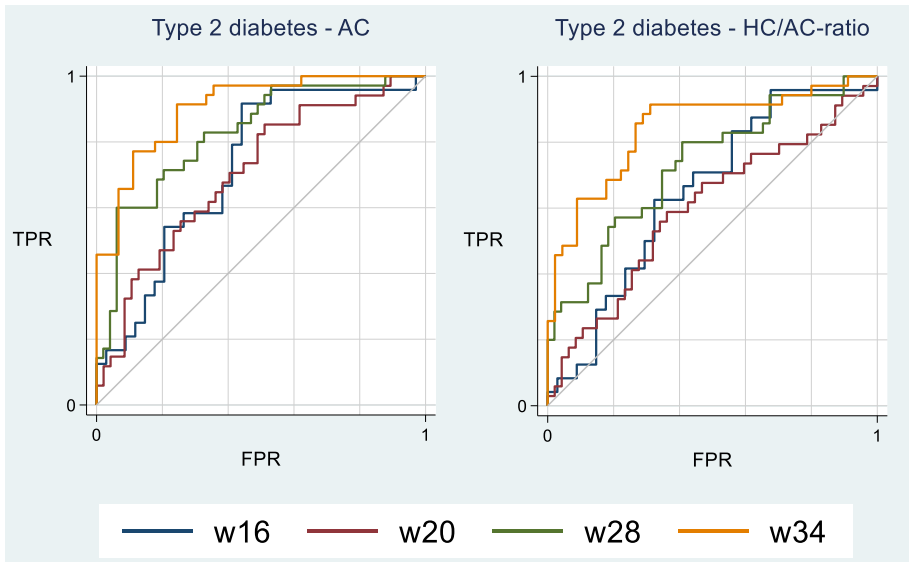
Figure 5.2.4 *Graphs comparing AUC for AC and HC/AC-ratio in T2DM pregnancies at each visit.*

The multivariate analysis including maternal characteristics and maternal HbA$_{1c}$ at each trimester improved the predictive performance of the univariate analysis from 20 weeks' gestation onwards for both AC and HC/AC-ratio (Table 5.2.10).

Type 2 diabetes		OR	*p* value	AUC	*p* value$_{DeLong}$
16w (n = 58)					
HC/AC z-score	Univariate	0.64	0.07	0.64	0.16
	Multivariate	0.62	0.09	0.75	
AC z-score	Univariate	2.19	**0.01**	0.71	0.14
	Multivariate	2.39	**0.01**	0.80	
20w (n = 81)					
HC/AC z-score	Univariate	0.64	0.12	0.59	**0.01**
	Multivariate	0.72	0.30	0.75	
AC z-score	Univariate	2.30	**<0.01**	0.69	**<0.05**
	Multivariate	2.51	**0.01**	0.80	
28w (n = 84)					
HC/AC z-score	Univariate	0.32	**<0.01**	0.73	**<0.01**
	Multivariate	0.11	**<0.01**	0.92	
AC z-score	Univariate	3.45	**<0.01**	0.83	**<0.01**
	Multivariate	11.7	**<0.01**	0.95	
34w (n = 80)					
HC/AC z-score	Univariate	0.17	**<0.01**	0.84	**0.02**
	Multivariate	0.15	**<0.01**	0.93	
AC z-score	univariate	4.99	**<0.01**	0.90	**0.04**
	multivariate	8.59	**<0.01**	0.97	

Table 5.2.10 Table 5.2.5 *Comparison of univariate and multivariate analysis HC/AC-ratio z-score and AC z-score predicting LGA in type 2 diabetes.*

Adjusted for maternal age, BMI, smoking, ethnicity, parity, mode of conception and first trimester HbA1c (16 weeks), second trimester HbA1c (20 weeks) and third trimester HbA1c (28 and 34 weeks).

The AUC for the univariate HC/AC-ratio z-score and AC z-score is compared to the multivariate HC/AC-ratio z-score and AC z-score using the DeLong method and the p value for that comparison is p value$_{DeLong}$.

Abdominal Circumference (AC), Area Under the receiver operating characteristic Curve (AUC), Head Circumference (HC), Head Circumference/Abdominal Circumference ratio (HC/AC), Odds Ratio (OR).

5.3. STUDY II: MATERNAL GLYCAEMIC LEVEL AND BIRTH WEIGHT IN PGDM

In Study II the cohort was divided regarding maternal glycaemic level at the first trimester. One woman with type 1 diabetes and 3 women with type 2 diabetes did not have a first trimester HbA_{1c} value, so these pregnancies were therefore excluded.

5.3.1. TYPE 1 DIABETES

In the study cohort 30% (53/179) of T1DM pregnancies were well-regulated (HbA_{1c} <53mmol/mol) in the first trimester. When comparing maternal characteristics between well-regulated and dysregulated in the first trimester, there was a higher incidence of nullipara and a lower incidence spontaneous conception and pregestational hypertension among those who were well-regulated (Table 5.3.1).

Type 1 diabetes Maternal Characteristics	First trimester Well-regulated (HbA_{1c} <53) n=53	First trimester Dysregulated (HbA_{1c} ≥53) n=126	p value
BMI (kg/m²)	26.9 ± 4.8	26.2 ± 4.9	0.42
Age at first trimester ultrasound (years)	29.4 ± 3.9	29.4 ± 5.1	0.98
Nullipara	36 (67.9%)	56 (44.4%)	**<0.01**
Conception - spontaneous	46 (86.8%)	121 (96.0%)	**0.02**
Ethnicity - Caucasian	52 (98.1%)	126 (100%)	0.12
Smoking	3 (5.7%)	13 (10.3%)	0.32
Pregestational hypertension [a]	2 (3.8%)	19 (15.1%)	**0.03**
Hypothyroidism	6 (11.3%)	17 (13.5%)	0.69
Aspirin [b]	11 (20.8%)	26 (20.6%)	0.99
Duration of diabetes (years)	13.2 ± 8.7	14.8 ± 8.7	0.26
Diabetic complications [c]	15 (28.9%)	42 (33.6%)	0.54
HbA_{1c} at first trimester (mmol/mol) (%)	46 ± 5 6.4 ± 2.6	67 ± 13 8.3 ± 3.3	**<0.01**
HbA_{1c} at second trimester (mmol/mol) (%)	41 ± 5 5.9 ± 2.6	55 ± 11 7.2 ± 3.1	**<0.01**
HbA_{1c} at third trimester (mmol/mol) (%)	44 ± 6 6.2 ± 2.7	57 ± 12 7.3 ± 3.2	**<0.01**

***Table 5.3.1** Maternal characteristics in type 1 diabetes divided by first trimester glycaemic level. Data are presented as n (%) or mean ± SD. Body mass index (BMI)*
[a] Defined as hypertension diagnosed and medicated before pregnancy.
[b] Treatment with 150 mg aspirin started before 16 weeks of gestation.
[c] Retinopathy, nephropathy, or neuropathy diagnosed before pregnancy.

Regarding obstetric outcomes, those who were well-regulated in the first trimester had a lower incidence of obstetric complications such as LGA at birth, preterm birth, Caesarean section, and severe neonatal hypoglycaemia (Table 5.3.2).

Type 1 diabetes Obstetric outcomes	First trimester Well-regulated (HbA$_{1c}$ <53) n=53	First trimester Dysregulated (HbA$_{1c}$ ≥53) n=126	*p* value
Gender (girl)	28 (52.8)	61 (48.4)	0.60
Birth weight (g)	3525 ± 599	3583 ± 798	0.64
Birth weight deviation (%)	19.5 ± 19.8	28.4 ± 21.4	**0.01**
Large-for-gestational-age [a]	27 (50.9)	91 (72.2)	**0.01**
Appropriate-for-gestational-age [b]	25 (47.2)	32 (25.4)	**<0.01**
Small-for-gestational-age [c]	1 (1.9)	3 (2.4)	0.84
Hypertensive disorders Gestational hypertension Preeclampsia	3 (5.7) 3 (5.7)	11 (8.7) 12 (9.5)	0.49 0.39
Gestational week at birth	36+6 ± 1+4	35+6 ± 2+1	**<0.01**
Preterm delivery < 37+0 weeks < 34+0 weeks	18 (34.0) 3 (5.7)	77 (61.1) 18 (14.3)	**<0.01** 0.10
Caesarean section Elective	27 (50.9) 11 (40.7)	95 (75.4) 55 (57.9)	**<0.01** 0.11
Post-partum haemorrhage [d]	4 (10.5)	7 (8.0)	0.64
Neonatal hypoglycaemia [e] Severe	34 (64.2) 11 (32.4)	96 (76.2) 50 (52.1)	0.10 **<0.05**
Apgar score < 7 at 5 minutes	1 (1.9)	2 (1.6)	0.89
Umbilical cord artery pH <7.0	2 (3.8)	3 (2.4)	0.61

***Table 5.3.2** Obstetric outcomes in type 1 diabetes divided by first trimester glycaemic level. Data are presented as n (%) or mean ± SD.*
[a] Defined as birth weight deviation ≥ 15%
[b] Defined as birth weight deviation < 15% and > -15%
[c] Defined as birth weight deviation ≤ -15%
[d] Blood volume ≥ 1000 ml
[e] Defined as neonatal blood glucose < 2.5 mmol/l measured within two hours after birth. Severe neonatal hypoglycaemia < 1.5 mmol/l

Among T1DM pregnancies who were well-regulated in the first trimester (n=53), there was a positive linear correlation between first trimester HbA$_{1c}$ and birth weight deviation (coef (95%CI) 1.68 (0.63-2.73) %/(mmol/mol), p < 0.01, R^2 = 0.17). In contrast, in T1DM pregnancies that were dysregulated in the first trimester (n=126), although not statistically significant, the coefficient was negative (coef (95%CI) -0.24 (-0.54-0.06) %/(mmol/mol), p = 0.11, R^2 = 0.02) (Figure 5.3.1).
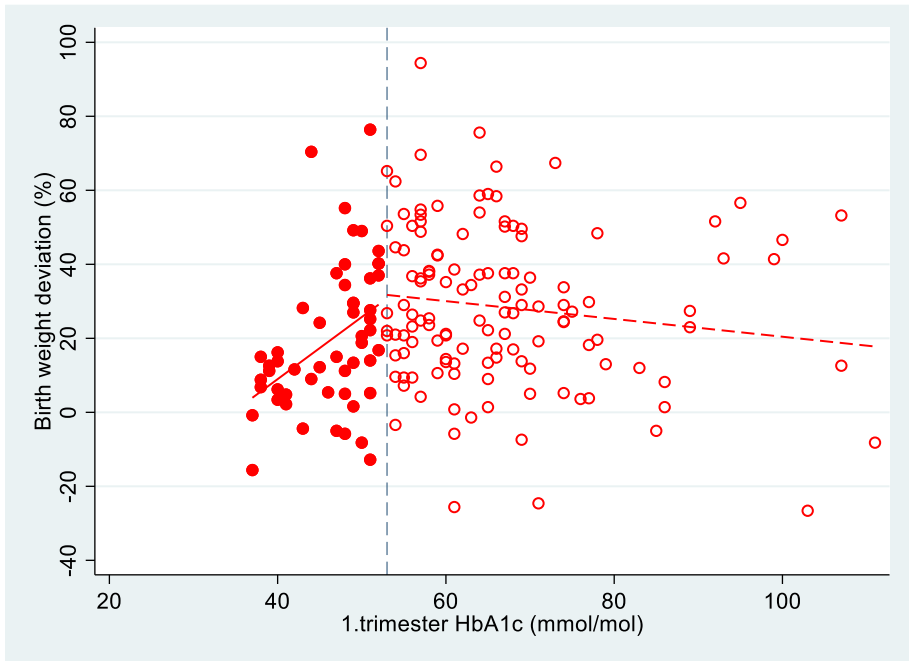
HbA$_{1c}$	n	Coef	R^2	p value	Interaction p value
All	179	0.10	0.005	0.34	
<53	53	1.68	0.168	**<0.01**	**<0.01**
≥53	126	-0.24	0.021	0.11	

Figure 5.3.1 *Scatterplot depicting the correlation between birth weight deviation (%) and first trimester HbA$_{1c}$ (mmol/mol) in type 1 diabetes pregnancies. The correlation is investigated by simple linear regression stratified on maternal glycaemic control using HbA$_{1c}$ 53 mmol/mol (7.0%) as a cutpoint.*

Pregnancies that were well-regulated in first trimester are represented by the red dots and the full red regression line, pregnancies that were dysregulated in first trimester are represented by the red circles and the red dotted regression line.

Below the figure the corresponding table present the data from the correlation analysis. Linear regression coefficient (Coef.) in %/(mmol/mol), Pearson's correlation coefficient (R^2).

In those T1DM pregnancies that were well-regulated at first trimester but became dysregulated in the third trimester, birth weight deviation was significantly increased when compared to those who remained well-regulated (median birth weight deviation (IQR); became dysregulated (n=47) 13.3 (5.0–27.6) % ; remained well-regulated (n=6) 37.3 (29.6–49.0) %, p = 0.01). In contrast, in those who were dysregulated at first trimester, birth weight deviation was independent of third trimester glycaemic control (median birth weight deviation (IQR); became well-regulated (n=47) 22.2 (14.8–38.6) % ; remained dysregulated (n=78) 29.0 (13.4–46.6) % (p = 0.55)) (Figure 5.3.2, Table 5.3.3).
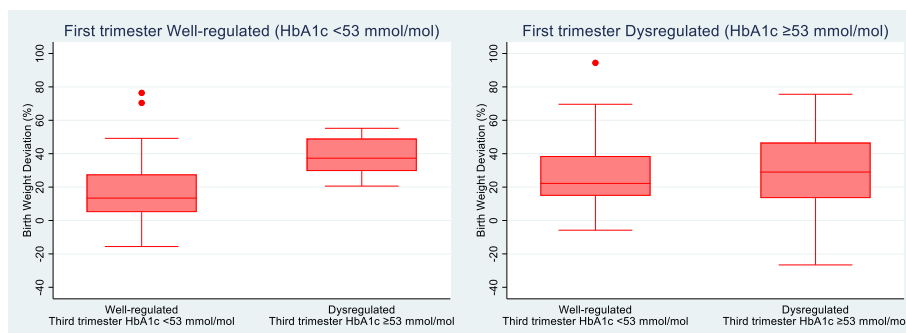
Figure 5.3.2 *Boxplot comparing birth weight deviation according to third trimester glycaemic level in type 1 diabetes pregnancies. Right: well-regulated in the first trimester, left: dysregulated in the first trimester.*

First trimester	Third trimester	Birth weight deviation (%) Median (IQR)	*p* value
Well-regulated HbA1c <53 (n=53)	Remained well-regulated HbA1c <53 (n=47)	13.4 (5.0 – 27.6)	**0.01**
	Became dysregulated HbA1c ≥53 (n=6)	37.3 (29.6 – 49.0)	
Dysregulated HbA1c ≥53 (n=125)	Remained dysregulated HbA1c ≥53 (n=78)	29.0 (13.4 – 46.6)	0.55
	Became well-regulated HbA1c <53 (n=47)	22.2 (14.8 – 38.6)	

Table 5.3.3 *Comparison between median birth weight deviation (%) and third trimester glycaemic level stratified on first trimester glycaemic level in type 1 diabetes pregnancies.*

5.3.2. TYPE 2 DIABETES

In the study cohort, 64% (54/84) of T2DM pregnancies were well regulated (HbA_{1c} <53mmol/mol) in the first trimester. When comparing maternal characteristics between well-regulated and dysregulated pregnancies in the first trimester, there were lower incidences of pregestational hypertension and diabetic complications among those who were well-regulated (Table 5.3.4).

Type 2 diabetes Maternal Characteristics	First trimester Well-regulated (HbA_{1c} <53) n=54	First trimester Dysregulated (HbA_{1c} ≥53) n=30	*p* value
BMI (kg/m^2)	31.7 ± 7.3	34.9 ± 7.4	0.06
Age at first trimester ultrasound (years)	33.1 ± 5.4	32.3 ± 4.7	0.53
Nullipara	17 (31.5%)	15 (50.0%)	0.09
Conception - spontaneous	47 (87.0%)	28 (93.3%)	0.37
Ethnicity - Caucasian	42 (77.8%)	25 (83.3%)	0.54
Smoking	11 (20.4%)	7 (23.3%)	0.75
Pregestational hypertension [a]	3 (5.6%)	9 (30.0%)	**<0.01**
Hypothyroidism	2 (3.7%)	1 (3.3%)	0.93
Aspirin [b]	12 (22.2%)	10 (33.3%)	0.27
Duration of diabetes (years)	2.9 ± 2.8	3.9 ± 3.6	0.15
Diabetic complications [c]	1 (1.9%)	6 (20.0%)	**<0.01**
HbA_{1c} at first trimester (mmol/mol) (%)	43 ± 6 6.1 ± 2.7	66 ± 11 8.2 ± 3.2	**<0.01**
HbA_{1c} at second trimester (mmol/mol) (%)	38 ± 5 5.6 ± 2.6	43 ± 9 6.1 ± 3.0	**<0.01**
HbA_{1c} at third trimester (mmol/mol) (%)	41 ± 8 5.9 ± 2.9	45 ± 1 6.3 ± 3.2	**<0.01**

Table 5.3.4 *Maternal characteristics in type 2 diabetes divided by first trimester glycaemic level. Data are presented as n (%) or mean ± SD. Body mass index (BMI)*
[a] Defined as hypertension diagnosed and medicated before pregnancy.
[b] Treatment with 150 mg aspirin started before 16 weeks of gestation.
[c] Retinopathy, nephropathy, or neuropathy diagnosed before pregnancy.

Regarding obstetric outcomes, those who were well-regulated in the first trimester gave birth at a later gestation and had a lower incidence of preeclampsia, early preterm birth, and neonatal hypoglycaemia (Table 5.3.5).

Type 2 diabetes Obstetric outcomes	First trimester Well-regulated (HbA$_{1c}$ <53) n=54	First trimester Dysregulated (HbA$_{1c}$ ≥53) n=30	*p* value
Gender (girl)	30 (55.6)	15 (50.0)	0.63
Birth weight (g)	3413 ± 721	3070 ± 908	0.06
Birth weight deviation (%)	11.8 ± 21.4	6.7 ± 23.2	0.31
Large-for-gestational-age [a]	23 (42.59%)	10 (33.33%)	0.41
Appropriate-for-gestational-age [b]	26 (48.15%)	15 (50.00%)	0.87
Small-for-gestational-age [c]	5 (9.26%)	5 (16.67%)	0.32

Hypertensive disorders
   Gestational hypertension
   Preeclampsia
	
	6 (11.1)
	3 (5.6)
		
		8 (26.7)
		6 (20.0)
			
			0.07
			0.04

Gestational week at birth	37+2 ± 1+5	36+1 ± 3+1	**0.04**
Preterm delivery < 37+0 weeks < 34+0 weeks	 11 (20.4) 1 (1.9)	 12 (40.0) 4 (13.3)	 0.05 **0.03**
Caesarean section Elective	33 (61.1) 14 (42.4)	18 (60.0) 11 (61.1)	0.92 0.20
Post-partum haemorrhage [d]	6 (20.0)	3 (21.4)	0.91
Neonatal hypoglycaemia [e] Severe	22 (40.7) 2 (9.1)	21 (70.0) 6 (28.6)	**0.01** 0.10
Apgar score < 7 at 5 minutes	1 (1.9)	1 (3.3)	0.67
Umbilical cord artery pH <7.0	2 (3.7)	1 (3.3)	0.93

Table 5.3.5 *Obstetric outcomes in type 2 diabetes divided by first trimester glycaemic level. Data are presented as n (%) or mean ± SD.*
[a] *Defined as birth weight deviation ≥ 15%*
[b] *Defined as birth weight deviation < 15% and > -15%*
[c] *Defined as birth weight deviation ≤ -15%*
[d] *Blood volume ≥ 1000 ml*
[e] *Defined as neonatal blood glucose < 2.5 mmol/l measured within two hours after birth. Severe neonatal hypoglycaemia < 1.5 mmol/l*

Among T2DM pregnancies who were well-regulated in the first trimester (n=57), there was a non-significant positive linear correlation between first trimester HbA$_{1c}$ and birth weight deviation (coef (95%CI) 0.82 (-0.11-1.75) %/(mmol/mol), p = 0.08, R^2 = 0.06). Notably, the coefficient was only about 50% of that in well-regulated T1DM pregnancies. Moreover, in T2DM pregnancies that were dysregulated in the first trimester (n=30), there was a significant positive correlation (coef (95%CI) 0.93 (0.19-1.66) %/(mmol/mol), p=0.02, R^2 = 0.19) (Figure 5.3.3).
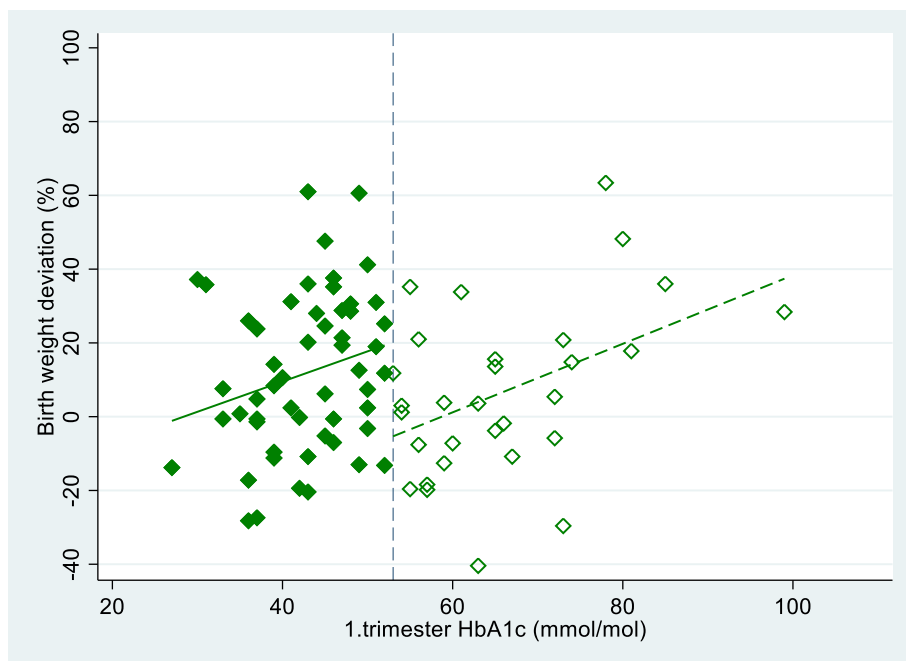
HbA$_{1c}$	n	Coef	R^2	*p* value	Interaction *p* value
All	84	0.17	0.011	0.34	
<53	54	0.82	0.057	0.08	0.85
≥53	30	0.93	0.193	**0.02**	

Figure 5.3.3 *Scatterplot depicting the correlation between birth weight deviation (%) and first trimester HbA$_{1c}$ (mmol/mol) in type 2 diabetes pregnancies. The correlation is investigated by simple linear regression stratified on maternal glycaemic control using HbA$_{1c}$ 53 mmol/mol (7.0%) as a cutpoint.*

Pregnancies that were well-regulated in the first trimester are represented by the green diamonds and the full green regression line, pregnancies that were dysregulated in the first trimester are represented by the open green diamonds and the green dotted regression line. Below the figure the corresponding table present the data from the correlation analysis. Linear regression coefficient (Coef.) in %/(mmol/mol), Pearson's correlation coefficient (R^2).

Among T2DM pregnancies who were well-regulated in the first trimester, the third trimester glycaemic level did not significantly affect birth weight deviation (median birth weight deviation (IQR); remained well-regulated (n= 51) 8.4 (-5.2–28.0) %; became dysregulated (n= 3) 28.6 (-3.2–35.8) % (p = 0.46)). However, in T2DM pregnancies who were dysregulated in the first trimester, birth weight deviation was lower in those who became well-regulated in the third trimester, when compared to those who remained dysregulated (median birth weight deviation (IQR); became well-regulated (n= 21) -1.8 (-10.8–5.4); remained dysregulated (n=9) 33.8 (20.8–36.0) % (p=0.01)) (Figure 5.3.4, Table 5.3.6).
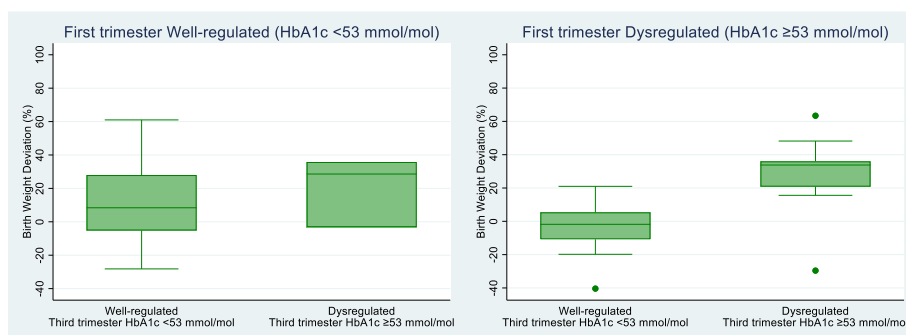
Figure 5.3.4 *Boxplot comparing birth weight deviation according to third trimester glycaemic level in type 2 diabetes pregnancies. Right: well-regulated in the first trimester, left: dysregulated in the first trimester.*

First trimester	Third trimester	Birth weight deviation (%) Median (IQR)	*p* value
Well-regulated HbA1c <53 (n=54)	Remained well-regulated HbA1c <53 (n=51)	8.4 (-5.2 – 28)	0.46
	Became dysregulated HbA1c ≥53 (n=3)	28.6 (-3.2 – 35.8)	
Dysregulated HbA1c ≥53 (n=30)	Remained dysregulated HbA1c ≥53 (n=9)	33.8 (20.8 – 36.0)	**<0.01**
	Became well-regulated HbA1c <53 (n=21)	-1.8 (-10.8 – 5.4)	

Table 5.3.6 *Comparison between median birth weight deviation (%) and third trimester glycaemic level stratified on first trimester glycaemic level in type 2 diabetes pregnancies.*

5.3.3. TYPE 1 DIABETES VS. TYPE 2 DIABETES STRATIFIED ON FIRST TRIMESTER MATERNAL GLYCAEMIC LEVEL

The differences between maternal characteristics in T1DM and T2DM did not change when stratifying on first trimester glycaemic level, except for the lack of difference in first trimester HbA_{1c} and diabetic complications among dysregulated T1DM and T2DM (Table 5.3.7, Table 5.3.8).

First trimester well-regulated Maternal Characteristics	Type 1 diabetes n=53	Type 2 diabetes n=54	p value
BMI (kg/m^2)	26.9 ± 4.8	31.7 ± 7.3	**<0.01**
Age at first trimester ultrasound (years)	29.4 ± 3.9	33.1 ± 5.4	**<0.01**
Nullipara	36 (67.9%)	17 (31.5%)	**<0.01**
Conception - spontaneous	46 (86.8%)	47 (87.0%)	0.97
Ethnicity - Caucasian	52 (98.1%)	42 (77.8%)	**<0.01**
Smoking	3 (5.7%)	11 (20.4%)	**0.02**
Pregestational hypertension [a]	2 (3.8%)	3 (5.6%)	0.66
Hypothyroidism	6 (11.3%)	2 (3.7%)	0.13
Aspirin [b]	11 (20.8%)	12 (22.2%)	0.85
Duration of diabetes (years)	13.2 ± 8.7	2.9 ± 2.8	**<0.01**
Diabetic complications [c]	15 (28.9%)	1 (1.9%)	**<0.01**
HbA_{1c} at first trimester (mmol/mol) (%)	46 ± 5 6.4 ± 2.6	43 ± 6 6.1 ± 2.7	**<0.01**
HbA_{1c} at second trimester (mmol/mol) (%)	41 ± 5 5.9 ± 2.6	38 ± 5 5.6 ± 2.6	**<0.01**
HbA_{1c} at third trimester (mmol/mol) (%)	44 ± 6 6.2 ± 2.7	41 ± 8 5.9 ± 2.9	**<0.01**

Table 5.3.7 *Maternal characteristics in first trimester well-regulated (HbA_{1c} < 53 mmol/mol) divided by diabetes type.*
Data are presented as n (%) or mean ± SD.
Body mass index (BMI)
[a] Defined as hypertension diagnosed and medicated before pregnancy.
[b] Treatment with 150 mg aspirin started before 16 weeks of gestation.
[c] Retinopathy, nephropathy, or neuropathy diagnosed before pregnancy.

First trimester dysregulated Maternal Characteristics	Type 1 diabetes n=126	Type 2 diabetes n=30	*p* value
BMI (kg/m^2)	26.2 ± 4.9	34.9 ± 7.4	**<0.01**
Age at first trimester ultrasound (years)	29.4 ± 5.1	32.3 ± 4.7	**0.01**
Nullipara	56 (44.4%)	15 (50.0%)	0.58
Conception - spontaneous	121 (96.0%)	28 (93.3%)	0.52
Ethnicity - Caucasian	126 (100%)	25 (83.3%)	**<0.01**
Smoking	13 (10.3%)	7 (23.3%)	0.06
Pregestational hypertension [a]	19 (15.1%)	9 (30.0%)	0.06
Hypothyroidism	17 (13.5%)	1 (3.3%)	0.12
Aspirin [b]	26 (20.6%)	10 (33.3%)	0.14
Duration of diabetes (years)	14.8 ± 8.7	3.9 ± 3.6	**<0.01**
Diabetic complications [c]	42 (33.6%)	6 (20.0%)	0.15
HbA$_{1c}$ at first trimester (mmol/mol) (%)	67 ± 13 8.3 ± 3.3	66 ± 11 8.2 ± 3.2	0.73
HbA$_{1c}$ at second trimester (mmol/mol) (%)	55 ± 11 7.2 ± 3.1	43 ± 9 6.1 ± 3.0	**<0.01**
HbA$_{1c}$ at third trimester (mmol/mol) (%)	57 ± 12 7.3 ± 3.2	45 ± 1 6.3 ± 3.2	**<0.01**

Table 5.3.8 *Maternal characteristics in first trimester dysregulated (HbA$_{1c}$ ≥ 53 mmol/mol) divided by diabetes type.*
Data are presented as n (%) or mean ± SD.
Body mass index (BMI)
[a] Defined as hypertension diagnosed and medicated before pregnancy.
[b] Treatment with 150 mg aspirin started before 16 weeks of gestation.
[c] Retinopathy, nephropathy, or neuropathy diagnosed before pregnancy.

Regarding the obstetric outcomes when comparing first trimester well-regulated T1DM and T2DM, the risk of neonatal hypoglycaemia was higher among T1DM (64% vs. 41%; p = 0.02), while there was no difference in the risks of LGA (51% vs. 43%, p = 0.39), nor when adjusted for maternal BMI, parity, duration of diabetes, and first trimester HbA$_{1c}$ (OR = 0.88, p = 0.82) (Table 5.3.9). However, when comparing first trimester dysregulated T1DM and T2DM, T1DM presented an increased risk of LGA (72% vs. 33%, p < 0.01), and preterm delivery (61% vs. 40%, p = 0.04), while T2DM had an increased risk of SGA (17% vs. 2%, p < 0.01), and gestational hypertension (27% vs. 9%, p = 0.01) (Table 5.3.10). The increased risk of LGA in first trimester dysregulated T1DM remained significantly increased when adjusted for maternal, BMI, parity, duration of diabetes, and first trimester HbA$_{1c}$ (OR = 11.73, p < 0.01).

First trimester well-regulated Obstetric outcomes	Type 1 diabetes n=53	Type 2 diabetes n=54	p value
Gender (girl)	28 (52.8)	30 (55.6)	0.78
Birth weight (g)	3525 ± 599	3413 ± 721	0.38
Birth weight deviation (%)	19.5 ± 19.8	11.8 ± 21.4	0.06
Large-for-gestational-age [a]	27 (50.9)	23 (42.59%)	0.39
Appropriate-for-gestational-age [b]	25 (47.2)	26 (48.15%)	0.92
Small-for-gestational-age [c]	1 (1.9)	5 (9.26%)	0.10
Hypertensive disorders Gestational hypertension Preeclampsia	3 (5.7) 3 (5.7)	6 (11.1) 3 (5.6)	0.31 0.98
Gestational week at birth	36+6 ± 1+4	37+2 ± 1+5	0.21
Preterm delivery < 37+0 weeks < 34+0 weeks	18 (34.0) 3 (5.7)	11 (20.4) 1 (1.9)	0.11 0.30
Caesarean section Elective	27 (50.9) 11 (40.7)	33 (61.1) 14 (42.4)	0.29 0.90
Post-partum haemorrhage [d]	4 (10.5)	6 (20.0)	0.27
Neonatal hypoglycaemia [e] Severe	34 (64.2) 11 (32.4)	22 (40.7) 2 (9.1)	**0.02** **0.04**
Apgar score < 7 at 5 minutes	1 (1.9)	1 (1.9)	0.99
Umbilical cord artery pH <7.0	2 (3.8)	2 (3.7)	0.99

Table 5.3.9 *Obstetric outcomes in first trimester well-regulated (HbA$_{1c}$ < 53 mmol/mol) divided by diabetes type.*
Data are presented as n (%) or mean ± SD.
[a] *Defined as birth weight deviation ≥ 15%*
[b] *Defined as birth weight deviation < 15% and > -15%*
[c] *Defined as birth weight deviation ≤ -15%*
[d] *Blood volume ≥ 1000 ml*
[e] *Defined as neonatal blood glucose < 2.5 mmol/l measured within two hours after birth. Severe neonatal hypoglycaemia < 1.5 mmol/l*

First trimester dysregulated Obstetric outcomes	Type 1 diabetes n=126	Type 2 diabetes n=30	*p* value
Gender (girl)	61 (48.4)	15 (50.0)	0.88
Birth weight (g)	3583 ± 798	3070 ± 908	**<0.01**
Birth weight deviation (%)	28.4 ± 21.4	6.7 ± 23.2	**<0.01**
Large-for-gestational-age [a]	91 (72.2)	10 (33.33%)	**<0.01**
Appropriate-for-gestational-age [b]	32 (25.4)	15 (50.00%)	**0.01**
Small-for-gestational-age [c]	3 (2.4)	5 (16.67%)	**<0.01**

Hypertensive disorders
    Gestational hypertension
    Preeclampsia
	11 (8.7)
	12 (9.5)
		8 (26.7)
		6 (20.0)
			0.01
			0.11

Gestational week at birth	35+6 ± 2+1	36+1 ± 3+1	0.61
Preterm delivery < 37+0 weeks < 34+0 weeks	77 (61.1) 18 (14.3)	12 (40.0) 4 (13.3)	**0.04** 0.89
Caesarean section Elective	95 (75.4) 55 (57.9)	18 (60.0) 11 (61.1)	0.09 0.80
Post-partum haemorrhage [d]	7 (8.0)	3 (21.4)	0.12
Neonatal hypoglycaemia [e] Severe	96 (76.2) 50 (52.1)	21 (70.0) 6 (28.6)	0.48 0.05
Apgar score < 7 at 5 minutes	2 (1.6)	1 (3.3)	0.53
Umbilical cord artery pH <7.0	3 (2.4)	1 (3.3)	0.77

***Table 5.3.10** Obstetric outcomes in first trimester dysregulated (HbA$_{1c}$ ≥ 53 mmol/mol) divided by diabetes type.*
Data are presented as n (%) or mean ± SD.
[a] Defined as birth weight deviation ≥ 15%
[b] Defined as birth weight deviation < 15% and > -15%
[c] Defined as birth weight deviation ≤ -15%
[d] Blood volume ≥ 1000 ml
[e] Defined as neonatal blood glucose < 2.5 mmol/l measured within two hours after birth. Severe neonatal hypoglycaemia < 1.5 mmol/l

5.4. STUDY III

During the FaPDi study period, 64 women with T1DM were eligible for inclusion. Of those, 35 women declined to participate, and 4 women were not invited to the study due to practical reasons, giving a total of 25 women included in the T1DM group. In the group with non-diabetes pregnancies, 40 women were included in the study. Two women were excluded after they had finished the study; one woman was excluded due to the diagnosis of chromosomal abnormality (Trisomy 21) postnatally, and the other was excluded because of gestational diabetes mellitus diagnosed in gestational week 28. Accordingly, 38 women constituted the non-diabetes reference group (Figure 5.4.1).
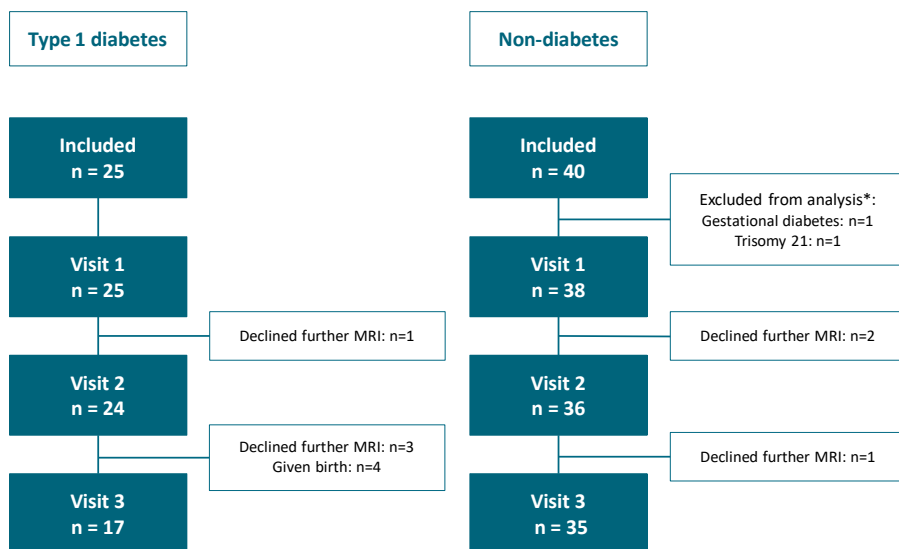
Figure 5.4.1 Flowchart of inclusion in Study III.

*Excluded after birth, but removed from all analysis throughout the study, and therefore not included in the flowchart at each visit.

When comparing T1DM with non-diabetes pregnancies, T1DM had a higher glycaemic level, higher prevalence of active smokers, pregestational comorbidities, use of aspirin during pregnancy and higher systolic blood pressure at visit 2 and 3. Regarding the remaining maternal characteristics, they were similar. In addition, the MRI examination at the third visit was performed one week earlier among those with T1DM compared to non-diabetes pregnancies (Table 5.4.1).

Maternal Characteristics	Non-Diabetes (n=38)	Type 1 diabetes (n=25)	p value
BMI (kg/m^2)	28.6 ± 6.4	28.7 ± 5.0	0.96
Age (years)	29.8 ± 4.4	29.6 ± 4.2	0.87
Nulliparous	17 (44.7)	12 (48.0)	0.80
Conception (spontaneous)	32 (84.2)	22 (88.0)	0.67
Ethnicity (Caucasian)	37 (97.4)	25 (100)	0.41
Active smoking at 1. trimester	0 (0.0)	4 (16.0)	**0.01**
Pregestational comorbidities	5 (13.2)	10 (40.0)	**0.01**
- Hypertension	0 (0.0)	1 (4.0)	0.21
- Hypothyroidism	3 (7.89)	6 (24.0)	0.07
- Hyperthyroidism	0 (0.0)	0 (0.0)	-
- Depression	4 (10.5)	4 (16.0)	0.52
- Microalbuminuria	0 (0.0)	1 (4.0)	0.21
- Hypercholesterolemia	0 (0.0)	1 (4.0)	0.21
Aspirin [a]	2 (5.26)	22 (91.7)	**<0.01**
Diabetes characteristics			
Duration of diabetes (years)	-	14.5 ± 8.4	-
Diabetes complications	-	13 (52.0)	-
- Retinopathy	-	12 (48.0)	-
- Nephropathy	-	0 (0.0)	-
- Neuropathy	-	1 (4.0)	-
Insulin pump therapy	-	14 (56.0)	-
Pregestational insulin dose (IE)	-	55.7 ± 27.0	-
HbA$_{1c}$ 1. trimester (mmol/mol)	-	58.6 ± 14.4	-
HbA$_{1c}$ 1. Trimester (%)	-	7.5 ± 3.5	-
HbA$_{1c}$ visit 1 (mmol/mol)	30.6 ± 3.3	50.6 ± 10.5	**<0.01**
HbA$_{1c}$ visit 1 (%)	4.9 ± 2.5	6.8 ± 3.1	
HbA$_{1c}$ visit 2 (mmol/mol)	29.9 ± 3.3	48.4 ± 11.6	**<0.01**
HbA$_{1c}$ visit 2 (%)	4.9 ± 2.5	6.6 ± 3.2	
HbA$_{1c}$ visit 3 (mmol/mol)	32.2 ± 3.6	49.1 ± 12.7	**<0.01**
HbA$_{1c}$ visit 3 (%)	5.1 ± 2.5	$6.6 \pm 3,3$	
Study visits			
Gestational age visit 1 (weeks)	17.1 ± 1.1	17.0 ± 1.1	0.61
Gestational age visit 2 (weeks)	28.5 ± 0.6	28.4 ± 0.9	0.59
Gestational age visit 3 (weeks)	35.6 ± 1.1	34.8 ± 0.8	**0.01**
Systolic blood pressure visit 1	118 ± 10	120 ± 11	0.58
Systolic blood pressure visit 2	114 ± 10	123 ± 9	**<0.01**
Systolic blood pressure visit 3	117 ± 11	126 ± 10	**<0.01**
Diastolic blood pressure visit 1	70 ± 10	71 ± 8	0.53
Diastolic blood pressure visit 2	67 ± 8	71 ± 9	0.09
Diastolic blood pressure visit 3	73 ± 10	78 ± 8	0.10

Table 5.4.1 *Data are presented as n (%) or mean $\pm$ SD.*
Body mass index (BMI)
[a] Missing one type 1 diabetes

Women with T1DM had a higher risk of obstetric complications such as preterm delivery, Caesarean section, and LGA at birth when compared to the non-diabetes group. Further, they had a higher EFW at visit 2 and visit 3. However, there were no differences between the two groups in Doppler flow measurements of UA, MCA, and UtA except for MCA at visit 3 (Table 5.4.2).

Obstetric Outcomes	Non-diabetes (n=38)	Type 1 diabetes (n=25)	p value
Gender (girl)	27 (71.1)	11 (44.0)	**0.03**
Birth weight (g)	3642 ± 507	3679 ± 630	0.80
Birth weight deviation (%)	1.20 ± 13.0	25.5 ± 22.0	**<0.01**
Appropriate-for-Gestational-Age	28 (73.7)	10 (40.0)	**<0.01**
Large-for-Gestational-Age	6 (15.8)	15 (60.0)	**0.01**
Small-for-Gestational-Age	4 (10.5)	0 (0.0)	0.09
Gestational age at birth (weeks)	40.1 ± 1.3	36.8 ± 1.3	**<0.01**
Preterm delivery	0 (0.0)	12 (48.0)	**<0.01**
Preeclampsia	3 (7.89)	4 (16.0)	0.32
Caesarean section (total)	6 (15.8)	15 (60.0)	**<0.01**
- Acute	5 (83.3)	7 (46.7)	0.07
Post-partum haemorrhage [a]	1 (2.63)	3 (12.0)	0.14
Apgar score < 7 at 5 minutes	0 (0.0)	2 (8.33)	0.07
Umbilical cord artery pH < 7.1	1 (3.23)	2 (10.0)[b]	0.32
Stillbirth	0 (0.0)	1 (4.00)	0.21
Placental MRI			
T2* (ms) visit 1	124.4 ± 17.8	133.5 ± 16.5	**<0.05**
T2* (ms) visit 2	104.5 ± 20.4	90.5 ± 21.6	**0.01**
T2* (ms) visit 3	62.7 ± 15.9	53.3 ± 15.6	**<0.05**
T2* z-score visit 1	0.0 ± 1.0	0.55 ± 0.96	**0.03**
T2* z-score visit 2	0.0 ± 1.0	-0.70 ± 0.97	**0.01**
T2* z-score visit 3	0.0 ± 1.0	-0.74 ± 0.97	**0.01**
Ultrasound			
EFW (%) visit 2	-7.0 ± 6.6	3.0 ± 10.5	**<0.01**
EFW (%) visit 3	-0.5 ± 10.2	18.0 ± 17.2	**<0.01**
UA PI z-score visit 2	0.0 ± 0.8	-0.2 ± 0.7	0.36
UA PI z-score visit 3	0.1 ± 0.9	0.0 ± 1.0	0.95
MCA PI z-score visit 2	-0.5 ± 0.9	-0.3 ± 0.8	0.38
MCA PI z-score visit 3	0.5 ± 0.9	-0.1 ± 1.0	**<0.05**
UtA PI z-score visit 2	-0.4 ± 0.9	-0.5 ± 1.0	0.68
UtA PI z-score visit 3	-0.06 ± 0.8	-1.0 ± 0.8	0.10

Table 5.4.2 *Data are presented as n (%) or mean ± SD.*
Magnetic Reasonance Imaging (MRI), Umbilical Artery Pulsatility Index (UA PI), Middle Cerebral Artery Pulsatility Index (MCA PI).

Of the 39 women with T1DM who did not participate in the study, 4 were not invited to participate in the study and 35 declined. The majority declined because they did not want to participate either because of lack of interest or time (n=26), and one because of mild claustrophobia; the remaining had to decline because they were unable to participate because of conditions relating to their job (n=8). There were no differences regarding maternal characteristics or obstetric outcomes among T1DM pregnancies who were included in the FaPDi cohort and those who were not (Table 5.4.3). Therefore, the women with T1DM who were included in the FaPDi cohort can be regarded a random sample of T1DM pregnancies in Aalborg University Hospital during the study period.

Maternal Characteristics	Not included Type 1 diabetes (n=39)	Included Type 1 diabetes (n=25)	p value
BMI (kg/m^2)	26.4 ± 4.77	28.7 ± 4.96	0.07
Age (years)	27.9 ± 5.12	29.6 ± 4.23	0.16
Nulliparous	20 (51.3)	12 (48.0)	0.80
Conception (spontaneous)	37 (94.9)	22 (88.0)	0.32
Ethnicity (Caucasian)	39 (100)	25 (100)	1.00
Pregestational comorbidities	8 (20.5)	10 (40.0)	0.09
- Hypertension	1 (2.56)	1 (4.00)	0.75
- Hypothyroidism	3 (7.69)	6 (24.0)	0.07
- Hyperthyroidism	0 (0.0)	0 (0.0)	-
- Depression	4 (10.3)	4 (16.0)	0.50
- Microalbuminuria	0 (0.0)	1 (4.00)	0.21
- Hypercholesterolemia	3 (7.69)	1 (4.00)	0.55
Aspirin*	38 (97.4)	22 (91.7)	0.30
Diabetes characteristics			
Duration of diabetes (years)	15.3 ± 7.54	14.5 ± 8.44	0.71
Diabetes complications	16 (41.0)	13 (52.0)	0.39
- Retinopathy	13 (33.3)	12 (48.0)	0.24
- Nephropathy	0 (0.0)	0 (0.0)	-
- Neuropathy	0 (0.0)	1 (4.0)	0.21
Insulin pump therapy	15 (38.5)	14 (56.0)	0.17
Pregestational insulin dose (IE)[†]	47.9 ± 22.9	55.7 ± 27.0	0.24
HbA$_{1c}$ 1. trimester (mmol/mol)	59.9 ± 14.3	58.6 ± 14.4	0.73
Obstetric Outcomes			
Gender (girl)	16 (41.0)	11 (44.0)	0.81
Birth weight (g)	3650 ± 646	3679 ± 630	0.86
Birth weight deviation (%)	22.7 ± 24.5	25.5 ± 22.0	0.64
AGA	14 (35.9)	10 (40.0)	0.78
LGA	22 (56.4)	15 (60.0)	0.74
SGA	3 (7.69)	0 (0.0)	0.16

Gestational age at birth (weeks)	37.1 ± 1.8	36.8 ± 1.3	0.46
Preterm delivery	11 (28.2)	12 (48.0)	0.11
Preeclampsia	3 (7.69)	4 (16.0)	0.30
Caesarean section (total)	22 (56.4)	15 (60.0)	0.77
- Acute	10 (45.5)	6 (40.0)	0.74
Post-partum haemorrhage[§]	6 (15.4)	3 (12.0)	0.70
Apgar score < 7 at 5 minutes[¶]	3 (7.69)	2 (8.33)	0.93
Umbilical cord artery pH < 7.1[‡]	3 (9.38)	2 (10.0)	0.94
Stillbirth	0 (0.0)	1 (4.00)	0.21

Table 5.4.3 *Data are presented as n (%) or mean ± SD.*
Body mass index (BMI), Appropriate for gestational age (AGA), Large for gestational age (LGA), Small for gestational age (SGA).
*Missing 1 included, †missing 2 not included and 3 included, §Loss of blood volume ≥ 1000 ml within 24 hours after birth, ¶missing 1 included, ‡missing 5 included and 7 not included.

5.4.1. PLACENTAL T2*

In T1DM pregnancies, placental T2* z-score (mean ± SD) was increased at visit 1 (0.55 ± 0.97, p = 0.03) but reduced at visit 2 (-0.72 ± 0.99, p = 0.01), and visit 3 (-0.71 ± 0.94, p = 0.01) when compared to non-diabetes pregnancies (Table 5.4.2, Figure 5.4.2).
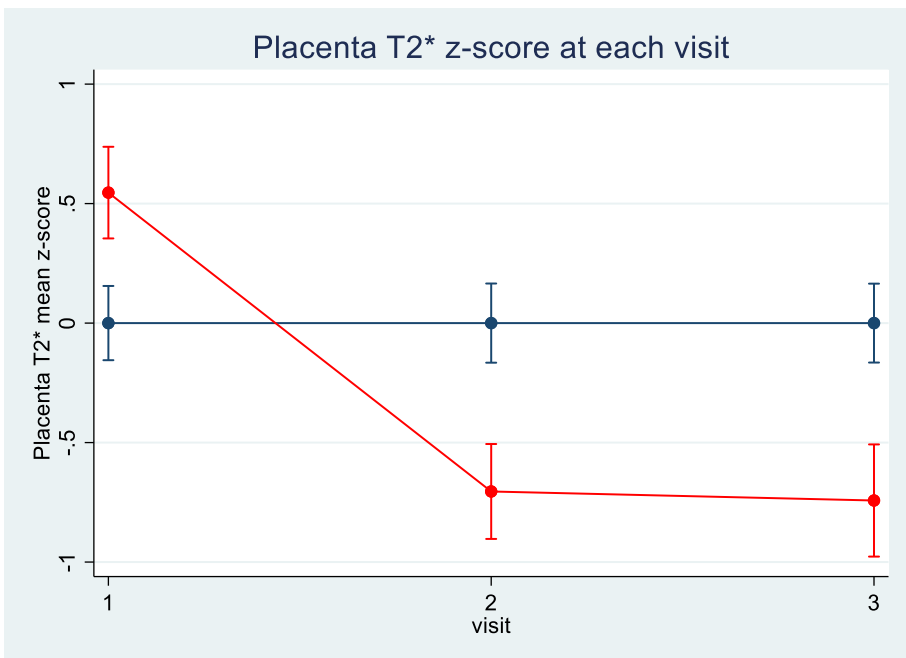

Figure 5.4.2 *Placenta T2* z-score (Mean, SE) in non-diabetes pregnancies (blue) and type 1 diabetes pregnancies (red) at each visit.*

5.4.2. Birth weight

Among pregnancies with T1DM, the median (IQR) birth weight deviation was increased when compared to non-diabetes pregnancies: 26.8 (6.8 – 39.2) % vs. 1.46 (-4.1 – 8.92) %, p < 0.01) (Figure 5.4.3).
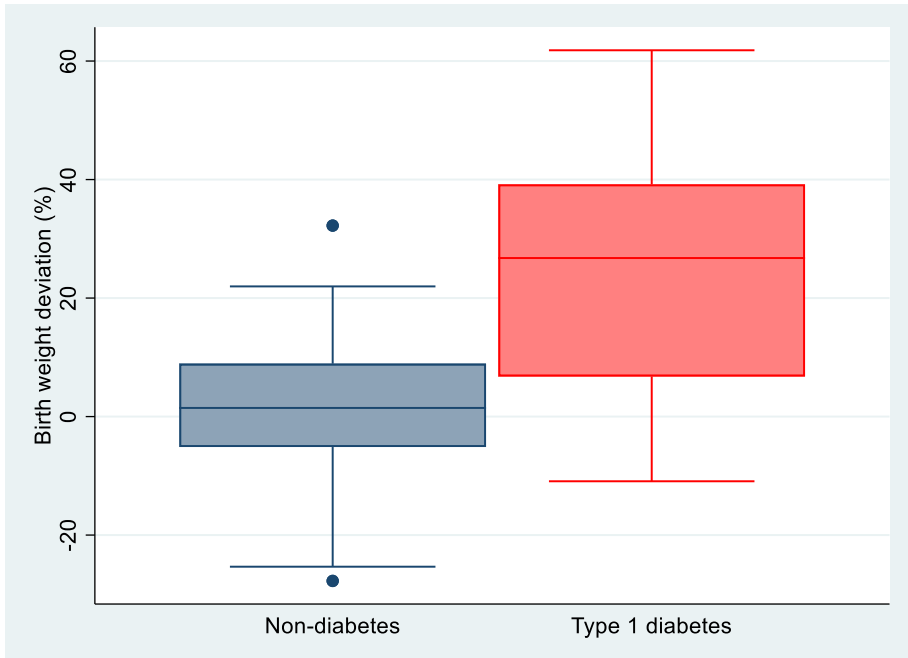
Figure 5.4.3 *Boxplot demonstrating birth weight deviation (median (IQR)) in Non-diabetes pregnancies (blue) compared to Type 1 diabetes pregnancies (red)*

When placental T2* z-score was correlated to birth weight deviation, there was a significant positive correlation at visit 2 for both groups and at visit 3 for T1DM pregnancies. More importantly, at all visits T1DM pregnancies had a significant higher birth weight deviation at any given placental T2* z-score value than non-diabetes pregnancies (mean intercept (95%CI); visit 1: 22.7 (13.6 – 31.8), visit 2: 29.6 (21.0 – 38.2), visit 3: 26.6 (16.6 – 36.6)) (Figure 5.4.4).
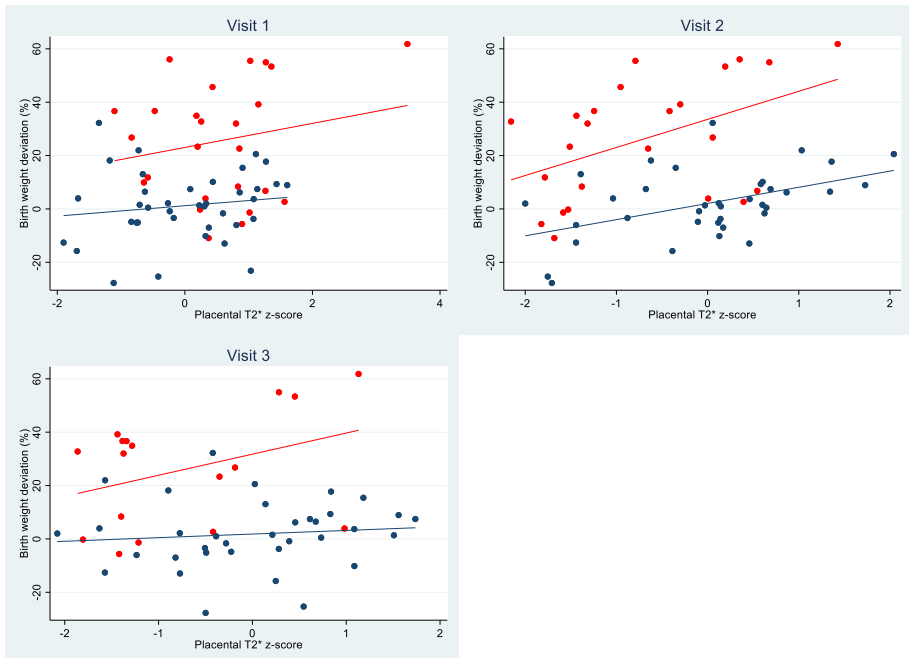
Figure 5.4.4 *Placental T2* z-score correlated with birth weight deviation (%) in type 1 diabetes (red) and non-diabetes (blue) at each visit.*

5.4.3. NORMAL AND REDUCED PLACENTAL T2*

Placental T2* z-score at visit 2 was used to define normal (z-score $\geq$ -1) and reduced (z-score < -1) placental T2*. The proportion of pregnancies with reduced placental T2* at visit 2 was higher in T1DM pregnancies when compared to non-diabetes pregnancies (46% vs. 19%, p = 0.03). In the following T1DM pregnancies are stratified on placental T2*. Regarding maternal characteristics, those with a reduced placental T2* at visit 2 were more likely nulliparous and insulin pump users and had a higher systolic blood pressure at visit 2 and 3, even thought it was within normal range. Moreover, they had a higher pregestational daily insulin dose and a longer duration of diabetes, although not significant (Table 5.4.4).

Type 1 diabetes	Normal T2* (n=13)	Reduced T2* (n=11)	p value
BMI (kg/m^2)	27.7 ± 3.9	30.1 ± 6.0	0.24
Age (years)	30.2 ± 2.9	29.2 ± 5.6	0.59
Nulliparous	7 (30.8)	8 (72.7)	**0.04**
Conception (spontaneous)	10 (76.9)	11 (100)	0.09
Ethnicity (Caucasian)	13 (100)	11 (100)	1.00
Active smoking at 1. trimester	2 (15.4)	1 (9.1)	0.64
Pregestational comorbidities	5 (38.5)	4 (36.6)	0.68
- Hypertension	0 (0.0)	1 (9.09)	0.27
- Hypothyroidism	3 (23.1)	2 (18.2)	0.77
- Hyperthyroidism	0 (0.0)	1 (9.09)	0.27
- Depression	1 (7.7)	2 (18.2)	0.44
- Microalbuminuria	0 (0.0)	1 (9.09)	0.27
- Hypercholesterolemia	1 (7.7)	0 (0.0)	0.35
Aspirin [a]	11 (84.6)	10 (100)	0.19
Diabetes characteristics			
Duration of diabetes (years)	11.9 ± 7.7	17.2 ± 9.0	0.14
Diabetes complications	6 (46.2)	6 (54.6)	0.68
- Retinopathy	6 (46.2)	5 (45.5)	0.97
- Nephropathy	0 (0.0)	0 (0.0)	-
- Neuropathy	0 (0.0)	1 (9.09)	0.27
Insulin pump therapy	3 (23.1)	10 (90.9)	**<0.01**
Pregestational insulin dose (IE)	50.1 ± 23.1	63.9 ± 31.5	0.25
HbA$_{1c}$ 1. trimester (mmol/mol)	57.8 ± 13.7	57.8 ± 15.4	0.99
HbA$_{1c}$ 1. Trimester (%)	7.4 ± 3.4	7.4 ± 3.6	
HbA$_{1c}$ visit 1 (mmol/mol)	50.7 ± 10.3	48.7 ± 9.8	0.64
HbA$_{1c}$ visit 1 (%)	6.8 ± 3.1	6.6 ± 3.0	
HbA$_{1c}$ visit 2 (mmol/mol)	48.9 ± 12.6	46.3 ± 10.1	0.58
HbA$_{1c}$ visit 2 (%)	6.6 ± 3.3	6.4 ± 3.1	
HbA$_{1c}$ visit 3 (mmol/mol)	45.3 ± 8.9	48.8 ± 9.4	0.44
HbA$_{1c}$ visit 3 (%)	6.3 ± 3.0	6.6 ± 3.0	
Study visits			
Gestational age visit 1 (weeks)	17.1 ± 1.3	16.9 ± 1.0	0.78
Gestational age visit 2 (weeks)	28.1 ± 1.1	28.8 ± 0.5	0.12
Gestational age visit 3 (weeks)	34.6 ± 0.7	34.9 ± 0.8	0.53
Systolic blood pressure visit 1	116 ± 8	124 ± 14	0.09
Systolic blood pressure visit 2	118 ± 7	128 ± 7	**<0.01**
Systolic blood pressure visit 3	120 ± 10	132 ± 5	**<0.01**
Diastolic blood pressure visit 1	71 ± 6	73 ± 10	0.68
Diastolic blood pressure visit 2	70 ± 7	72 ± 10	0.54
Diastolic blood pressure visit 3	76 ± 9	80 ± 7	0.28

Table 5.4.4 *Data are presented as n (%) or mean ± SD.*
Normal T2: z-score > -1. Reduced T2*: z-score ≤-1. One with type 1 diabetes did not participate in visit 2 and is therefore not included in the stratification.*
Body mass index (BMI). [a] Missing one type 1 diabetes with normal T2 *

Regarding the obstetric outcomes, those with a reduced T2* had smaller neonates at birth and a higher incidence of preeclampsia and post-partum haemorrhage. There were no differences between the two groups in ultrasound assessed EFW and Doppler flow in UA and MCA, only in visit 3 the UtA was higher among those with reduced placental T2*, though within normal range. (Table 5.4.5).

Type 1 diabetes	Normal T2* (n=13)	Reduced T2* (n=11)	*p* value
Gender (girl)	5 (38.5)	5 (45.5)	0.73
Birth weight (g)	4017 ± 483	3359 ± 578	**0.01**
Birth weight deviation (%)	35.8 ± 21.4	14.7 ± 17.9	**0.02**
Appropriate-for-Gestational-Age	3 (23.1)	6 (54.5)	0.11
Large-for-Gestational-Age	10 (76.9)	5 (45.5)	0.11
Small-for-Gestational-Age	0 (0.0)	0 (0.0)	-
Gestational age at birth (weeks)	37.0 ± 1.5	36.7 ± 1.0	0.57
Preterm delivery	5 (38.5)	6 (54.6)	0.43
Preeclampsia	0 (0.0)	4 (36.4)	**0.02**
Caesarean section (total)	8 (61.5)	7 (63.6)	0.92
- Acute	2 (25.0)	4 (57.1)	0.21
Post-partum haemorrhage [a]	0 (0.0)	3 (27.3)	**0.04**
Apgar score < 7 at 5 minutes	0 (0.0)	2 (18.2)	0.11
Umbilical cord artery pH < 7.1	1 (10.0)	1 (10.0)	1.00
Stillbirth	0 (0.0)	0 (0.0)	-
Placental MRI			
T2* (ms) visit 1	138.7 ± 18.7	129.7 ± 10.5	0.17
T2* (ms) visit 2	106.9 ± 15.2	71.2 ± 5.9	**<0.01**
T2* (ms) visit 3	64.2 ± 16.3	43.6 ± 5.7	**<0.01**
T2* z-score visit 1	0.81 ± 1.17	0.34 ± 0.53	0.23
T2* z-score visit 2	0.04 ± 0.67	-1.59 ± 0.26	**<0.01**
T2* z-score visit 3	-0.07 ± 0.97	-1.34 ± 0.43	**<0.01**
Ultrasound			
EFW (%) visit 2	3.1 ± 11.2	2.9 ± 10.2	0.96
EFW (%) visit 3	20.0 ± 17.7	16.0 ± 17.6	0.63
UA PI z-score visit 2	-0.3 ± 0.8	-0.1 ± 0.7	0.69
UA PI z-score visit 3	-0.1 ± 0.8	0.1 ± 1.2	0.68
MCA PI z-score visit 2	-0.1 ± 0.9	-0.6 ± 0.7	0.15
MCA PI z-score visit 3	0.1 ± 0.7	-0.2 ± 1.2	0.53
UtA PI z-score visit 2	-0.6 ± 0.8	-0.4 ± 1.3	0.53
UtA PI z-score visit 3	-1.4 ± 0.7	-0.6 ± 0.8	**0.04**

Table 5.4.5 *Data are presented as n (%) or mean ± SD.*
Normal T2: z-score > -1. Reduced T2*: z-score ≤-1. One participant with type 1 diabetes did not participate in visit 2 and is therefore not included in the stratification.*
Magnetic Reasonance Imaging (MRI), Umbilical Artery Pulsatility Index (UA PI), Middle Cerebral Artery Pulsatility Index (MCA PI).
[a] Loss of blood volume ≥ 1000 ml within 24 hours after birth

In T1DM pregnancies, birth weight deviation was increased for those with normal placental T2* compared to those with reduced T2* (median (IQR)) 39.2 (22.6 – 55.0) % versus 11.8 (-1.4 – 32.8)%., p < 0.01. Equivalent figures for non-diabetes participants were 2.1 (-3.4 – 9.3)% versus -6.0 (-25.3 – 4.0)%, p = 0.03 (Figure 5.4.5). Noteworthy, in T1DM pregnancies with reduced placental T2*, no neonates were SGA at birth (0%) whereas 46% were LGA (Table 5.4.5).
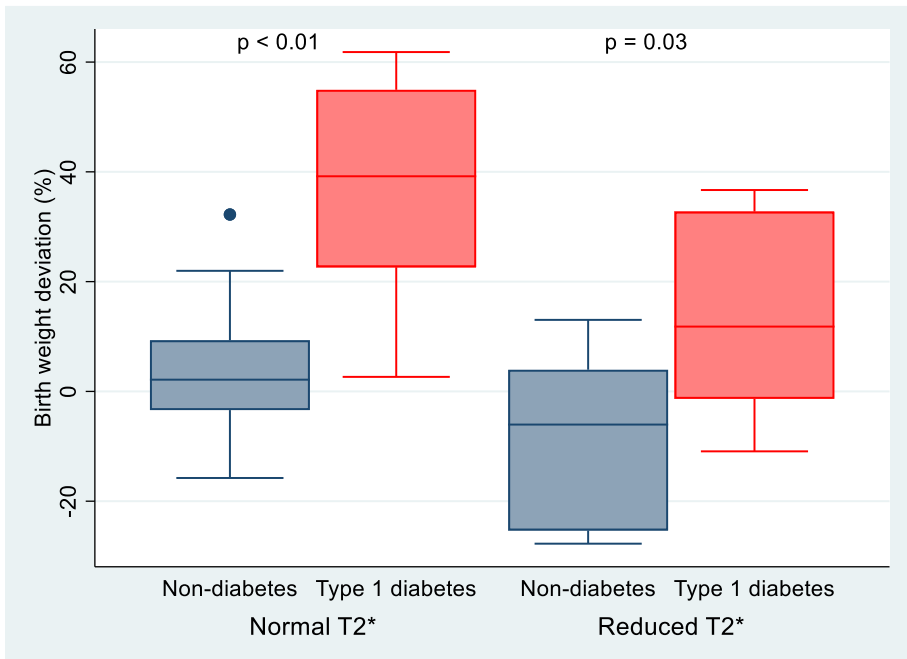

Figure 5.4.5 *Boxplot demonstrating birth weight deviation (median (IQR)) in Non-diabetes pregnancies (blue) compared to Type 1 diabetes pregnancies (red) stratified on placental T2* z-score at visit 2.*
Normal T2: z-score ≥ -1.0, Reduced T2*: z-score < -1.0.*

A significant correlation between maternal glycaemic level and birth weight deviation was found only in T1DM pregnancies with normal placental T2* (Table 5.4.6, Figure 5.4.6).

		n	Coef. (CI95%)	R^2	*p* value
1. trimester	All type 1 diabetes	25	0.33 (-0.31 – 0.97)	0.03	0.29
	Normal T2*	13	1.10 (0.37 – 1.84)	**0.50**	**0.01**
	Reduced T2*	11	-0.20 (-1.07 – 0.66)	0.03	0.61
Visit 1	All type 1 diabetes	25	0.60 (-0.27 – 1.46)	0.08	0.17
	Normal T2*	13	1.41 (0.40 – 2.43)	**0.46**	**0.01**
	Reduced T2*	11	-0.16 (-1.53 – 1.21)	0.01	0.80
Visit 2	All type 1 diabetes	25	0.69 (-0.07 – 1.45)	0.13	0.07
	Normal T2*	13	1.16 (0.34 – 1.98)	**0.47**	**0.01**
	Reduced T2*	11	-0.02 (-1.35 – 1.31)	<0.01	0.97
Visit 3 [a]	All type 1 diabetes	24	0.59 (-0.13 – 1.31)	0.12	0.10
	Normal T2*	12	0.91 (0.02 – 1.80)	**0.34**	**<0.05**
	Reduced T2*	11	0.03 (-1.29 – 1.35)	<0.01	0.96

Table 5.4.6 *Correlation between HbA$_{1c}$ and birth weight deviation (%) at each visit in type 1 diabetes. Normal T2*: z-score >-1. Reduced T2*: z-score ≤-1.*
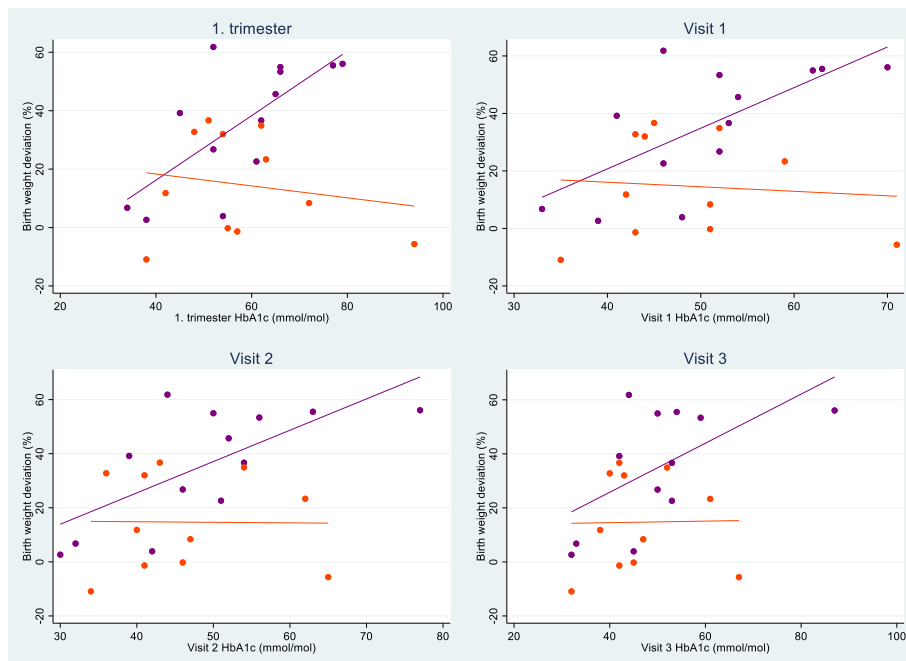[a] *One missing, due to no HbA$_{1c}$ taken after visit 2.*

Figure 5.4.6 *Correlation between HbA$_{1c}$ and birth weight deviation (%) in the 1. trimester and at each visit in type 1 diabetes pregnancies (T1DM) stratified on placental T2* z-score at visit 2.*
Normal T2*: z-score ≥ -1.0 (Purple dots). Reduced T2*: z-score < -1.0 (Orange dots).

5.4.4. HbA$_{1c}$

Placental T2* z-score was not correlated with maternal HbA$_{1c}$ level among T1DM pregnancies (Table 5.4.7).

T2*z-score	n	HbA$_{1c}$ 1. trimester		HbA$_{1c}$ visit 1		HbA$_{1c}$ visit 2		HbA$_{1c}$ visit 3[a]	
		R^2	*p* value	R^2	*p* value	R^2	*p* value	R^2	*p* value
Visit 1	25	0.01	0.62	0.05	0.27	-	-	-	-
Visit 2	24	0.01	0.61	<0.01	0.92	<0.01	0.96	-	-
Visit 3	17	0.01	0.79	<0.01	0.80	<0.01	0.79	0.01	0.75

Table 5.4.7 *Correlation between HbA$_{1c}$ and T2* z-score at each visit in type 1 diabetes pregnancies.*
[a] One missing, due to none HbA$_{1c}$ taken after visit 2.

5.4.5. BLOOD PRESSURE

In T1DM pregnancies there was a significant negative correlation between placental T2* z-score and systolic blood pressure at all visits. Such correlation was not found in non-diabetes pregnancies (Figure 5.4.7). There was no correlation between diastolic blood pressure and placental T2* z-score (Table 5.4.8)

Blood pressure	Non-diabetes (n=38)			Type 1 diabetes (n=25)		
	Coef. (95% CI)	R^2	*p* value	Coef. (95% CI)	R^2	*p* value
Systolic visit 1	0.70 (-3.01 – 4.41)	<0.01	0.71	-4.79 (-9.54 – -0.05)	0.17	**<0.05**
Systolic visit 2	-1.28 (-4.65 – 2.09)	0.02	0.45	-4.92 (-8.16 – -1.67)	0.31	**<0.01**
Systolic visit 3	-0.22 (-4.30 – 3.85)	<0.01	0.91	-5.76 (-9.62 – -1.90)	0.39	**<0.01**
Diastolic visit 1	1.34 (-2.19 – 4.88)	0.02	0.45	-0.34 (-4.04 – 3.36)	<0.01	0.85
Diastolic visit 2	0.96 (-1.88 – 3.81)	0.01	0.50	-1.87 (-5.73 – 1.99)	<0.01	0.33
Diastolic visit 3	-0.36 (-4.01 – 3.29)	<0.01	0.84	-2.97 (-6.73 – 0.80)	0.15	0.11

Table 5.4.7 *Correlation between systolic and diastolic blood pressure at each visit and T2* z-score at visit 2.*
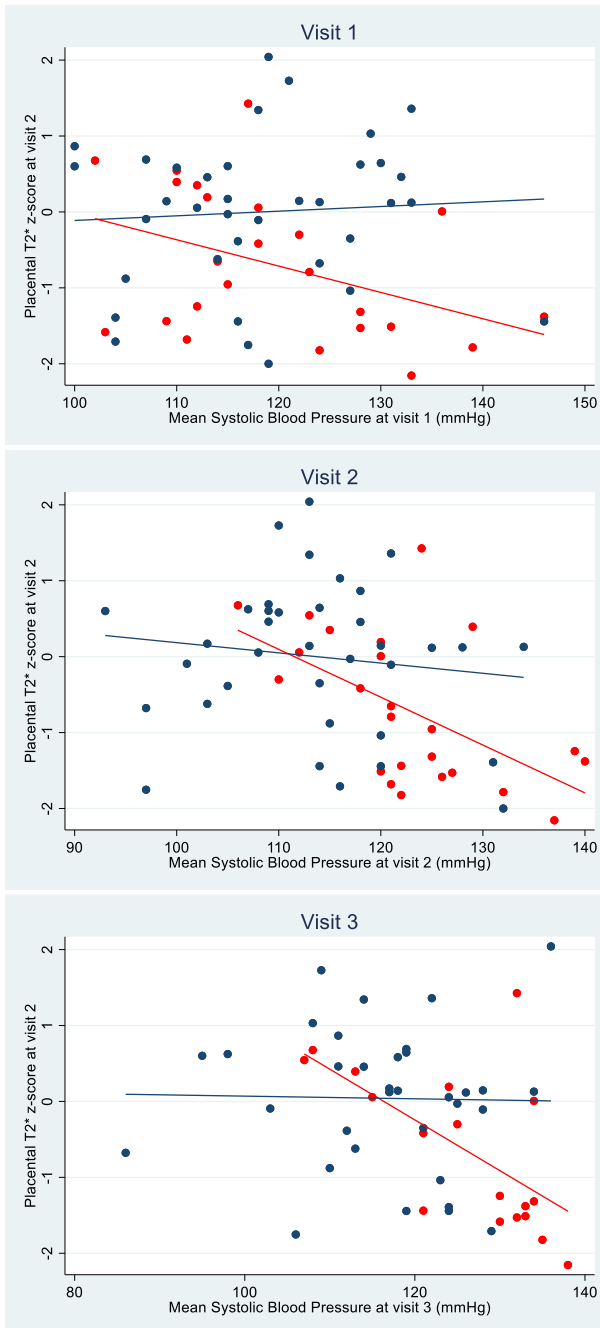
Figure 5.4.7 *Correlation between mean systolic blood pressure at each visit and placental T2* z-score at visit 2 in type 1 diabetes pregnancies (red) and non-diabetes pregnancies (blue).*

CHAPTER 6. DISCUSSION

The studies in this thesis investigate different aspects of fetal growth and placental function in PGDM pregnancies.

6.1. FETAL GROWTH IN DIABETES PREGNANCIES

In Study I the principal finding was that PGDM pregnancies were associated with a general fetal overgrowth with increased z-scores of all fetal biometry (HC, AC and FL) from 20 weeks' gestation. The predictive performance of EFW and AC regarding LGA at birth was similar, and both performed significantly better than the HC/AC-ratio.

The strengths of Study I are that the diabetes diagnosis was manually validated by SLR from patient records and that separate analyses were performed according to diabetes type. Furthermore, clinical practice during the study was standardized following national guidelines, and the population was from a well-defined geographical area. Limitations of this study are the incomplete ultrasound assessments of the fetal biometry at 16 weeks' gestation and that the reference curve of EFW (125) can only be applied after 22 weeks' gestation. Sample size was relatively small as pregestational diabetes is a rare condition, and this was a single centre study.

Fetal growth in diabetes pregnancies is thought to be asymmetric, with LGA associated mainly with an increase in AC (10,38). The increase in AC is caused by an increased fat mass and by a larger liver (10,133,134). However, Study I finds a general fetal overgrowth including an increase in HC and FL although not to the same extent as AC. This may explain why the HC/AC-ratio was not better than AC alone in the prediction of LGA at birth. This finding could be attributed to the effect of insulin as a growth factor influencing the growth of all tissue.

Previous studies have described how fetal biometry can predict LGA at birth in unselected populations (46,135,136). In diabetes pregnancies however, studies on the predictive performance of fetal biometry in regards to LGA often combines PGDM and GDM in their analysis (33,137). Studies find that AC is the strongest predictor of LGA at birth in PGDM pregnancies with AUC =0.85 (41,42).These findings are somewhat in accordance with those of Study I even though they investigated PGDM as a combined group. In contrast to Study I, a previous study did not find an increase

in HC and FL in either T1DM or T2DM LGA neonates when compared to non-LGA neonates from 17 to 37 weeks' gestation, and they found only an increased growth of AC among the LGA neonates (10). Hence, that study emphasised the use of HC/AC ratio in monitoring fetal growth in PGDM pregnancies.

Study I demonstrated that the predictive performance of all fetal biometry was low and not clinically applicable in mid pregnancy; however, at later gestation both AC, EFW and HC/AC-ratio had high performances in predicting LGA at birth. This finding was previously described in several studies, with the predictive performance of AC being AUC=0.78 at 30 weeks' gestation increasing to AUC = 0.85 at 36 weeks' gestation in one study and another study showed that combining maternal factors and fetal biometry to predict LGA increased over gestation: 43.9% (19-24 weeks), 56.9% (30-34 weeks), and 64.2% (35-37 weeks) (42,46,136). The increase in the predictive performance with increasing gestational age is expected; however, it is less clinically relevant in relation to preventing LGA.

Important differences were revealed between T1DM and T2DM in the correlation between fetal biometry and LGA as Study I did separate analyses in contrast to many previous studies (38,41,138,139). This was particularly true in the multivariate analysis where only in T2DM was the predictive performance improved when including maternal characteristics which could be related to the differences in maternal characteristics and glycaemic control between T1DM and T2DM. Moreover, the growth of AC is more pronounced in T1DM LGA fetuses compared to T2DM LGA fetuses, as demonstrated in a previous study (10).

In non-diabetes pregnancies, prediction of LGA is improved when combining fetal biometry and maternal factors (136). Moreover, it is well known that there is a correlation between maternal hyperglycaemia and LGA at birth (13,14,140). Hence, including maternal HbA_{1c} in the predictive model could further improve the prediction of LGA in PGDM pregnancies (34,42). In Study I the inclusion of maternal characteristics and HbA_{1c} in the multivariate analyses only improved the predictive performance in T2DM, whereas this was not found in T1DM pregnancies. Similar results were shown in a previous publication where a significant correlation between mater HbA_{1c} and LGA at birth was found only in T2DM pregnancies, but not in T1DM pregnancies (141). These findings indicate that fetal growth in the two diabetes types responds differently on maternal factors, which underlines the different pathology of the two conditions.

6.2. MATERNAL GLYCAEMIC CONTROL

Study II found that first trimester HbA$_{1c}$ was positively correlated with birth weight deviation only in well-regulated T1DM pregnancies. Moreover, becoming well-regulated in late pregnancy did not alter fetal growth. Thus, in T1DM, birth weight is mainly correlated with early glycaemic level. This is opposed to T2DM pregnancies in which improved glycaemic control in late pregnancy could reduce fetal overgrowth.

The strengths of Study II are that the diabetes diagnosis was manually validated by SLR from patient records; moreover, data was generally complete with only a few exceptions. Furthermore, clinical practice during the study was standardized following national guidelines, and the population was from a well-defined geographical area. Limitations were that nearly half the patients did not have an HbA$_{1c}$ taken in the year up to their conception, and therefore we included the earliest first trimester HbA$_{1c}$ for the analysis, as this value likely reflected the periconceptional glycaemic level. Sample size was relatively small as pregestational diabetes is a rare condition, and this was a single centre study.

The importance of differentiating between T1DM and T2DM pregnancies is evident from the results in Study II, which showed differences in maternal characteristics and obstetric outcomes between diabetes types. These differences are in accordance with previous studies (17,142) and may partly explain the differences between studies. (9,14,55). Study II also demonstrates that the contribution of HbA$_{1c}$ to birth weight deviation is highly dependent on first trimester glycaemic level, with the contribution of first trimester HbA$_{1c}$ on the variation in birth weight varying from 2-19%. Such findings may partly explain the inconsistency of the previous literature, as studies without stratification of diabetes type and glycaemic level reported a correlation as low as 5-6% of the variation in birth weight deviation, which could be explained by first trimester HbA$_{1c}$ (14,18). Study II also demonstrated that T1DM pregnancies are at increased risk of giving birth to a LGA neonate compared to T2DM, which is in line with previous findings (9,16,17,52). The increased risk of LGA in T1DM remained after adjustment for maternal BMI, parity, duration of diabetes and first trimester HbA$_{1c}$.

When stratifying first trimester maternal glycaemic levels, the majority of differences remained between well-regulated T1DM and T2DM and dysregulated T1DM and T2DM, respectively, regarding maternal characteristics, except from diabetic complications and first trimester HbA$_{1c}$ when comparing the dysregulated groups. Meanwhile, when examining the obstetric outcomes, the well-regulated T1DM and T2DM had fever differences as they only varied in the higher rate of neonatal hypoglycaemia in well-regulated T1DM. This was not found when comparing the dysregulated groups, where T1DM pregnancies had a higher incidence of gestational hypertension, LGA neonates, and preterm birth. These results also highlight the

necessity to differentiate between T1DM and T2DM regardless of maternal glycaemic level.

When examining T1DM, there was a positive correlation between first trimester HbA_{1c} and birth weight deviation but only in those who were well-regulated in the first trimester. This was not found in dysregulated T1DM; to the contrary, the correlation between first trimester HbA_{1c} and birth weight deviation was negative albeit not significant. A similar finding was presented in a Danish study that found the correlation between maternal pre-pregnancy glycaemic level and birth weight deviation to be inversely U-shaped in women with T1DM (54). Moreover, in those T1DM that were dysregulated in the first trimester, birth weight deviation was independent of the third trimester glycaemic level. This finding is in accordance with a previous study demonstrating that optimized glycaemic control in the third trimester did not reduce the risk of LGA in T1DM pregnancies (141). These studies thereby highlight the importance of good glycaemic control already early in pregnancy in T1DM. The findings also show that other factors than maternal glycaemic level determine birth weight in T1DM pregnancies.

In T2DM there was a positive correlation between first trimester HbA_{1c} and birth weight deviation in both well-regulated and dysregulated pregnancies. The majority of T2DM pregnancies that were dysregulated in the first trimester became well-regulated in the third trimester, which might explain the parallelly shifted linear regression lines when analysing the first trimester HbA_{1c} in the well-regulated and dysregulated T2DM groups as seen in Figure (5.3.3). As opposed to T1DM, Study II showed that T2DM might benefit from an improved glycaemic regulation in the third trimester, which is supported by another study that finds a reduction in HbA1c in the third trimester may reduce the risk of LGA at birth in T2DM (141).

The findings in Study II demonstrate that the two diabetes types have a different pathophysiology and that factors other than HbA_{1c} may contribute to determine fetal growth in PGDM pregnancies. One such factor is likely the placental function as described in Study III.

6.3. PLACENTAL T2* IN DIABETES PREGNANCIES

Study III demonstrated that placental function as assessed by placental T2* was reduced in T1DM pregnancies compared to non-diabetes pregnancies. In T1DM pregnancies with normal placental T2* mean birth weight deviation was +39% and well correlated to maternal HbA_{1c} level. However, in those with reduced placental T2*, mean birth weight deviation was +12% and not correlated to maternal HbA_{1c} level. Thus, placental function may modify the effect of maternal glycaemic level on fetal growth.

The strengths of Study III are that it involved two well characterised groups that are comparable except for their diabetes status and that one single person (SLR) performed all segmentations of placental T2* ROIs. Limitations are that of all eligible women with T1DM pregnancies, only 29% were included, and moreover, 17% of the included T1DM participants did not complete all three study visits.

In Study III, T1DM pregnancies showed a lower mean placental T2* value at 28 and 36 weeks' gestation compared to non-diabetes pregnancies, suggesting a reduced placental function. As a low placental T2* in non-diabetes pregnancies is associated with low placental oxygenation (30), abnormal placental histology indicating vascular malperfusion (143), low birth weight, and hypertensive disorders of pregnancy (102). Reduced placental function in PGDM pregnancies is supported by large cohort studies demonstrating an increased risk of placenta related complications of pregnancy, such as preeclampsia, asphyxia, acute Caesarean section, and stillbirth in PGDM pregnancies (3,17,144,145). Furthermore, cordocentesis performed in the third trimester found a higher level of fetal acidosis in PGDM pregnancies when compared with non-diabetes pregnancies (91,92). This is in accordance with another study suggesting an impaired oxygen diffusion across the placenta in PGDM pregnancies (21), which may be explained by thickening of the placental membrane, caused by proliferation of endothelial cells (146). Thus, there is evidence to support that placental function is reduced in PGDM pregnancies when compared to non-diabetes pregnancies.

Surprisingly Study III found a higher mean placental T2* value at 17 weeks' gestation in T1DM pregnancies compared to non-diabetes pregnancies. The high placental T2* at gestational week 17 must be interpreted with caution as the T2* values depend not only on the amount of deoxyhemoglobin in the tissue (99–101). It might also be associated with oxidative stress in early pregnancy, which may lead to impaired placental function in late pregnancy (147).

Direct assessment of placental function in vivo is challenging. In modern obstetrics ultrasound measurements are used, where isolated low birth weight < 3rd centile or low birth weight < 10th centile combined with increased UA PI are regarded proxies of placental dysfunction (25). SGA, however, is a rare event in PGDM pregnancies; as described in Study I and Study II, PGDM pregnancies are often complicated by fetal overgrowth (17,18,148,149). Additionally, in PGDM pregnancies the sensitivity of UA Doppler in the detection of placental dysfunction may be reduced compared to non-diabetes pregnancies (85–87). One study found a decrease in UA PI in relation to LGA neonates in PGDM pregnancies (88). The findings of Study III also support that ultrasound measurements may be less useful in detecting placental dysfunction in T1DM pregnancies, as there were no differences between those with normal or reduced placental T2* regarding EFW, UA PI, and MCA PI. At third visit UtA PI was higher among those pregnancies with reduced placental T2*, however for both groups UtA PI were within normal range. Hence, in PGDM pregnancies, the risk of placental

dysfunction is increased, but the current ultrasound methods to detect placental dysfunction may be less valid than in non-diabetic pregnancies.

Large cohort studies have found a positive correlation between maternal HbA_{1c} in late pregnancy and birth weight in T1DM pregnancies (17,142). However, the correlation is not as strong as one would expect. In the first trimester the correlation is inconsistent (11,34). These findings indicate that other factors may contribute to fetal growth. In study III we found that the correlation between HbA_{1c} and birth weight was modified by placental function, thus this finding may partly explain the inconsistency in previous studies regarding the correlation between maternal glycaemic level and fetal growth. This finding is in line with a previous study investigating the correlation between placental function and birth weight in T1DM pregnancies by use of the angiogenic serum marker placental growth factor (PlGF) as a proxy of placental function. In T1DM pregnancies, placental function modified the effect of maternal glycaemic level on birth weight. This study finds that in diabetes pregnancies with a suboptimal glycaemic status, those with a healthy placental (high PlGF) had higher birth weight than those with an unhealthy placenta (low PlGF) (81). This study supports the findings of study III which emphasize that in T1DM pregnancies the correlation between maternal glycaemic control and birth weight may be modified by placental function.
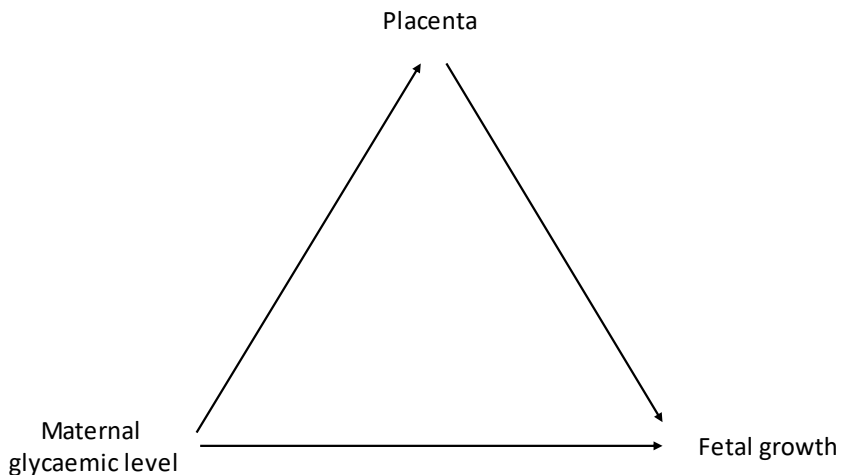

Figure 6.3.1 *Illustration of the association between maternal glycaemic level, placenta, and fetal growth.*

Surprisingly Study III found no correlation between HbA$_{1c}$ at any gestational age and placental T2*. One would expect placental function to be negatively associated with higher HbA$_{1c}$ levels. However, a previous publication in pregnancies complicated by PGDM found that high UtA PI, which is related to impaired placental function, was strongly associated to maternal vasculopathy prior to pregnancy. Whereas the correlation between UtA PI and HbA$_{1c}$ was only modest (69).

In Study III we found reduced placenta T2* to be associated with the use of insulin pump. Insulin pumps are mainly provided to patients with dysregulated diabetes, resistant to standard care. Use of insulin pump may therefore be regarded a proxy of long term poor glycaemic control, which is a substantial burden on the maternal cardiovascular system. In addition, we found placental T2* to be negatively correlated to the systolic blood pressure at each visit, even if the blood pressure remained within normal range. This finding underlines the importance of the maternal cardiovascular function in relation to placental function. Our findings suggest that in T1DM pregnancies the placental function is related to the long term effects of diabetes on the maternal cardiovascular system rather than the glycaemic level during pregnancy.

CHAPTER 7. CONCLUSIONS

The three studies are concluded in the following:

Study I

- In PGDM pregnancies, LGA at birth is characterized by a general fetal overgrowth including both AC and HC.
- AC and EFW are significantly better predictors of LGA than the HC/AC-ratio.
- Including maternal characteristics and HbA$_{1c}$ in the predictive model only improved the performance in T2DM pregnancies.

Study II

- In PGDM pregnancies, the correlation between HbA$_{1c}$ and birth weight depends on diabetes type and first trimester glycaemic level.
- In T1DM pregnancies birth weight was mainly correlated with early glycaemic level.
- In T2DM pregnancies, improved glycemic control in late pregnancy may reduce fetal overgrowth.

Study III

- In T1DM pregnancies, placental function as assessed by placental T2* was reduced compared to non-diabetes pregnancies.
- Low birth weight is not a good proxy of placental dysfunction in T1DM pregnancies, as birth weight was increased regardless of placental T2*.
- Placental function may modify the effect of HbA$_{1c}$ on birth weight in T1DM pregnancies.

The overall conclusion of this thesis is that PGDM neonates are characterized by a general fetal overgrowth, partly caused by hyperglycaemia, but placental function may alter the effect of glucose on fetal growth.

CHAPTER 8. PERSPECTIVES

This thesis demonstrates that pregnancies complicated by PGDM are characterized by fetal overgrowth, and this may be due to maternal hyperglycaemia. The glycaemic level in early pregnancy is of particular importance, as hyperglycaemia is thought to have a negative effect on placentation and thereby placental function throughout pregnancy. By use of T2* weighted placental MRI it is demonstrated that placental function is reduced in PGDM pregnancies when compared to non-diabetic pregnancies. This finding underlines that PGDM pregnancies are high risk, as the placental supply of oxygen and nutrients may not meet the high metabolic demand of the large diabetic fetus.

Such knowledge is important in a clinical perspective, as it should lead to a critical revision of the definition of normal fetal growth in pregnancies complicated by PGDM. In dysregulated PGDM pregnancies fetal overgrowth is expected, and therefore LGA should be considered "normal" fetal growth, while AGA fetuses are likely growth restricted due to placental dysfunction. Accordingly, in these high-risk pregnancies, fetuses are rarely SGA; therefore, such a finding is not a good proxy of placental dysfunction.

Current fetal monitoring in PGDM pregnancies is challenged by inaccurate weight estimates and lack of correlation between fetal size and placental function. In addition, Doppler flow measurements of UtA, UA and MCA are insufficient in predicting placental dysfunction. Thus, additional methods are needed to directly evaluate placental function. Study III showed that in PGDM pregnancies, T2* weighted placental MRI can assess placental function. MRI availability is limited, however, and costs are high. Other methods to evaluate placental function directly would be maternal serum markers of placental function such as PlGF. Future studies should include such biomarkers, as blood samples are easy to obtain, not time consuming and therefore more cost-effective. Future studies could also incorporate placental histology to obtain a better understanding of important differences between the PGDM and non-diabetic placenta.

This thesis finds a significant correlation between fetal overgrowth and maternal HbA_{1c}. However, the correlation may not be as strong as one would anticipate. This may be related to the fact that maternal HbA_{1c} provides an average value of the maternal glycaemic level over a six-to-eight-week period but disregards the daily variation in glucose level that inevitably occurs in diabetes. With the increasing use

of continuous glucose monitoring (CGM) during pregnancy, new opportunities to investigate fluctuations in maternal blood glucose that better reflect the fetal supply of glucose will become available. Studies suggest that variations in blood glucose including parameters such as "time-in-range" or "time-above-range" are better predictors of LGA than mean glucose values.

Early identification of placental dysfunction is highly attractive in a clinical perspective, as it provides an opportunity to predict and ultimately prevent adverse obstetric outcomes. This thesis demonstrates higher placental T2* in PGDM pregnancies compared to non-diabetic pregnancies in gestational week 17. The biological explanation behind this finding needs to be further explored. However, several publications suggest that the placenta in a PGDM pregnancy is exposed to increased vascularization and oxidative stress in early pregnancy – which could be reflected by increased placental T2* value. Currently, the only effective treatment of placental dysfunction is aspirin obtained before gestational week 16. The majority (92%) of the T1DM participants in Study III used aspirin during pregnancy to improve placental perfusion through a better transformation of the spiral arteries into low resistance vessels.

Placental function is an important factor to consider in the understanding of the complex correlation between maternal blood glucose and fetal growth, as it may modify the effect of glucose on fetal growth. Surprisingly, placental function was not directly related to maternal glycaemic level in pregnancy, but there were interesting associations with use of insulin pump and maternal systolic blood pressure throughout pregnancy. These findings suggest that maternal cardiovascular health, which is related to long term glycaemic control may play an important role in regard to placental function. Future research should focus on understanding the basis of the correlations between maternal glycaemic level, placental function and fetal growth and include pregestational inventions in order to improve pregnancy outcomes in these high risk pregnancies.

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