The effect of maternal diabetes on pre- and postnatal growth

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The effect of maternal diabetes on pre- and postnatal growth

Het effect van maternale diabetes op pre- en postnatale groei

(met een samenvatting in het Nederlands)

Proefschrift

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door

Nurah Marjam Hammoud

geboren op 29 oktober 1984 te Willemstad, Curaçao

There is a theory which states that if ever anyone discovers exactly what the Universe is for and why it is here, it will instantly disappear and be replaced by something even more bizarre and inexplicable.

There is another theory which states that this has already happened.

Douglas Adams, *The Restaurant at the End of the Universe*

Table of contents


The single story creates
stereotypes, and the
problem with stereotypes is
not that they are untrue, but
that they are incomplete.
They make one story
become the only story
Chimamanda Ngozi Adichie

Chapter 1

Introduction & aims of this thesis

Diabetes is complicating more and more pregnancies, and this is mainly due to an increase in women with type 2 diabetes mellitus (DM2) and in women developing gestational diabetes mellitus in the course of pregnancy (GDM). Type 1 diabetes mellitus (DM1) affects about 0.3% of pregnancies, both in the UK and in the Netherlands [1, 2]. Nationwide data on the incidence of type 2 diabetes during pregnancy are scarce, but incidences have reached over 1 percent in countries with a rapid increase in obesity rates [3-5]. An increase in maternal age during pregnancy also contributes to an increasing incidence of type 2 diabetes. The incidence of GDM depends largely on the presence of nationwide screening programs and on the applied threshold values of screening and diagnostic tests. With universal second trimester screening using the outcome-related strict 75g OGTT threshold values as suggested by the International Association of Diabetes in Pregnancy Study Groups (IADPS), GDM may affect as much as 18% of pregnancies [6]. However, the proposed threshold values have not yet been accepted universally [7].

It is important for both patient and clinician to classify pregestational diabetic women into DM1 or DM2, because medical management will pose different challenges. DM1 accounts for approximately 5% of all cases of diabetes in pregnancy and is defined by the presence of one or more autoimmune markers, which result from pancreatic β-cell destruction. This condition leads rapidly to an absolute insulin deficiency with insulin treatment becoming a vital prerequisite. DM2 on the other hand is related to a slowly progressive insulin secretory defect on the background of insulin resistance. DM2 is treated with a combination of lifestyle modifications and oral glucose-lowering drugs such as metformin. When treatment with non-insulin agents fails to achieve sufficient glycemic control, insulin therapy is initiated. GDM is a form of diabetes that is solely seen in pregnancy with affected women having a risk of up to 60% to develop DM2 later in life. Higher maternal BMI, insulin treatment and greater weight gain after pregnancy are positively associated with later DM2 [8, 9]. GDM occurs when maximal β-cell-function (maximal insulin secretion) fails to meet increased insulin requirements, which is due to an increased insulin resistance during pregnancy. The risk of GDM is related to the maximal β-cell-function of a given individual and the demands posed on the β-cells by the degree of increased insulin resistance during this given pregnancy. The relative contribution of both phenomena can vary widely between individual pregnant women, with varying gestational ages (GA) when the disease begins. Because of the usually minor degree of hyperglycemia in GDM, GDM is rarely detected based on maternal symptoms. GDM is usually detected either at a fixed GA with screening or diagnosed later in pregnancy because of fetus-related signs such as fetal growth acceleration or polyhydramnios. The time of detection of GDM is rarely the time of first occurrence of GDM. The pathophysiology of GDM is very much akin to that of DM2 and it is not surprising that many women develop DM2 after pregnancy.

GDM is not clearly overt diabetes and is currently diagnosed in the Netherlands either through a 2-h 75-g oral glucose tolerance test (OGTT) or a 2-step approach with a 1-h 50-g (nonfasting) screening followed by a 3-h 100-g OGTT for those who are screen positive

[10]. Lastly, in a minority of cases there are other specific types of pre-pregnancy diabetes due to other causes, e.g., genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug-induced diabetes (such as in the treatment of HIV/AIDS or after organ transplantation); these forms are not included in this thesis [11, 12].

Diabetes and pregnancy

In 1989 the St Vincent declaration was signed, stating that "pregnancy outcome of diabetic women should approximate that of the non-diabetic women" in the next 5 years [13]. Currently, almost 3 decades later, clinicians are still frustrated by continuing increased adverse outcome rates despite reasonable mean HbA1c levels and despite increasing rates of planned pregnancies [2, 14]. Efforts are being made to improve preconceptional and prenatal care, since lack of preconceptional counseling and care is related to poorer pregnancy outcome [15]. Special attention should be paid to women with DM2, since they are more often from an ethnic minority living in a deprived area, are less likely to receive preconceptional counseling and are more likely to use potentially harmful medications at conception [16]. In the Netherlands preconceptional counseling in DM2 does not reach the high coverage that is nowadays present in DM1 [17].

Complications – short term
Maternal diabetes is linked to short-term consequences for the offspring. In pregnancies complicated by pregestational diabetes and treated with insulin, the birthweight distribution is shifted to the right with a high mean birthweight z-score of around +1.3SD [2, 18, 19], with subsequent higher risks for assisted vaginal delivery or caesarean section (CS) [18]. Excessive fetal growth is expressed either as "macrosomia" or "large-for-gestational-age" (LGA) depending on the definition used, with cut-off points of either a birthweight > 4000 g or above the 90th percentile for gestational age, respectively. LGA occurs in up to 42-62% of pregnancies complicated by DM1 [2, 18, 20-24], in 30-56% of pregnancies complicated by DM2 [25, 26] and in 9-20% of pregnancies complicated by GDM [27-29].

Macrosomia is associated with short-term sequelae including prolonged labor, birth injury, neonatal asphyxia, hypoglycemia, polycythemia, respiratory distress syndrome and perinatal death [30-32]. Also, the risk of shoulder dystocia, planned CS and emergency CS due to cephalopelvic disproportion and fetal asphyxia are increased [33, 34]. In women with DM1 the risk for perinatal mortality is still 3.5 to a 5 fold increased [2, 19, 35]. Fortunately, perinatal mortality has decreased, given the fact that it was still around 9.5% in the 1970s [36].

The incidence of congenital malformations remains increased, especially in women with DM1 or DM2 [37-39]. This risk is related to first trimester glycemic control (HbA1c), but

also remains higher in women with HbA1c levels that are almost normal: ''almost good is not good enough'' [2, 40]. The incidence of spontaneous abortions is also related to glucose control, be it at much higher HbA1c-values than with congenital malformations [40].

Regarding short-term outcome of pregnancies in women with GDM, LGA occurs more frequently than in non-diabetic pregnancies, but it is uncertain whether this is affected by the timing of diagnosis of GDM and whether diagnosis was based on screening or symptoms (e.g. accelerated fetal growth or macrosomia, polyhydramnios and/or polyuria, polydipsia). Moreover, it is unknown whether asymmetrical fetal growth, with a decreased head-to-abdomen circumference ratio, only occurs in fetuses born LGA or whether abnormal growth also occurs in fetuses with a weight within the normal range. Increased abdominal circumference is due to an increase in the subcutaneous adipose tissue mass as a consequence of fetal hyperinsulinemia since this tissue is very sensitive to stimulation by insulin, in contrast to the head and skull.

Complications – long term

Accelerated growth during fetal life, stimulated by excessive exposure to glucose, may extend into late childhood [41]. Offspring from women with diabetes are at risk for obesity, cardiovascular disease and metabolic syndrome with an increased risk for developing DM2 and impaired glucose tolerance [42-48]. Breaking this vicious cycle of fetal adiposity to adolescent obesity by prevention and better control of diabetes during pregnancy is a major public health challenge for future generations. Pediatric obesity is not only a problem for high-income countries, because in emerging economies childhood obesity is also rising. Childhood obesity brings about adult adiposity, with subsequent higher risks for morbidity (impaired glucose tolerance, respiratory problems, hypertension, metabolic syndrome), disability and premature death [49].

Why is maternal diabetes crucial for offspring development?

It is now widely accepted that a range of diseases has their origins in the intrauterine environment. In the 1960s Pedersen postulated the concept of maternal hyperglycemia that causes fetal hyperglycemia because glucose readily passes the placenta, which in turn may cause fetal macrosomia [50-52]. Pederson described that women with diabetes who were treated for a longer period delivered smaller babies, that had less hypoglycemia, less amniotic fluid and that could withstand labor better; indicating beneficial effects of treatment of maternal diabetes [51]. Freinkel later extended his concept of fuel-mediated teratogenesis, in which changes in fetal hyperinsulinemia lead to wide-ranging changes in the fetus: fetal islets, fat stores, muscles and even changes in the neuroendocrine, habitus and brain, possibly leading to behavioral abnormalities as a consequence of fuel-related damage to cerebral structures [53]. The abnormal intrauterine environment that the fetus is exposed to, may give rise to a concurrent pathologic phenotype later in life, given than genetic make-up can give rise to a variety of different physiological or morphological states in response to different environmental conditions during development [54].

The Developmental Origins Of Health And Disease (DOHAD), also known as the 'Barker hypothesis' states that both intrauterine under- and over nutrition program adaptations of the fetal metabolism to cope with an adverse postnatal environment, that is either deprived off or enriched with suitable nutrients [54-56]. The relation between birthweight and subsequent cardiovascular disease (hypertension, mortality) and diabetes is U shaped, with higher rates at both ends of the spectrum: thus both low and high birthweight infants are at increased risk of later disease [57, 58]. Infants with a high birthweight tend to experience a higher long term weight gain, leading to adiposity [59].

In the context of maternal diabetes it is still unknown which factors play an important role as to the development of later obesity in their offspring. Is it the type of diabetes in pregnancy (DM1, DM2, GDM), symmetrical vs asymmetrical (disproportionate) intrauterine growth, being LGA at birth, higher maternal BMI or perhaps nutrition and/or lifestyle during childhood? Factors that are not always mutually exclusive and may even be interrelated.

Public concern

The increasing prevalence of prepregnancy diabetes is of major public concern, given the greater duration of disease when diagnosed at a younger age [60, 61]. Additionally, obesity in young women is also increasing and the continuing rise of this condition is estimated to add a combined 6–8·5 million incident cases of diabetes worldwide, annually [49, 62, 63]. The increase in diabetes and obesity cause a major health care and economic burden, not only by compromising the productive life span, but also by increasing health-care costs. By the year 2030, increases in obesity-related diseases are projected to add $48–66 billion a year to health-care costs in the USA and by £1·9–2 billion a year in the UK [62].

For pregnancies complicated by diabetes, it is estimated that the highest pregnancy costs are for women with DM1, both in outpatient costs as well as pharmacy costs. Women with GDM have the lowest mean costs of all diabetic patients [4]. With universally applied preconception care in women with pregestational diabetes in the USA, about 1,5 thousand adverse birth outcomes (birth defects and perinatal mortality) may be prevented annually, with a lifetime societal cost savings of up to $5.5 billion [64].

Aims of this thesis

Many questions regarding short and long term outcome of pregnancies of women with diabetes are still unanswered. In this thesis we have tried to find an answer to some of them:

1. Do pregnancy outcomes differ, when GDM is diagnosed through screening or is based on signs and symptoms? (Chapter 2)
2. How are the fetal growth trajectories in women with DM1, DM2 and GDM and is disproportionate growth restricted to fetuses being LGA or not? (Chapter 3)
3. Is intrauterine adiposity, defined as an abnormal fetal head-to-abdomen circumference ratio (HC/AC ratio), related to childhood obesity, and is this relation similar for the three distinct types of diabetes during pregnancy? (Chapter 4)
4. What is the relationship between birthweight (centile) and postnatal BMI and height in offspring of women with diabetes during pregnancy, and which factors affect this relationship? (Chapter 5 and 6)
5. Are there differences in nutrition and lifestyle during childhood between offspring from the three distinct types of diabetes during pregnancy? (Chapter 7)

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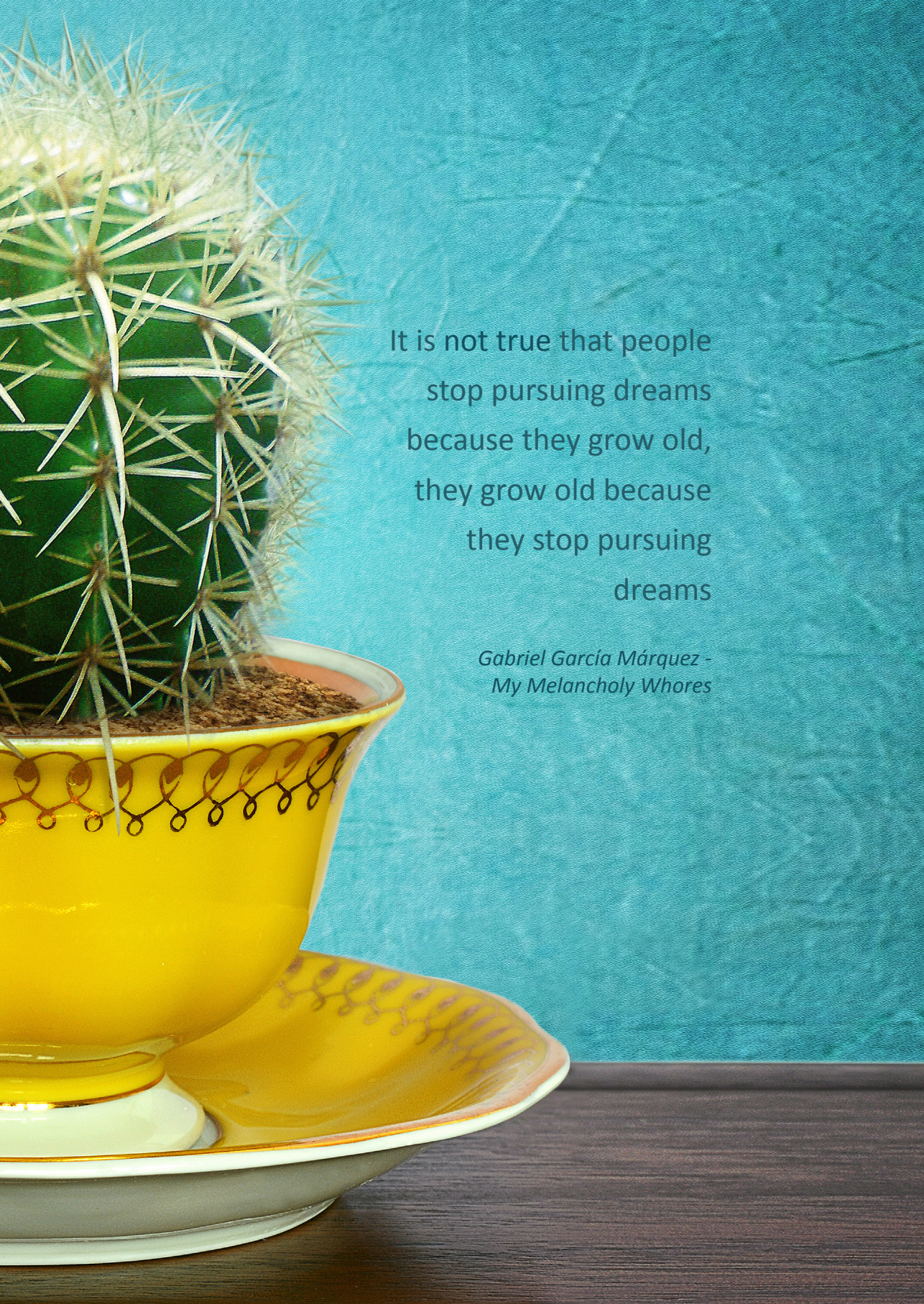
It is not true that people
stop pursuing dreams
because they grow old,
they grow old because
they stop pursuing
dreams
Gabriel García Márquez -
My Melancholy Whores

Chapter 2

Gestational diabetes mellitus diagnosed by screening or symptoms: does it matter?

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Abstract

Objective

To investigate whether outcome differs between pregnancies complicated by gestational diabetes mellitus (GDM), which was either detected by risk-factor based screening when no clinical signs are apparent (screening-group) or due to clinical signs of hyperglycemia (e.g. accelerated fetal growth or hydramnios) (screening-group).

Methods

A retrospective cohort of 249 patients with GDM treated between 2006 and 2009 were identified: 74 in the diagnosis-group and 175 in the screening-group. Fetal macrosomia was defined as an abdominal circumference (FAC) ≥90th percentile at the time of diagnosis of GDM. Large for gestational age (LGA) was defined as a birthweight ≥90th percentile, corrected for gestational age, parity and sex.

Results

GDM was diagnosed 4 weeks later in the diagnosis-group. At diagnosis of GDM, more infants in the diagnosis-group had a FAC ≥p90 and at birth more infants in this group were LGA.

Conclusion

GDM diagnosed by screening is associated with a lower incidence of fetal and neonatal macrosomia than GDM diagnosed by clinical symptoms. A later diagnosis of GDM is more prevalent in presumed low-risk pregnancies. These results favour a policy of routine screening.

Recently, two large randomised clinical trials have shown that treatment of women with gestational diabetes mellitus (GDM) reduces the incidence of adverse pregnancy outcomes (e.g. macrosomia, shoulder dystocia and instrumental deliveries) [1, 2]. This finding has unequivocally established GDM as a disease entity requiring adequate detection and treatment. GDM is defined as any degree of carbohydrate intolerance first detected during this pregnancy irrespective whether it persists after pregnancy or not [3]. Both insulin resistance and a degree of relative beta cell deficiency contribute to the pathogenesis of GDM.

GDM is not a single disease but rather a heterogeneous disease entity. The impact of GDM is dictated by the timing of the occurrence of the carbohydrate intolerance and this in turn is largely determined by the relative contributions of both beta cell deficiency and increased insulin resistance. Since there is not a simple biomarker test that can be repeated frequently during pregnancy, the moment of actual occurrence of GDM cannot be pinpointed precisely. The absence of a quick, simple and easily repeatable test is just one of the unsolved problems of detecting GDM.

More important is the ability to make a distinction between screening and diagnosis. Diagnosis means applying a diagnostic test when signs and symptoms indicate the possible presence of a disease, which in the case of GDM are pregnancy related, such as macrosomia, polyhydramnios and polyuria.

However, many women with GDM do not have signs and symptoms of the disease. Screening is therefore mandatory, although the controversy remains as to whether all women should be screened or only those with risk factors. Including only those at risk (i.e. selective screening), a number of women with GDM will be missed but they might possibly be diagnosed later in pregnancy on the basis of symptoms. It is debatable whether late detection and treatment affects outcome negatively.

We performed a study to assess characteristics and outcome of GDM diagnosed on the basis of signs and symptoms and that detected on the basis of screening.

Patients and methods

Between January 2006 and August 2009, 283 women with pregnancies complicated by GDM were seen at our outpatient clinic. Multiple gestations (*n*=16), congenital malformations (*n*=7) and pregnancies complicated by pre-eclampsia (*n*=11) were excluded.

GDM was identified by selective screening in a high-risk population based on maternal risk factors, adapted from the ADA-criteria [3] (screening-group):

- History of diabetes in a first degree relative
- History of gestational diabetes in previous pregnancy
- A previous macrosomic baby

- Previous unexplained fetal death
- Maternal obesity
- Ethnic group more at risk for GDM

Low risk pregnancies were not routinely screened, only when pregnancy related clinical signs and symptoms of hyperglycemia, e.g. accelerated fetal growth or macrosomia, polyhydramnios and/or polyuria, polydipsia were present. In that case diagnostic testing was performed (diagnosis-group).

In all pregnancies a random glucose was measured in the first trimester of pregnancy to identify women who might have pregestational diabetes. Screening was done with a 50-grams oral glucose loading (GCT) with a measurement after 1 hour. With a glucose level of ≥140 mg/dl, a diagnostic 100-grams OGTT was performed.

In case of suspicion for GDM on the basis of clinical signs and symptoms, the 100-grams OGTT was done without the screening procedure [3]. The women in the diagnosis-group were not previously subjected to screening tests (OGTT or GCT) in the current pregnancy.

All women were given dietary instructions and were instructed to self-monitor capillary blood-glucose levels. Insulin treatment was started in 144 cases (57,8%) because of elevated maternal glucose levels with some reticence in case of absence of fetal overgrowth.

Demographic, maternal, fetal and neonatal data were recorded. Fetal size at the time of diagnosis of GDM was assessed by means of ultrasound. Fetal macrosomia was defined as an abdominal circumference (FAC) >90th percentile.

Z-scores for the neonatal birthweight corrected for gestational age (GA) were calculated using the following formula: Z-score = $(X_{GA}-M_{GA})/SD_{GA,}$ where X_{GA} is the measured birthweight at that gestational age (GA), M_{GA} is the 50th percentile at this GA and SD_{GA} is the standard deviation of the mean value at this GA according to the Netherlands Perinatal Registry data from 2001 (available at http://www.perinatreg.nl). Large for gestational age (LGA) was defined as birthweight >p90th percentile (z-score>1.282 SD-units) and severe LGA as a birthweight >97.7, corrected for gestational age, parity and sex (z-score>2.00).

For normally distributed variables, mean ± SD were used, skewed data were expressed as median (5th–95th percentile). Analysis was performed with the appropriate (non-) parametric tests. SPSS version 17.0 was used.

Results

Of the 249 GDM pregnancies that were identified, 175 (70%) belonged to the screening-group and 74 (30%) to the diagnosis-group.

Patients in the diagnosis-group were more often of original European background, had a lower BMI and were more often multiparous than the screening-group (Table 2.1). GDM was diagnosed on average 4 weeks later in the diagnosis-group compared to the screening-group (27 versus 31 weeks; p <0,001). In the screening-group, 61,1% was treated with insulin; and in the diagnosis-group 49,3% (NS, Table-I).

Fetuses of the screening-group were less likely to be macrosomic (FAC >p90th) at the time of diagnosis of GDM: 32,7% versus 68,1%. Gestational age at delivery was similar in the two groups. Neonates in the diagnosis-group had higher birthweights and z-scores for birthweight compared to those of the screening-group, with a higher incidence of LGA, (36,5 versus 17,1%, p=0,001) and severe LGA (16,2 versus 5,1%, p=0,004).

Discussion

This study shows that late diagnosis and macrosomia at birth is particularly frequent in presumed low-risk populations without maternal risk factors. These aspects favour a policy of routine screening. This finding, although logical, has in our opinion never been reported before. Interestingly, a study performed in Sweden investigating the compliance to local guidelines for the screening of GDM showed similar results [4]. In this study three groups were included, including screening on the basis of signs and symptoms of GDM (e.g. glucosuria, macrosomia and hydamnios). Especially this latter subgroup had an increased risk for giving birth to a macrosomic infant. Similar to our report, approximately one-third of pregnancies complicated by GDM had clinical signs and symptoms.

Our data indicate that the 'screening' and 'diagnosis' group represent different entities. Prognosis of GDM depends on the distribution of these two groups within the populations studied. However, such a distinction is usually not made in several landmark studies reporting on outcome of GDM [1, 2, 5].

Our findings support a policy of routine screening, given the better outcome in the screening-group. However, this finding should be interpreted with caution since we applied screening in a high-risk group from outpatients in an academic hospital and not in the entire population. The diagnosis-group, on the other hand, consisted predominantly of low-risk women (Caucasian, near normal BMI) who might have benefited from an earlier diagnosis and treatment, whereas in this study they were diagnosed relatively late.

When fetal macrosomia is present at diagnosis of GDM, about 40% of these fetuses will also be LGA at birth with current treatment. Earlier diagnosis and treatment of GDM before the occurrence of fetal macrosomia may improve neonatal outcome. Given the association between birthweight and childhood obesity in different populations of infants of GDM pregnancies [6, 7], the importance for the long-term outcome is significant. Flexible treatment of GDM depending on high- and low-risk FAC may well be possible, as

*Table 2.1 Gestational characteristics in GDM pregnancies according to the method of detection of GDM (diagnosis versus screening); Values given are numbers (percentages), mean ± SD or medians (5^{th} – 95^{th} percentile). NICU= admission to the neonatal intensive care; admission to the medium care is standard. *Missing cases n=9*

	All	diagnosis-group	screening-group	p
	n = 249	*n* = 74	*n* = 175	
Maternal characteristics				
Age (years)	33,1 ± 4,8	32,7 ± 4,9	33,3 ± 4,8	NS
Ethnicity: Caucasian (n,%)	128 (51,2)	46 (62,2)	82 (46,9)	0,036
Length (cm)	166 ± 6,9	168 ± 6,5	165 ± 6,8	0,003
Weight (kg)	75,0 (58,0-120,0)	73,0 (57,0-97,7)	78,5 (59,8-124,3)	0,006
BMI (kg/m²)	27,9 (20,6-42,9)	26,0 ± 3,8	30,2 ± 7,0	<0,001
BMI >25.0 and < 30.0 kg/m²	75 (30,1)	29 (39,2)	46 (26,3)	<0,001
BMI ≥ 30 kg/m²	73 (29,3	7 (9,5)	66 (37,7)	<0,001
Primiparous (n,%)	69 (27,7)	29 (39,2)	40 (22,9)	0,01
Smoking during pregnancy (n,%)	5 (2,0)	2 (2,7)	3 (1,7)	NS
Alcohol use during pregnancy (n,%)	1 (0,4)	0	1 (0,6)	NS
Folic acid at conception (n,%)	109 (43,8)	36 (48,6)	73 (41,7)	NS
Gestational diabetes and treatment				
Gestational age at diagnosis (weeks)	28 (12-36)	31 (22-37)	27 (10-34)	<0,001
Insulin treatment (n,%)	144 (57,8)	37 (49,3)	107 (61,1)	NS
Gestational age at start insulin treatment (weeks)	31,0 (13,1- 36,0)	33,0 (23,8-38,5)	30,0 (11,1-34,0)	<0,001
Glycemia				
Glycemia in 100g-OGTT				
fasting (mmol/l)	5,777 ± 0,84	5,526 ± 0,96	5,882 ± 0,77	0,006
2hrs post-load (mmol/l)	7,564 ± 2,06	7,568 ± 1,63	7,555 ± 2,21	NS
HbA1c at booking (%) / (mmol/mol)	5,5 ± 0,5 / 37	5,5 (4,8-6,2) / 37	5,4 (4,8-6,5) / 36	NS
Fetal size				
FAC >90^{th} percentile* (n, %)	104 (41,8)	49/72 (68,1)	55/168 (32,7)	NS
Hypertension				
Pre-conceptional hypertension (n,%)	10 (4,0)	1 (1,3)	9 (5,1)	NS
PIH (n,%)	19 (7,6)	2 (2,7)	17 (9,7)	N
Delivery				
Gestational age at delivery (days)	272,3 ± 9,7	271,1 ± 11,4	272,7 ± 8,8	NS
Caesarean section (n,%)	67 (26,9)	20 (26,7)	47 (26,8)	NS
Preterm (GA <37weeks) (n,%)	14 (5,6)	6 (8,1)	8 (4,6)	NS
Neonatal				
Birthweight (grams)	3561,3 ± 524,1	3702,1 ± 611,9	3501,5 ± 471,2	0,006
Z-score	0,479 ± 1,14	0,894 ± 1,26	0,302 ± 1,04	<0,001
Male (n,%)	137 (55,0)	44 (59,5)	93 (53,1)	NS
Macrosomia (> 90^{th} percentile; n,%)	57 (22,9)	27 (36,5)	30 (17,1)	0,001
Severe macrosomia (> 97.7^{th} percentile; n,%)	21 (8,4)	12 (16,2)	9 (5,1)	0,004
NICU (n, %)	8 (3,2)	2 (2,7)	6 (3,4)	NS

advocated by Kjos e.a. [8]. But most importantly, GDM should be defined accurately in high- and low-risk pregnancies, taking the FAC at diagnosis into account.

A recent survey has shown that different countries use a variety of screening approaches [9]. Half of the countries recommend universal screening for GDM; however, even in the latter countries the percentage of women that are actually screened may not be much higher than 10%. There is a difference in the compliance to screening in the several countries and also a lack of definition for screening. The current discussion concentrates on the criteria of an abnormal OGTT: should we identify all cases or should we concentrate on the more severe cases of GDM? [10]. In our opinion the first step should be the implementation of universal screening to identify more severe cases. This will already be a major step in most countries. Later on stricter criteria may be determined, depending, among others, on economical resources [10]. There is still a lot to improve in the diagnosis of GDM.

In conclusion, FAC when diagnosing GDM influences the neonatal outcome. Therefore researchers and clinicians should be aware that the FAC influences study outcome. We suggest that observational, implementation and intervention studies be stratified for fetal size at diagnosis, since the incidence in neonatal macrosomia is dependent on FAC at diagnosis. With selective screening the price to pay is late detection of macrosomia in women to be considered at low risk of GDM. The size of the problem needs to be defined with adequate definitions. International guidelines are necessary for clear definitions of screening and diagnosing.

Author's contribution

N. Hammoud collected and analysed the data and wrote the manuscript, H. De Valk and G. Visser contributed to the data analysis and co-wrote the manuscript, D. Biesma co-wrote the manuscript.

Declaration of Interest

Nothing to declare.

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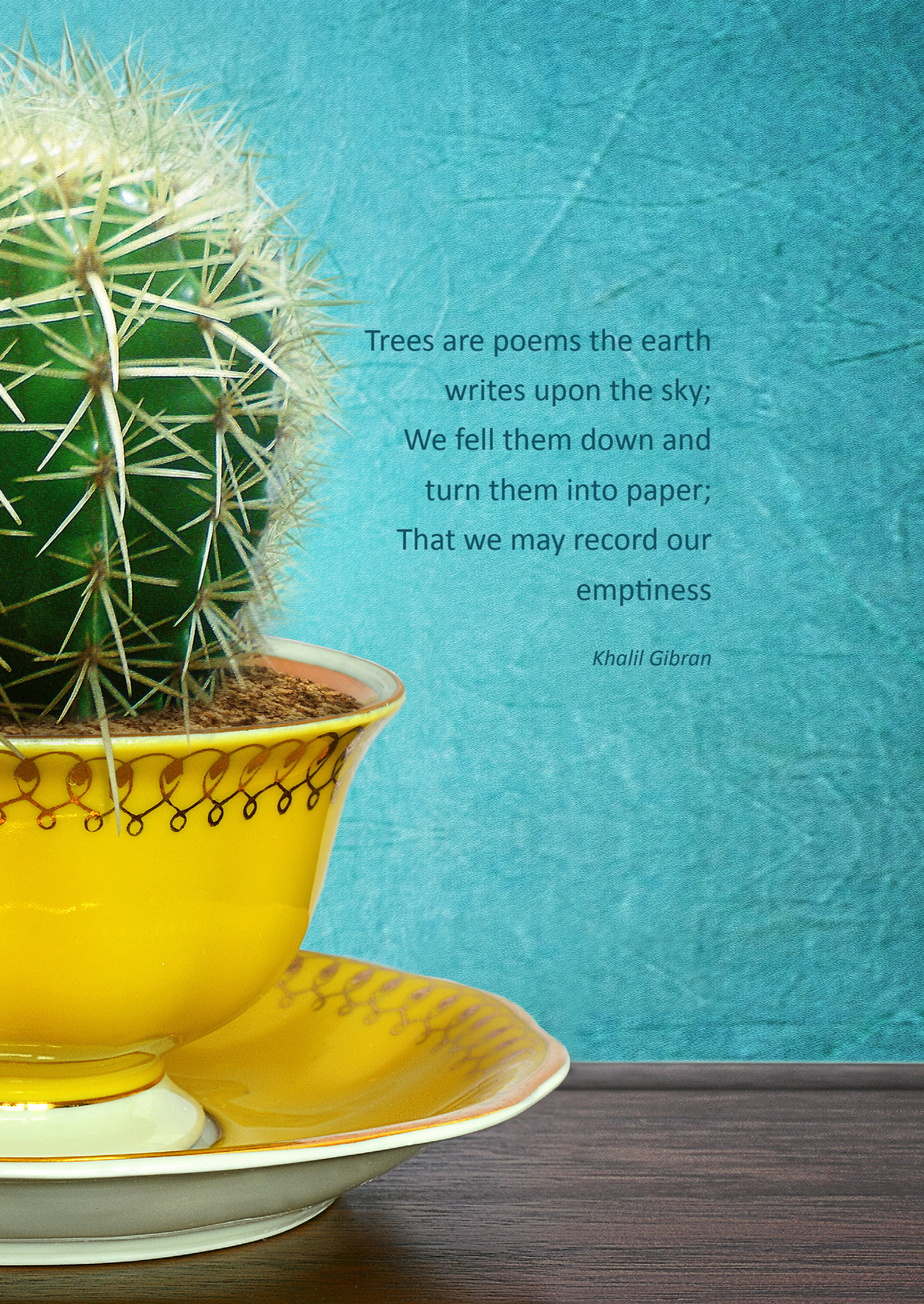
Trees are poems the earth
writes upon the sky;
We fell them down and
turn them into paper;
That we may record our
emptiness
Khalil Gibran

Chapter 3

Fetal growth profiles of macrosomic and non-macrosomic infants of women with pregestational or gestational diabetes

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Abstract

Objective

To assess fetal growth profiles in an unselected group of pregnant women with either type 1 diabetes (DM1), type 2 diabetes (DM2) or gestational diabetes (GDM), with emphasis to inter-group differences and development of (disproportionate) fetal growth and macrosomia.

Methods

Second and third trimester longitudinal ultrasound measurements of fetal growth were made in 77 women with DM1, 68 women with DM2 and in 99 women with GDM. Altogether 897 ultrasound examinations were obtained. 145 uncomplicated pregnancies with 843 ultrasound examinations were included as controls. Ultrasound data included head circumference (HC), abdominal circumference (AC), femur length (FL) and HC/AC ratio.

Results

The AC, but not HC and FL evolved differently in diabetic pregnancies, with a smaller AC in early pregnancy and larger AC at term (significant for DM1 and DM2). Most striking differences were found for the HC/AC ratio, especially in DM1. HC/AC growth trajectories of both macrosomic and non-macrosomic fetuses differed from that of the controls and the HC/AC ratio at term was lower in all diabetic subgroups apart from non-macrosomic DM2.

Conclusions

We found altered (disproportionate) fetal growth in macrosomic and non-macrosomic fetuses of women with type 1 diabetes, type 2 diabetes and gestational diabetes. This indicates that the abnormal intrauterine environment affects the majority of these infants. Growth profiles differed among these groups, with most prominent growth deviations in fetuses of women with type 1 diabetes. The latter was most likely due to a poorer glucose control. In monitoring fetal growth in diabetic pregnancies the HC/AC ratio should be used to assess altered fetal growth.

Macrosomia is associated with both short and long term sequelae including prolonged labour, shoulder dystocia and neonatal asphyxia [1-3]. Macrosomia (birthweight ≥90th percentile) is a frequent complication in diabetic pregnancies [4, 5]. Macrosomia occurs in up to 42-62% of pregnancies complicated by type 1 diabetes (DM1) [6-11], in 30-56% of pregnancies complicated by type-2 diabetes (DM2) [12, 13] and in 10-20% of pregnancies complicated by gestational diabetes (GDM) [14, 15]. Fetal macrosomia in diabetic pregnancies is partly due to increased fat mass and higher percent body fat [16]. Neonates are disproportionately large-for-gestational-age [17, 18] and the total fat index in neonates from GDM pregnancies is higher than that in infants from control pregnancies [19]. Disproportionate macrosomia results in a higher incidence of hyperbilirubinemia, severe hypoglycemia and perinatal acidosis compared to non-macrosomic infants and proportionate macrosomic infants [20].

Knowledge of the fetal growth profiles leading to macrosomia in diabetic pregnancies is important for understanding of the pathophysiology, because it may help to design preventive strategies. However, there is limited information on the growth profiles in diabetic pregnancies in general. Previous studies in diabetic pregnancies in general have indicated that fetal growth accelerates between 18 and 24 weeks of gestation [21-23]. Older studies have reported growth acceleration from 32 weeks onwards [24, 25]. Greco et al have studied pregnancies in DM1 and found an acceleration in abdominal circumference (AC) at 24 weeks of gestation [26]. Recently, Mulder et al analysed the onset of fetal overgrowth in DM1 and showed that accelerated AC growth in midpregnancy is associated with LGA-neonates [27]. The only study performed to compare the different diabetic entities showed an accelerated fetal AC from 28 weeks onwards, with no differences between the subtypes of diabetes treated with insulin [28]. To the best of our knowledge, studies on disproportionate intrauterine fetal growth (i.e. head circumference (HC)/AC) in diabetic pregnancies are lacking. The same holds for stratified analyses in DM1, DM2 and GDM and for infants with a normal or increased birth weight.

It was the aim of the present study to assess fetal growth profiles in an unselected group of pregnant women with either DM1, DM2 or GDM, with emphasis to intergroup differences and development of (disproportionate) macrosomia.

Research Design and Methods

This study was conducted at University Medical Center Utrecht, the Netherlands. All singleton pregnancies complicated by DM1, DM2 and GDM, with a gestational age (GA) of more than 20 weeks, between 2000 and 2010 were included. Growth profiles were compared to those of a local control group. The local control groups consisted of uncomplicated pregnancies with serial ultrasound examinations for scientific purposes [29, 30].

Pregnancies with missing dating scans were excluded from this study. There were no infants with major congenital malformations. There was one child with a clubfoot and

hypospadias, one child with an atrial septal defect type II, in which surgery was not required and one child with a palatoschisis. All these children were from type 1 diabetic pregnancies. Furthermore, there was one child who was diagnosed at the age of 5 months with scafocephaly, this condition was not known at birth. These children are included in the analyses. One pregnancy was randomly selected in women with subsequent pregnancies during the study period. Preterm delivery was defined as a gestational age at delivery before 37 weeks.

DM1 was defined as diabetes starting before the age of 30 with initiation of insulin treatment within three months of diagnosis and low or undetectable c-peptide and/or GAD-positivity and/or an episode of keto-acidosis. The diagnosis of DM2 was accepted when patients were treated preconceptionally with oral glucose-lowering medication or were preconceptionally changed from oral medication to insulin treatment or were long-term treated with insulin and had never experienced a keto-acidotic episode and were GAD-negative with, if available, a normal or elevated c-peptide level. GDM was diagnosed by a 100-grams oral glucose tolerance test according to the ADA-guidelines [31].

Data from all diabetic pregnancies was entered in the database, including demographic, maternal, fetal and neonatal data. Maternal glycemic parameters included HbA1c in all three trimesters, except in GDM. GDM was generally diagnosed in the 2nd trimester, with no 1st trimester HbA1c available. The control groups were healthy, uncomplicated pregnancies. A systematic OGTT was only performed in the control group in women with risk factors for GDM and in women with clinical signs and symptoms of hyperglycemia. For demographics of the control groups we refer to the publications by van Vuuren et al and Pistorius et al [29, 30].

Ultrasound data were retrospectively collected from a separate database recorded in Bureau Medical Automation (BMA) software 'Mosos'. Fetal measurements included head circumference (HC), abdominal circumference (AC) and femur length (FL), which were shown in absolute numbers (millimetres). HC/AC ratio was also included, calculated by dividing the absolute HC in mm with the absolute AC in mm. The HC/AC ratio was used as a putative index for disproportionate growth. Macrosomia was defined as a birthweight greater than the 90th percentile corrected for gestational age, sex, parity and ethnicity, according to the Dutch growth charts [32]; severe macrosomia was defined as birthweight ≥ the 97.7th percentile. Neonates were classified according to presence or absence of macrosomia.

Fetal growth in the diabetic pregnancies was analysed on the basis of 4 or 5 ultrasound examinations, all performed between GA 17 weeks and 36 weeks. In the uncomplicated control group, 5 to 9 ultrasound examinations were performed between 20 and 36 weeks; HC, AC and FL were recorded.

Statistical analysis

General analysis
Differences in baseline variables in women with DM1, DM2 and GDM were tested with ANOVA for continuous variables and χ^2 or Fisher's exact test for categorical variables. A p-value of less than 0.05 was considered statistically significant.

Fetal growth analysis
Fetal growth profiles of DM1, DM2 and GDM separately and between the diabetic pregnancies were analyzed using linear mixed modelling (LMM) [33, 34]. This flexible modelling technique addresses the correlation of repeated measures obtained within the same subject as a random effect. Also, time-independent and time-dependent fixed effects were analyzed using LMM.

LMM models were estimated for the growth profiles in AC, HC, HC/AC ratio and FL in time. Fixed effects were the covariates diabetes type (DM1, DM2 or GDM), macrosomia (yes or no), time (GA in days), and the interaction between time and diabetes type. Random effects were the intercept and time. Potential confounders were maternal ethnicity, length, pre-pregnancy weight and BMI, HbA1c in all 3 trimesters and fetal sex. Confounders were identified when the regression coefficient changed > 10% in either direction when adding the confounder in the model.

Type III tests for fixed effects and covariance parameters were used for interpretation of growth patterns for AC, HC, HC/AC ratio and FL. Growth profiles are defined as linear coefficients during gestation, expressed in regression coefficient (B) and standard error (se). Analyses were performed using SPSS version 17.0 for Windows.

Results

General Characteristics
We included 77 women with DM1, 68 with DM2 and 99 with GDM. Altogether 897 ultrasound examinations were obtained. 145 uncomplicated pregnancies with 843 ultrasound examinations were included as the control group. Maternal characteristics of the diabetic pregnancies are listed in Table 3.1. Patients with DM1 were mostly Caucasian and were taller than patients with DM2 or GDM. Patients with DM1 were 19 kg and 4 kg slimmer than those with DM2 and GDM, respectively; women with DM2 had the highest prepregnancy BMI. Parity was lower in DM1 with about half of these women being nulliparous.

Maternal HbA1c-values were higher in DM1 compared to DM2 and GDM, yet all values indicate generally acceptable glycemic control. GDM was detected at a mean gestational age of 26.3±5.9 weeks. Insulin treatment was applied in 35.1% of these women.

Table 3.1 General characteristics of the study population. Values are given in median (range) or numbers (percentages). HbA1c in trimester 2 and 3 are given in mean ± SD.
*P-values are given for the relations ‡ DM1 vs DM2; * DM1 vs GDM; ⊥ DM 2 vs GDM.*

	DM1	DM2	GDM	P
Total (%)	***77 (31.6)***	***68 (27.9)***	***99 (40.6)***	
Sociodemographic characteristics				
Age (years)	33 (23- 44)	35 (25 – 42)	34 (20-43)	NS
Caucasian (n,%)	71 (92.2)	31 (45.6)	67 (67.7)	0.002 ‡; 0.002 *
Height (cm)	170 (151 – 186)	166 (153-183)	165 (146-180)	0.005 ‡; 0.002 *
Prepregnancy weight (kg)	72 (50- 98)	91 (46 – 169)	76 (45 – 170)	0.000 ‡; 0.000⊥
Prepregnancy BMI (kg/m²)	24.9 (17.7-33.2)	33.3 (18.0–58.5)	26.6 (19.4-60.1)	0.000 ‡; 0.000 ⊥; 0.005 *
Primiparous (n,%)	42 (54.5)	16 (23.9)	28 (28.3)	0.000 ‡; 0.000 *
Glycemic control				
HbA1c 1st trimester (%)	7.1 (5.3 – 9.9)	6.8 (4.7-12.1)	NA	NS
HbA1c 2nd trimester (%)	6.37 (± 0.8)	5.99 (±0.8)	5.70 (±0.7)	0.014 ‡; 0.049 *
HbA1c 3rd trimester (%)	6.46 (±0.8)	5.94 (±0.8)	5.97 (±0.8)	0.001 ‡; 0.017 *
Neonatal characteristics				
Gestational age at delivery (wks)	37 (31- 40)	38 (30 – 42)	39 (31 – 42)	0.002 ⊥; 0.000 *
Preterm delivery (n, %)	25 (32.5)	15 (22.1)	13 (13.1)	0.006 *
Birthweight (grams)	3520 (1100-5585)	3485(1190-4745)	3600 (1500-4890)	NS
Macrosomia (≥90th percentile)	27 (35.1)	19 (27.9)	24 (24.2)	NS
Severe macrosomia (≥97.7th percentile)	16 (20.8)	5 (7.4)	10 (10.1)	NS
Male sex (n, %)	34 (44.2)	35 (51.5)	49 (49.5)	NS
Maternal characteristics				
Pre-eclampsia (n, %)	6 (8.0)	7 (10.3)	5 (5.1)	NS
Caesarean section (n, %)	50 (64.9)	35 (51.5)	23 (23.2)	0.000 ⊥; 0.000 *

Pregnancy outcome is shown in table 3.1. The rate of macrosomia was comparable between groups: DM1 35.1%, DM2 27.9% and GDM 24.2%. GA at delivery was higher in GDM compared to either DM1 or DM2 with concomitant lower incidence of preterm delivery. There was a high Caesarean section rate, especially in women with DM1.

Growth profiles

AC in DM1, DM2, GDM and controls is shown in Figure 3.1a. The AC evolved differently in the diabetic groups than in the controls, with a smaller AC at early pregnancy and a larger AC at term in the diabetic pregnancies. The slope was significantly higher in DM1 and DM2 pregnancies, compared to controls (B = 1.69, 1.65; p <0.001, p 0.001; respectively; controls B = 1.45). Ethnicity, maternal prepregnancy weight and BMI, HbA1c in all trimesters and fetal sex did not affect the slope of AC growth, whereas maternal length did (p =0.018).

The median value of AC, HC, HC/AC ratio and FL at the beginning of the measurements (GA 17 wks) and at 37 weeks of gestation, are displayed for all groups in table 3.2.

Table 3.2 Extraction of measurements through LMM for the AC, AC, HC/AC ratio and FL at the beginning of the measurements (at GA 17 weeks) and at the end (GA 37+3 weeks). Values are displayed for DM1, DM2, GDM and the control group. These values are further categorized for the complete group (as shown in figure 1) and for (non-) macrosomic neonates (figure 3 and 4).

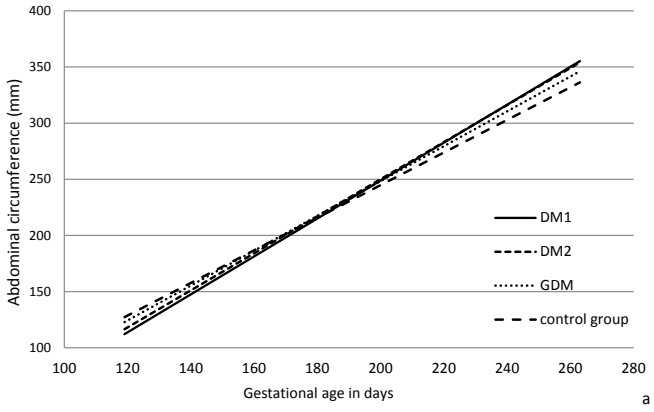
		AC (mm)		***HC (mm)***		***HC/AC ratio***		***FL (mm)***	
Group	*Subgroup*	GA, 17 weeks	GA, 37+3 weeks	GA, 17 weeks	GA, 37+3 weeks	GA, 17 weeks	GA, 37+3 weeks	GA, 17 weeks	GA, 37+3 weeks
DM1	Total	112	355	146	346	1,21	0,95	24	73
	Non-macrosomia	115	344	145	343	1,20	0,98	25	72
	Macrosomia	108	378	145	352	1,23	0,89	25	75
DM2	Total	117	354	144	358	1,16	1,00	25	74
	Non-macrosomia	118	346	142	359	1,16	1,02	25	73
	Macrosomia	115	371	148	355	1,18	0,93	26	76
GDM	Total	123	346	152	346	1,18	0,98	27	73
	Non-macrosomia	125	341	152	344	1,17	0,99	27	73
	Macrosomia	118	361	160	350	1,20	0,96	28	73
Controls	Total	127	336	149	352	1,20	1,02	31	71

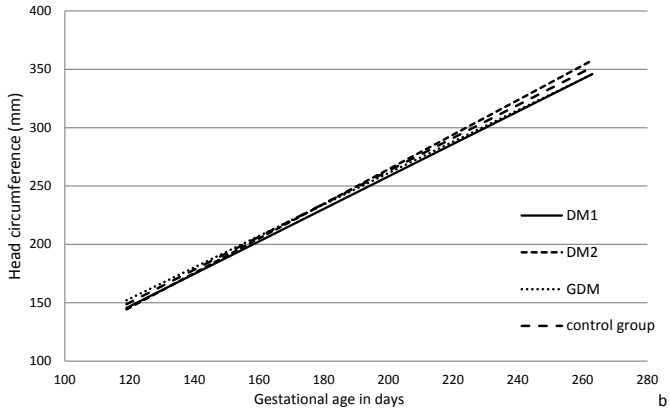
HC and FL did not differ between DM1, DM2 and GDM and controls (Table 3.2 and figure 3.1b). HC/AC ratio is displayed in figure 3.1c. The slope in DM1 (B = -0.0018) was significantly different from DM2 (B= -0.0012; p 0.004), GDM (B = -0.0013; p 0.031) and controls (B = -0.0013; p 0.004). DM2, GDM and control group were comparable. DM1 had the highest HC/AC ratio at early gestation and the lowest ratio at 37 weeks of gestation (table 3.2). Contrastingly, DM2, GDM and the control group had an approximately similar slope running roughly parallel to each other. No confounders were identified, e.g. B was comparable when adding each confounder in the model.

In figure 3.2a-c growth profiles for AC are shown for normal birthweight, macrosomia and severe macrosomia, separately, for in DM1, DM2 and GDM. Within DM1 pregnancies, the slope was significantly different between the 3 subgroups (B = 1.59; 1.73; 1.98; all p values <0.003).

In pregnancies complicated by DM2, only macrosomia and non-macrosomia could be compared due to the small number of severely macrosomic neonates (*n* = 4). The slope was lower in non-macrosomic neonates compared to the macrosomic ones (B = 1.60; 1.78; p <0.001).

For GDM, the slopes for non-macrosomic and macrosomic neonates were lower than that of severe macrosomic neonates (B = 1.50; 1.62; 1.82; p <0.001, p 0.045, respectively).





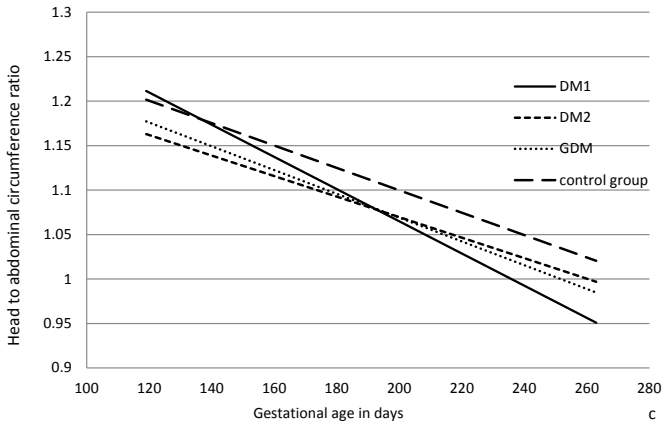
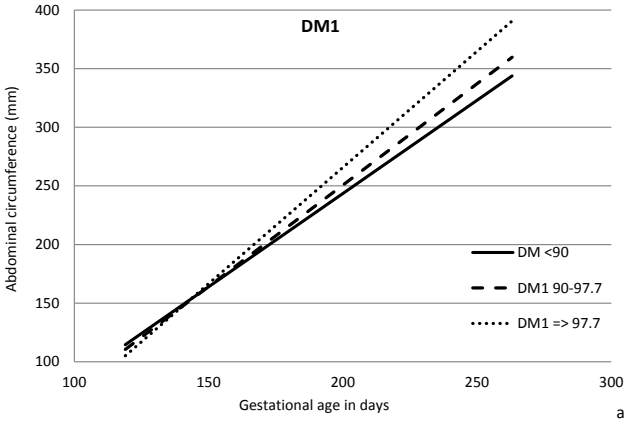
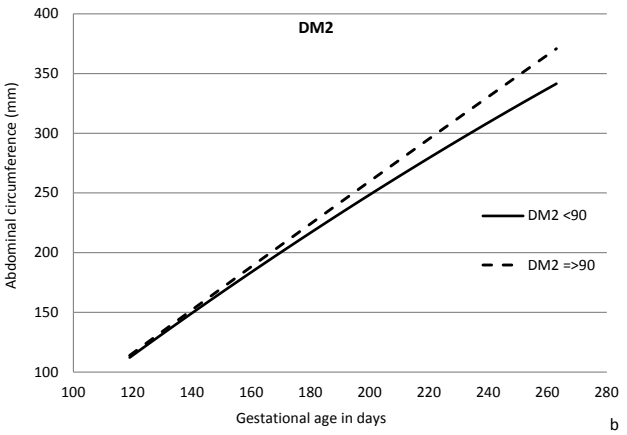


Figure 3.1 (a) Abdominal circumference (AC), (b) head circumference (HC) and (c) head to abdominal circumference ratio (HC/AC ratio) in DM1, DM2, GDM and the control group against GA.





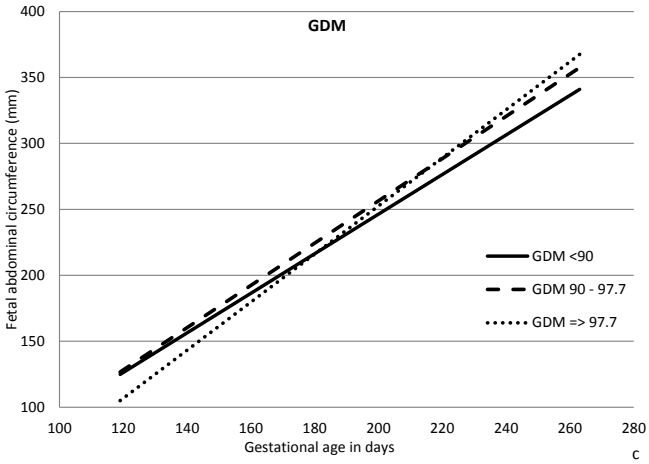


Figure 3.2 Abdominal circumference (AC) in (a) DM1, (b) DM2 and (c) GDM pregnancies, subdivided according to non-macrosomia (birthweight <90th percentile); macrosomia (birthweight ≥90th percentile) and severe macrosomia (birthweight ≥97.7th percentile).

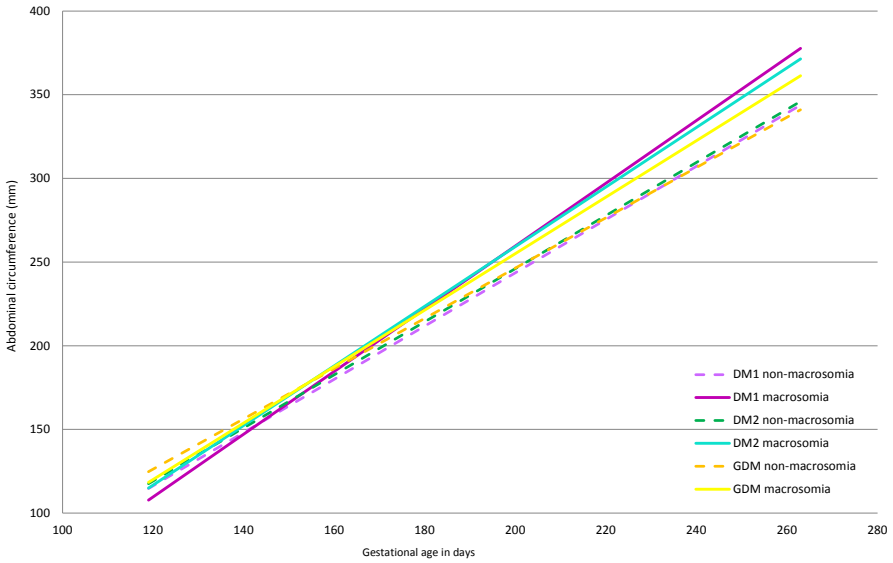


Figure 3.3 Abdominal circumference (AC) in DM1, DM2 and GDM pregnancies, subdivided according to non-macrosomic (birthweight <90th percentile) and macrosomic infants (birthweight ≥90th percentile)

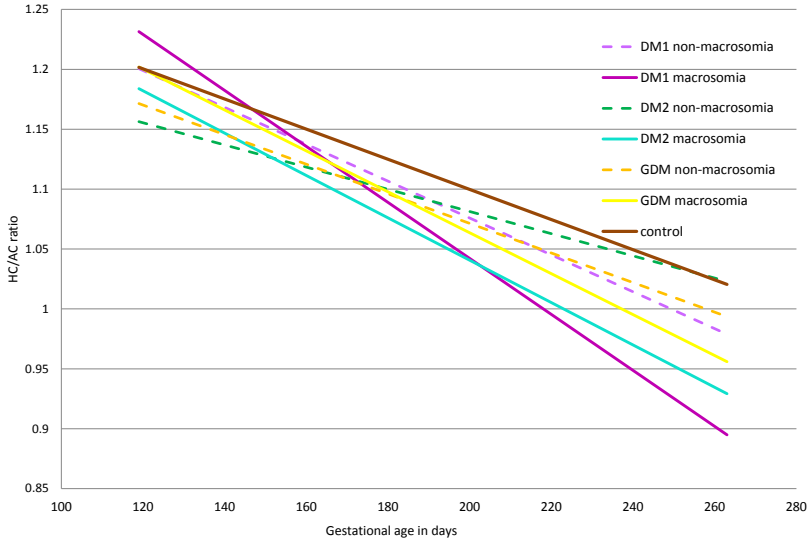


Figure 3.4 HC/AC ratio DM1, DM2 and GDM pregnancies, subdivided according to non-macrosomic (birthweight <90th percentile) and macrosomic infants (birthweight ≥90th percentile)

In Figure 3.3 we compared growth profiles of macrosomic and non-macrosomic infants between DM1, DM2 and GDM pregnancies. Growth profiles for AC of the macrosomic neonates of DM1 and DM2 were comparable (B = 1.87, 1.78; p NS), as well as those of DM2 and GDM (B = 1.78, 1.68, respectively; figure 3.3). The slope was higher in macrosomic neonates of DM1 than in macrosomic GDM (B 1.87 compared to 1.68; p=0.002). In non-macrosomic neonates, GDM had lower slopes than DM1 and DM2 (B = 1.50 compared to 1.59 and 1.59 respectively; p 0.010 and 0.019). Between the latter groups there was no significant difference. Overall, macrosomic infants of DM1 had the highest prenatal AC slope, which was significantly different from all other groups except DM2 macrosomia.
The prenatal growth profiles for HC did not differ significantly between macrosomic and non-macrosomic neonates of DM1, DM2 and GDM (figure not shown).

Finally, we examined the growth profiles expressed as HC/AC ratio for macrosomic and non-macrosomic neonates in DM1, DM2 and GDM pregnancies (Fig 3.4). Macrosomic DM1 infants had the steepest slope, with the highest HC/AC ratio at early pregnancy, and the lowest 37 weeks of gestation (B = -0.00236 versus –0.001767 and -0.01705, respectively for macrosomic DM2 and GDM; p 0.005, p 0.006). Macrosomic infants of DM2 and GDM had a comparable slope.

For non-macrosomic neonates only the HC/AC slopes between, DM1 and DM2 were different, where DM1 has a higher slope (B= -0.00154 versus -0.00093; p=0.024). Overall, the slopes for the non-macrosomic neonates were lower than those for the macrosomic neonates. At term the HC/AC ratio was lower than that in controls for all diabetic subpopulations, apart from non-macrosomic DM2 (figure 3.4).

Discussion

Disproportionate fetal growth has been widely discussed in the context of maternal diabetes, among others to explain the high incidence of shoulder dystocia. However, systematic studies addressing disproportionate growth during pregnancy are lacking and neonatal studies are scarce and incomplete. The present study showed that disproportionate growth occurs both in type 1, type 2 and in gestational diabetes, mainly in macrosomic infants, but also in infants with a normal birthweight. This illustrates that the abnormal intrauterine environment affects the majority of infants. This fits with the observation that there are not two cohorts of infants of women with diabetes, one with a normal growth and one with an accelerated growth, but that the whole population has shifted to the right (e.a. towards a higher birth weight) [35]. It also fits with a study indicating that crown-heel length and head circumference in infants of women with diabetes are identical to controls, but that birthweight is higher [19]. Thirdly, it fits with the recent observation in women with type 1 and type 2 diabetes that indicators of poor placentation in early pregnancy are related to normal birthweight and indicators of normal placentation to increase birthweight; i.e. fetal overgrowth in both instances [36]. Our data also indicate that growth trajectories of fetuses of women with diabetes, should not be taken together as has been done in the past, but should be analysed separately.

Our data on early growth acceleration in DM1 matches the profiles as reported by Greco et al and Mulder et al, studies limited to type 1 diabetes solely [26, 27]. A study by Lim et al showed no difference in the intrauterine growth trajectory for AC and FL in DM1, DM2 and GDM [28], in contrast to our findings. In our population the AC was smaller in DM1 at early gestation and largest at term, as compared to DM2 and GDM. Macrosomia at birth was also most frequent in this group, in contrast to that in the population described by Lim et al in which birthweight centiles did not differ significantly. Data on HC/AC ratio were not given by these authors.

The smaller AC in early gestation in DM1 and DM2 may be due to a poorer placentation in early gestation. It has been shown that first trimester HbA1C is inversely correlated to markers of early placentation (PAPPA) [37]. Early growth delay has been described in DM1 with lower crown-rump-lengths in the 1st trimester and an acceleration in biparietal diameter starting in the early 2nd trimester onwards [38]. Early growth delay has been attributed to several factors: delayed conception, delayed implantation, impaired development of the yolk sac, temporary arrest of embryonic growth during organogenesis and slow embryonic growth rate. The absence of differences between GDM and controls in early pregnancy is understandable in the light of the fact that glucose metabolism is supposedly still normal in GDM women at that age.

Overall the most striking growth deviation occurred in DM1. Both the early growth delay and later excessive growth may be due to poorest diabetic control, which in this study was illustrated by highest HbA1c values (significant for 2nd and 3rd trimester). HbA1C values, however, were better than generally published in literature, which emphasizes that in glycemic control 'almost good is not good enough' [39]. Correlations between fetal growth and HbA1c – although significant [28, 39, 40] - are generally low, indicating that other parameters may influence fetal growth or that HbA1c is a rather insensitive marker for glucose control, especially in the slightly abnormal range (2-4 SD). Others have suggested that there is 'a low glucose threshold for maximal effects on the rate of fetal growth' [28].Earlier we have found in women with type 1 diabetes that HbA1c values did not differ between fetuses that did become macrosomic or otherwise, but that second trimester 24 hour glucose profiles were significantly higher in the macrosomic cases [41].

The strength of this study is that we compared fetal growth profiles in ultimately macrosomic and non-macrosomic infants of women with Type 1, Type 2 and gestational diabetes mellitus separately, with the same technique and during the same time period, with description of disproportionate growth. To our knowledge, this has not been done before. Also control data came from our institute and were obtained in the same time period [29, 30]. The HC/AC ratio, as found in our control population closely fits the one published in literature [42].

In conclusion, we found altered (disproportionate) fetal growth in macrosomic and non-macrosomic fetuses of women with type 1 diabetes, type 2 diabetes and gestational

diabetes. Growth profiles differed among these groups, with most prominent growth deviations in fetuses of women with type 1 diabetes. The latter was most likely due to a poorer glucose control, although HbA1C values were better than generally published in literature. This data emphasize that regarding glycemic control 'almost good is not good enough'. In monitoring fetal growth in diabetic pregnancies the HC/AC ratio should be used to assess altered fetal growth.

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I’m going somewhere,
my shoes said so
Juan-Carlos Goilo - the unknown path

Chapter 4

Intrauterine adiposity and BMI in 4 to 5 year old offspring from diabetic pregnancies

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In press for Neonatology ©

Abstract

Objectives

Pregnancies complicated by maternal diabetes are associated with disproportionate intrauterine growth that subsequently may lead to pediatric adiposity. We investigated whether disproportionate intrauterine growth leads to differences in body mass index (BMI) in 4 to 5 year old offspring from pregnancies complicated by type 1, type 2 or gestational diabetes.

Methods

Ultrasound data of fetal head to abdominal circumference (HC/AC ratio) obtained between 32 and 36 weeks gestational age were related to offspring anthropometrics that were retrieved from infant welfare centers.

Results

We obtained data from offspring of 27 women with type 1 diabetes (ODM1), 22 of women with type 2 diabetes (ODM2) and 24 of women with gestational diabetes mellitus (OGDM). Ultrasound measurements for HC/AC ratio were performed at a mean of 33-34 weeks, with a mean Z-score of the HC/AC ratio of -0.801, -0.879 and 0.017 in ODM1, ODM2 and OGDM, respectively. Mean BMI SDS was highest in ODM2 as compared to ODM1 and OGDM. In ODM1 there was a negative correlation between HC/AC ratio and BMI SDS at the ages of 4 and 5 years, but not in ODM2 or OGDM. Birthweight z-score was positively correlated to BMI SDS in offspring of women with type-2 diabetes or GDM.

Conclusion

Disproportionate intrauterine growth, expressed as HC/AC ratio, was inversely related with BMI SDS in ODM1 at the ages of 4 and 5 years, but not in ODM2 or OGDM. Weight and maybe also obesity in ODM1 is likely to be related to intrauterine adiposity, whereas overweight in ODM2 and OGDM seems more related to others factors such as birthweight centile, maternal obesity and altered lifestyle factors during childhood.

Maternal diabetes is linked to short-term consequences for offspring with a birthweight distribution shifted to the right, a high mean birthweight z-score and increased incidence of macrosomia [1-3], as well as higher risks for assisted vaginal delivery and caesarean section [2]. As children, adolescents and adults, offspring from women with diabetes are at risk for obesity, type 2 diabetes and the metabolic syndrome [4-10]. The fuel-mediated teratogenesis described by Pedersen and later extended by Freinkel states that maternal hyperglycemia leads to increased transplacental transfer of glucose, lipids and amino acids which in turn lead to fetal hyperinsulinism and increased growth. Maternal insulin itself does not cross the placenta. The effect of maternal metabolic abnormalities is reflected in wide-ranging changes in fetal islets, fat stores and muscles and perhaps even changes in habitus' [11]. This cascade, set off by an abnormal intrauterine environment, may lead to changes in offspring phenotype [12]. Intrauterine over-nutrition programs adaptations of the fetal metabolism in order to cope with enriched intrauterine nutrients, which might echo into postnatal life and result in an increased risk for pediatric adiposity [12].

Not all tissues are sensitive to the effect of fetal hyperinsulinism. Insulin stimulates growth of subcutaneous fat depots but has no effect on the growth of the brain and skull. Fetal hyperinsulinism and disproportionate growth may therefore be reflected in utero by a lower head-to-abdominal circumference ratio (HC/AC ratio), even in neonates with a normal birthweight [13-15]. To the best of our knowledge, there are no studies, in which measures of intrauterine adiposity have been related to childhood BMI.

We explored whether disproportionate intrauterine growth, expressed HC/AC ratio, is associated with a higher childhood BMI in 4 to 5 year old offspring from women with type 1, type 2 or gestational diabetes. Additionally, we analysed whether weight at birth is correlated to BMI in these infants.

Methods

Women with a pregnancy complicated by type 1, type 2 or gestational diabetes who delivered in the University Medical Center Utrecht, the Netherlands, between 2000 and 2006, were contacted to participate in a follow-up study regarding offspring growth. Maternal characteristics at pregnancy and pregnancy outcomes were retrieved from records of the UMC Utrecht. None of the women with type 1 diabetes mellitus were diagnosed with micro-angiopathy. Two women in this group had hypertension. Gestational diabetes was diagnosed using a 75-g oral glucose tolerance test in 22 (92%) of cases; the other patients were diagnosed through elevated fasting glucose levels or an abnormal glucose profile. The Medical Ethics Committee of the University Medical Center approved this study.

Ultrasound data on head circumference (HC) and abdominal circumference (AC) between 32 and 36 weeks of gestation were retrieved from the patient records. When 2 measurements were available, the mean was calculated. HC/AC ratio was calculated by dividing the absolute HC in mm by AC in mm and the z-score for HC/AC ratio was

calculated as follows: (HC/AC ratio minus mean HC/AC ratio for gestational age) divided by z-score HC/AC ratio for gestational age [16].

Offspring height and weight were retrieved from infant welfare records after parental informed consent was received. BMI was calculated as weight/height^2 and expressed as kg/m^2. Overweight and obesity were calculated based on the International Obesity Task Force (IOTF) cut-off values [17]. BMI SDS was calculated based on national age and gender specific data [18].

For the comparison between data of offspring from women with type 1 (ODM1), type 2 (ODM2) or gestational diabetes mellitus (OGDM), categorical variables were compared through the Chi-square test and for continuous variables the student t-test was used with normally-distributed parameters and the Mann–Whitney U test with skewed parameters. Data were analysed using IBM® SPSS Statistics version 23.0 for Mac.

Results

Between 2000 and 2006 27 ODM1, 22 ODM2 and 24 OGDM were analysed. Maternal and offspring characteristics are shown in table 4.1. Preconceptional maternal BMI was highest in women with type 2 diabetes mellitus, followed by gestational diabetes and type 1 diabetes with a mean BMI of 31.9, 27.7 and 24.8kg/m^2, respectively ($p<0.001$). All women with type 1 and type 2 diabetes were treated with insulin during pregnancy, as well as 50% of women with gestational diabetes. Mean HbA1c levels during pregnancy were below 6.6%, which is slightly higher than the normal mean in pregnancy of 4.4–5.6% and there were no statistically significant differences between the groups [19]. Third trimester fetal measurements were performed at a mean of 33-34 gestational weeks with the lowest Z score for HC/AC ratio in ODM2, followed by ODM1 and OGDM ($p <0.001$). Mean birthweight was comparable between the three groups. One-third to 50% of the infants were LGA at birth, with the highest incidence in ODM1 (NS).

Table 4.1 characteristics of study population

	ODM1	ODM2	OGDM	p
n	*27*	*22*	*24*	
Maternal characteristics				
Pregestational BMI (kg/m^2)	24.8±4.2	31.9±7.3	27.7±5.2	<0.001
Age at delivery (years)	34±3.7	34±4.8	34±5.7	NS
Primiparous (%)	13 (48)	4 (18)	10 (42)	<0.05
Mean preconceptional A1C (%)	7.1±0.88	6.6±0.55	N/A	NS
Mean pregnancy A1C (%)	6.6±0.98	6.1±0.74	5.9±0.82	NS
Insulin use in pregnancy (%)	27 (100)	22 (100)	12 (50)	<0.001
Pre-eclampsia (%)	3 (11)	1 (4.5)	2 (8)	NS
Caesarean section (%)	18 (67)	4 (18)	11 (46)	<0.05
Offspring characteristics				
Gestational age HC/AC ratio (weeks)	34±1.0	33±1.7	34±1.6	NS
Mean HC/AC ratio	0.989±0.08	0.990±0.04	1.023±0.06	NS
Z-score HC/AC ratio	- 0.801±1.21	-0.879±0.56	0.017±0.06	<0.001
Gestational age at delivery (weeks)	37±1.3	38±1.7	39±2.0	<0.05
Female gender (%)	13 (48)	11 (50)	13 (54)	NS
Birthweight (g)	3506±556	3701±509	3582±576	NS
Large for gestational age (%)	13 (48)	9 (41)	8 (33)	NS
Overweight (including obesity) at 4-5y	2 (7)	8 (36)	4 (17)	<0.05
Obese at 4-5 y	0	4 (18.2)	1 (4.2)	<0.05

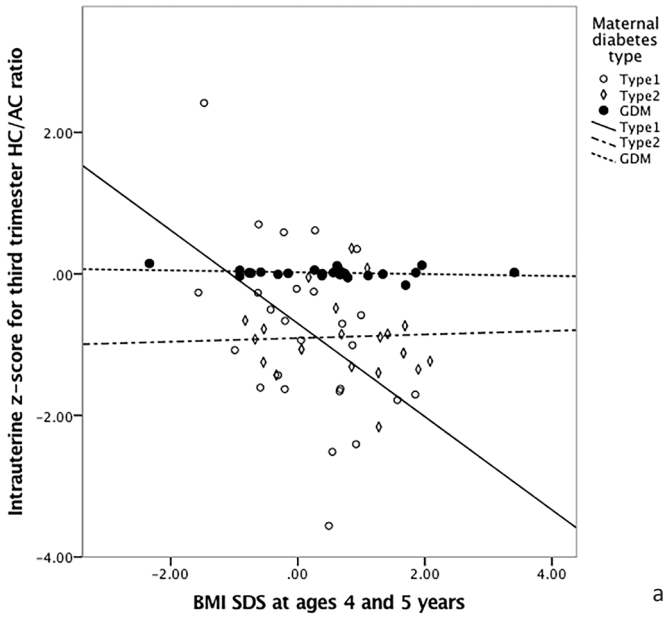
*Table 4.2 BMI SDS and correlations with fetal head to abdominal circumference ratio (HC/AC) and birthweight Z-score; Legend: * significant p <0.05*

	ODM1	*n*	ODM2	*n*	OGDM	*n*	p
n	**27**		**22**		**24**		
BMI SDS at age 4	0.15±0.8	27	1.12±1.6	22	0.37±0.2	21	0.03
BMI SDS at age 5	0.07±1.6	3	2.19±2.2	8	0.87±1.1	7	0.19
Correlations	**ODM1**	**p**	**ODM2**	**p**	**OGDM**	**p**	
BMI SDS ages 4-5 * HC/AC ratio	- 0.46*	0.02	0.07	0.74	- 0.25	0.24	
BMI SDS ages 4-5 * BW z-score	0.29	0.15	0.45*	0.04	0.53*	0.00	

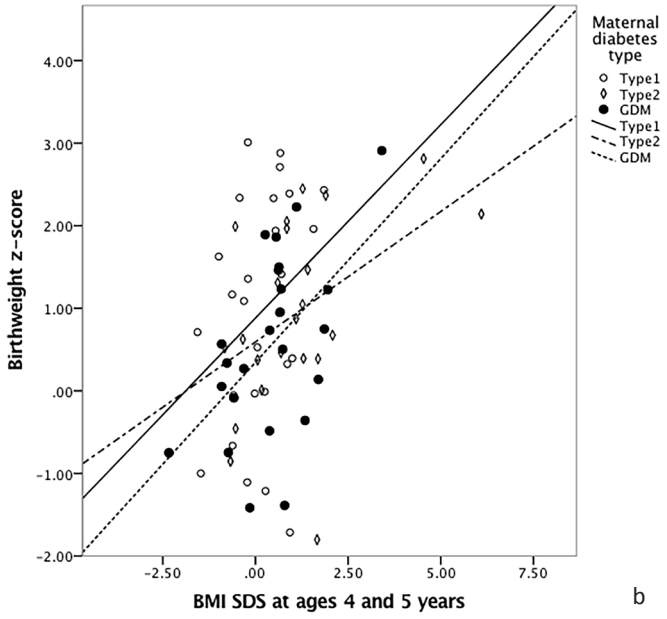
At the age of 4 to 5 years, the percentage overweight (including obesity) was highest in ODM2, followed by OGDM and lowest in ODM1 (36, 17 and 7%, respectively; p <0.05). None of the ODM1 was obese at these ages, whereas 18% of ODM2 and 4% of OGDM were obese (p <0.05). Mean BMI SDS was also highest in ODM2 as compared to ODM1 and OGDM, although differences between groups were only significant at the age of 4 years (table 4.2).

Offspring BMI in relation to the fetal HC/AC ratio

The correlation between BMI SDS at 4-5 years and intrauterine HC/AC ratio is shown in



a



b

Figure 4.1 Scatter plot for intrauterine Z-score for HC/AC ratio (y-axis) and standard deviation score (SDS) for BMI for offspring aged 4 to 5 years in ODM1, ODM2 and OGDM (a); scattor plot for birthweight z-score and SDS for BMI in offspring aged 4 to 5 years in ODM1, ODM2 and OGDM (b);
A single measurement per child; HC/AC ratio, head-to-abdominal circumference ratio; SDS, standard deviation score; BMI, body mass index

figure 4.1A. In this figure a single BMI SDS is presented for each child with BMI SDS at either 4 or 5 years of age. In ODM1 there was an inverse correlation between HC/AC ratio and BMI SDS (r -0.46; p= 0.02; table 4.2, figure 4.1a); in other words, the higher the abdominal circumference in relation to the HC, the higher the BMI SDS. In ODM2 nor in OGDM, such an association was not found.

The correlation between birthweight z-score and BMI SDS is shown in figure 4.1B. The birthweight z-score was positively correlated to BMI SDS in ODM2 (r 0.45; p 0.04) and OGDM (r 0.53; p <0.01; table 4.2, figure 4.1b), but was not significant for ODM1 (r 0.29, NS).

Conclusion

In conclusion, we found that disproportional fetal growth as a consequence to fetal hyperinsulinism was related to the BMI in 4-5 year old infants of women with type-1 diabetes, which suggests an effect of an abnormal intra-uterine environment on later outcome. This suggests, that offspring BMI in ODM1 partly has its origins in intrauterine programming, expressed as fetal abdominal adiposity [19]. In contrast, we found no evidence that disproportionate fetal growth in ODM2 and OGDM was related to overweight at early childhood. For the latter groups, birthweight z-score gave a better prediction of BMI SDS. In these groups, with the highest BMI in the mothers, intrauterine adiposity does not seem to be a risk factor for offspring adiposity, whereas birthweight (centile) is.

There are many studies that have shown that infants of women with diabetes have an increased rate of overweight/adiposity. However, when correcting for maternal BMI most of these associations disappear, suggesting that maternal obesity is the most important factor related to childhood obesity and/or metabolic syndrome [6, 20-22]. In one follow-up study in infants aged 16, it was clearly shown that maternal BMI was the driving factor behind childhood obesity [20]. The presence of maternal GDM did not affect outcome, but in combination with maternal obesity it resulted in the highest incidence of overweight in offspring [20]. In other words, maternal obesity seems the most important factor, with diabetes as an additional risk factor.

In our study the highest incidence of LGA occurred in infants of women with type-1 diabetes, but these infants had the lowest BMI and lowest incidence of overweight at the age of 4 to 5 years. The highest BMI was found in offspring of women with type-2 diabetes who themselves had by far the highest BMI. These data strengthen the concept that maternal BMI is probably the most important factor affecting overweight/obesity in offspring. The relation between HC/AC ratio and childhood overweight in women type-1 diabetes, may well show the additional effect of abnormal fetal growth in women with a normal BMI; an effect that might have been overruled by other maternal factors in case of overweight in women with type-2 diabetes or GDM.

Childhood obesity may also be related by other factors during the first years of life such as lifestyle, but unfortunately, there are no studies investigating lifestyle and eating habits in nurturing of offspring of women with diabetes.

In conclusion, we found that disproportional fetal growth as a consequence to fetal hyperinsulinism was related to overweight/obesity in infants of women with type-1 diabetes, which suggests an effect of an abnormal intra-uterine environment on later outcome. In offspring of women with type-2 diabetes or GDM this relation was absent, indicating that other factors such as maternal obesity, may have played a more important role. Larger studies are necessary to validate our findings.

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Disclosure statements

The authors have nothing to disclose

Contribution to Authorship

N.H. wrote manuscript, researched data; H.V, G.V., reviewed/edited manuscript, contributed discussion, D.B. contributed to discussion.

Details of Ethics Approval

The ethical approval was granted by the Medical Ethics Committee at the University Medical Center, Utrecht in the Netherlands (application number 13/179, reference number WAG/om/13/053639) on the 09th of April 2013.

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We delight in the beauty
of the butterfly, but rarely
admit the changes it has
gone through to achieve
that beauty
Maya Angelou

Chapter 5

Growth and body mass index during the first 14 years of life in offspring from women with type 1 or type 2 diabetes mellitus

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Abstract

Background

Infants of women with pregestational diabetes are at risk for developing obesity in later life. It was the aim of this study to identify subgroups at highest risk, by studying growth profiles of offspring from women with type 1 or 2 diabetes mellitus (ODM1, ODM2) until the age of 14 years.

Methods

Women with type 1 or 2 diabetes were contacted and information from infant welfare centers was received for 78 ODM1 and 44 ODM2. Mean BMI and height standard deviation scores (SDS) were calculated and data from the 2009 Dutch growth study was included in a random-effects model.

Results

BMI SDS profiles differed between ODM1 and ODM2, with the highest mean BMI SDS profiles in ODM2. Other factors that affected the growth profiles in these infants included the presence of maternal obesity, LGA at birth and in ODM2 a Dutch-Mediterranean origin.

Conclusions

Offspring of women with diabetes have higher BMI SDS profiles than those in the Dutch growth study, with the highest BMI SDS in ODM2 who are LGA at birth and having obese mothers. Preventive strategies for offspring adiposity may include pursuing lower prepregnancy maternal BMI, prevention of LGA at birth and prevention of increased weight gain during childhood.

Maternal hyperglycaemia in pregestational diabetes is associated with foetal hyperinsulinism and asymmetrical foetal overgrowth expressed as a higher abdominal circumference compared to head circumference, even in neonates with a normal birthweight [1-4]. This cascade not only leads to short-term neonatal problems, but also forms the basis for problems later in life, with increased risks for obesity and associated metabolic disorders [5, 6].

As adolescents, offspring from pregnancies complicated by type 1 or type 2 diabetes (DM1; DM2) are at risk for developing type 2 diabetes mellitus [7, 8]. Offspring growth trajectories, expressed as BMI and height trajectories, could be helpful in identifying those children at risk for obesity. For instance, in a non-diabetic cohort study [9] an accelerated rise in BMI after the age of 2 predicted later development of DM2. Also the cumulative incidence of DM2 has been shown to be positively related to BMI at each age from age 4 years onwards [10].

Postnatal linear growth and BMI trajectories of infants from diabetic women may identify those with the greatest risk to develop diabetes and/or metabolic syndrome. Cross-sectional studies, which included offspring BMI at a single age, have shown higher BMI (standard deviation score (SDS)) in offspring of women with either DM1 [8, 11, 12] or DM2 [7, 13, 14] compared to controls. A small study has shown that offspring of DM2 women have a higher BMI than offspring of DM1 women or non-diabetic controls [15]. A retrospective cohort showed, however, a similar BMI between offspring of DM1 women and controls [16]. Due to the cross-sectional design and methodology of these studies, growth patterns were not available. Also differences in methodology and definitions of overweight/obesity make comparisons difficult. The few longitudinal studies performed in offspring from pregestational diabetic pregnancies have shown different growth trajectories between large for gestational age (LGA) and non-LGA offspring of DM1 pregnancies [17] and higher risks of overweight in offspring of DM1[18] or DM2 [14].

There are no longitudinal studies comparing growth of offspring of DM1 and DM2 women, which might be crucial to formulate preventive strategies in these high-risk groups. Data on height of offspring from women with diabetes are also lacking; such data may help to identify the weight component in the equation towards possible childhood overweight/obesity. Therefore, the aim of the current study was to construct growth trajectories for offspring of women with type 1 and type 2 diabetes, expressed as height and BMI SDS trajectories, with subgroups of LGA and non-LGA offspring. This was done to assess possible differences in postnatal growth trajectories and to identify infants with the most pathological growth pattern, possibly resulting in overweight.

Patients and methods

Patients

The study group consisted of singleton offspring of women with type 1 diabetes (ODM1) and type 2 diabetes (ODM2) who delivered in the University Medical Centre Utrecht, the Netherlands between 1990 and 2006. Women with gestational diabetes were excluded from this study. All these women were contacted in 2013 and were invited to participate by consenting to retrieve individual offspring growth charts from the Dutch infant welfare and school health centres. The parents completed a questionnaire including questions regarding maternal and paternal height, current weight, comorbidities and ethnicity; also parents provided the most recent height and weight of the child, measured either by a health professional or themselves. The welfare centres have a high coverage and record infant weight, supine length (<2.0 years) and height (≥2.0 years) on specified dates between birth and 4 years (1, 4, 6, 9, 11, 14, 18, 24, 36, 45 months). Thereafter, children are measured in the school health service at 5.5, 11 and 13 years, with a variance of 1-2 years around these time points. Trained health care professionals perform the measurements. Infants' length and standing height was measured to the nearest 0.1 cm. Up to 15 months children were weighed naked. Older children were weighed wearing underwear only, on calibrated mechanical or electronic step scales. Weight was to the nearest 0.1 kg. The medical ethics committee of the University Medical Centre Utrecht approved this study.

Methods

Baseline maternal characteristics at pregnancy and pregnancy outcomes were retrieved from records of the UMC Utrecht. Parents provided information regarding their own current height and weight, educational status and current height and weight for each child when they completed the written questionnaire. *Birthweight (BW) SDS* was calculated as follows: (BW minus mean BW for gender, parity and gestational age)/SD for gender, parity and gestational age, based on Dutch reference data [19]. *LGA* was defined as a BW ≥90th percentile corrected for gestational age, gender, and parity [19]. *Conditional target height (cTH)* of offspring was calculated based on parental height according to Hermanussen & Cole [20] and adapted to Dutch growth standards [21]. *Length and height* of ODM1 and ODM2 were expressed as SDS for age and gender based on the Fifth Dutch Growth Study performed in 2009 [22]. *BMI* was calculated from height and weight with the following formula: weight (kg) / (height (m))^2. BMI was expressed as a SDS for the 1980 nation-wide growth study, in which SDS 0 equals the age- and gender-specific mean of the 1980 Dutch reference population [23]. The latter data are still the normative standard for BMI in the Netherlands. However, our data were also compared to the 2009 Dutch BMI data, see below [24].

Values from the Fifth Dutch Growth Study and subgroup analyses

Since the BMI of Dutch children has increased from the 1980s onwards, we also calculated mean BMI SDS for children of Dutch origin participating in the 2009 (Fifth) Dutch Growth Study [24]. The values of the 2009 nation-wide study were plotted

in the BMI SDS graphs for visual comparison of our offspring from the diabetic pregnancies, in order to show the effect of the obesity epidemic in a nation-wide cohort. The ODM2 group was a heterogeneous group with 50% of Mediterranean origin, therefore a subgroup analyses of this group was performed. BMI SDS of Dutch-Mediterranean children was calculated based on a 50-50% mixed sample of Dutch-Mediterranean children participating in the 2009 (Fifth) Dutch Growth Study [24, 25]. These values are plotted in the BMI SDS graphs of ODM2 for visual comparison to the nation-wide BMI SDS of Dutch-Mediterranean children.

Statistical analysis

For comparison of ODM1 and ODM2 at baseline, categorical variables were compared through the Chi-square test; continuous variables with the t-test and non-parametric variables with the Mann–Whitney U test.

The longitudinal analyses fitted smooth, flexible curves with a random-effects model to estimate the growth trajectories of ODM1, ODM2, non-LGA ODM1, non-LGA ODM2, LGA ODM1 and LGA ODM2. Mixed model addresses the correlation of repeated height and BMI SDS measurements obtained within the same child, as well as time-independent variables (maternal age at delivery, parity, educational level, employment hours, marital status, ethnicity, breast feeding, preconceptional HbA1c, mean pregnancy HbA1c, paternal BMI, paternal ethnicity or paternal diabetes) and accommodates to the available values in the dataset. Fixed effects were the covariates maternal diabetes type (DM1, DM2), LGA (yes, no), time (age in years), and the interaction between time and maternal diabetes type to show increases or decreases in growth over time. Random effects were intercept and time. Potential confounders were the previously mentioned time-independent variables; there were labelled as covariates in a sensitivity analysis. If the addition of a covariate to the model changed the estimate with more than 10%, we considered this a confounder. In a next step, we checked whether these potential confounders changed the model by visual inspection of the graphs.

Given the known rapid decreases in BMI SDS during the first year of life in infants born LGA, both in (non)-diabetic populations [10, 14, 17, 26], we separately analysed the growth trajectories in infancy.

In a model with the factors as fixed effects and random effects (mentioned before), the models were examined using the Akaike information criterion (AIC) and Bayesian information criterion (BIC). The best model fit had the lowest AIC and BIC, which included a linear and square interaction of diabetes with age, with intercept and age as a random effect, in order to determine the trajectories for BMI and height SDS. Consequently, for the growth SDS points in the square model, the values of ODM1, ODM2, and both non-LGA and LGA ODM1 and ODM2 were modelled as

SDS=intercept+β_{0ij}+β_{1ij}(age)+β_{2ij}(age)^{**2}, where β_0 represents the intercept, β_i is the diabetes type (e.g. maternal DM1 or DM2), β_j is LGA and age is offspring age in years (^{**2}=square). The mixed model values for BMI SDS are available in supplemental table 5.1. Data were analysed using IBM® SPSS Statistics version 23.0 for Mac and Microsoft® Excel® for Mac 2011. Software prepared by the Dutch Growth Research Foundation, Growth Analyser 3.5, was used to calculate height SDS using the 2009 data from the Fifth Dutch Growth Study [22] and BMI SDS using the 1980 Dutch nationwide data which are still the normative standards for Dutch children [23].

Results

From 1990 to 2006, 150 ODM1 and 70 ODM2 were identified, of which we received parental informed consent for offspring growth charts from 78 (52%) and 44 (63%), from respectively 52 and 32 mothers. From these parents we received a completed questionnaire for 51 (65% of responders) ODM1 and 21 (48% of responders) ODM2. Age at childbirth and pregestational BMI from mothers who participated were comparable to non-responders.

Baseline characteristics

One of the included infants had a small ventricular septum defect. All mothers were treated with insulin during their pregnancies. The average±SD number of height and weight measurements per child between birth and 14 years of age was 8±2, with 629 measurements for ODM1 and 342 for ODM2.

Some women had more children in the current study. Therefore, we subdivided table 1 into maternal and offspring characteristics with different numbers and certain maternal and paternal characteristics (e.g. ethnicity) valid for all pregnancies within that family. All mothers with DM1 were Caucasian as well as 96% of their partners (table 5.1). In contrast, 46% of mothers with DM2 were of Mediterranean descent, as were all partners in this subgroup. Maternal BMI in ODM2 was 6 points higher than ODM1. Conditional target height was significantly lower for girls in ODM2 compared to ODM1; between the boys there were no significant differences. The women with DM1 had a higher caesarean section rate than those with DM2; the relatively lower birthweight of DM1 infants was consistent with the shorter gestational age. 46% of ODM1 were LGA and 43% of ODM2. Only 2 infants had a birth weight below the 10th centile (one in each group).

BMI SDS trajectories: 1 to 12 months

At age 1 month, LGA ODM1 and LGA ODM2 have a higher BMI, as was to be expected giving their high birthweight. All BMI SDS trajectories showed a negative slope with decreasing BMI SDS (figure 5.1A, 5.1B). Even though LGA ODM2 had the highest BMI SDS values, there were no statistically significant differences compared to ODM1.

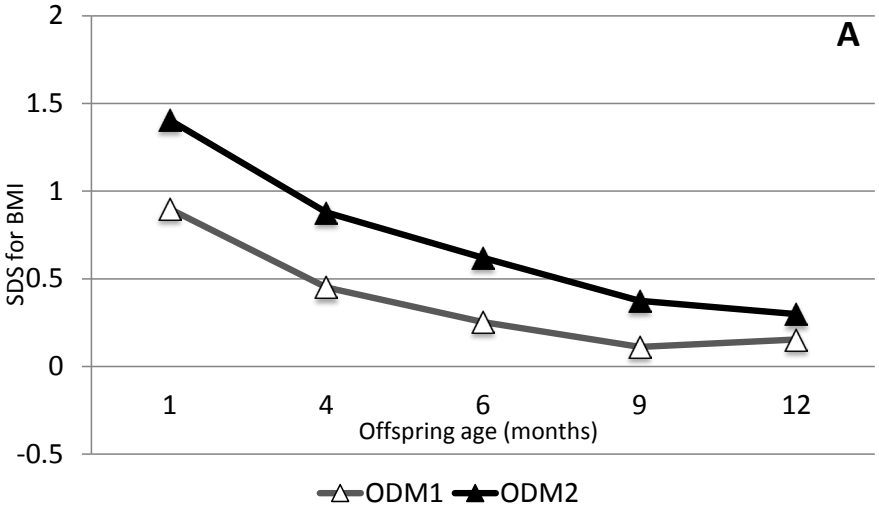
BMI SDS trajectories for primiparous women are shown in supplementary table 1. Due to comparable results, all offspring are included in the analyses.

Table 5.1 Baseline characteristics of the study populations
Values are n (%) or mean (±SD) or median (interquartile range) ¶;
* Eldest infant of the mother born our center (e.g. primiparous women);
** 7 – 18 missing values; *** 38 - 58 missing values.

	ODM1	ODM2	p
***n* of infants**	**78**	**44**	
Prepregnancy maternal BMI (kg/m^2)¶	24 (4.3)	31 (7.6)	<0.05
Maternal BMI > 25/<=30 kg/m^2 (%)	19 (24.4)	16 (37.2)	<0.05
Maternal BMI > 30kg/m^2 (%)	4 (5.1)	23 (53.5)	
Maternal age at delivery (years)	33±4	34±5	NS
Multiparous (%)	37 (47)	36 (82)	<0.05
Mean preconceptional A1C (%) ***	7.1±0.9	6.7±1.0	NS
Mean pregnancy A1C (%) ***	6.3±1.0	6.1±0.8	NS
Pre-eclampsia (%)	9 (11.5)	2 (4.5)	NS
Caesarean section (%)	46 (59)	14 (32)	<0.05
Gestational age at delivery (weeks) ¶	37 (2)	38 (1)	<0.05
Female gender (%)	49 (63)	23 (52)	NS
Birthweight (g) ¶	3527 (859)	3725 (528)	<0.05
Birthweight SDS ¶	1.02 (2.0)	0.96 (1.2)	NS
Large-for-gestational age (LGA) (%)	37 (47)	19 (43)	NS
Neonatal admissions on medium or ICU (%)	53 (78)	21 (48)	<0.05
Breast-feeding at 1 week (%) ***	40 (71)	15 (63)	NS
Conditional target height boys (cm)	182.2 ± 5.8	179.6 ± 4.3	NS
Conditional target height girls (cm)	170.2 ± 4.1	166.5 ± 5.2	<0.05
	ODM1	ODM2	p
n* of women	**52**	**32**	
Maternal ethnicity Caucasian (%)	52 (100)	17 (53)	<0.05
Paternal ethnicity Caucasian (%)	50 (96)	17 (53)	<0.05
Current paternal BMI (kg/m^2) ¶ **	24 (4.5)	27 (5.0)	0.04
Maternal education (university of applied sciences)(%)	19 (37)	4 (13)	<0.05
Maternal fulltime job (%) **	5 (16)	2 (15)	NS

BMI SDS trajectories: 1 to 14 years

BMI SDS trajectories are shown in figures 5.1C and 5.1D, in which the values of the 2009 Dutch growth study are also shown. Growth trajectories of ODM1 and ODM2 were significantly different from each other (age p <0.001; age2 p 0.004).



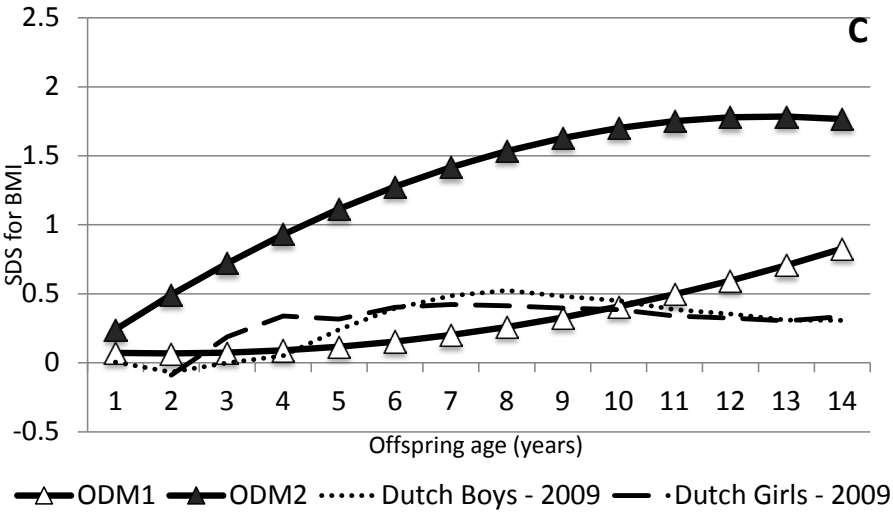
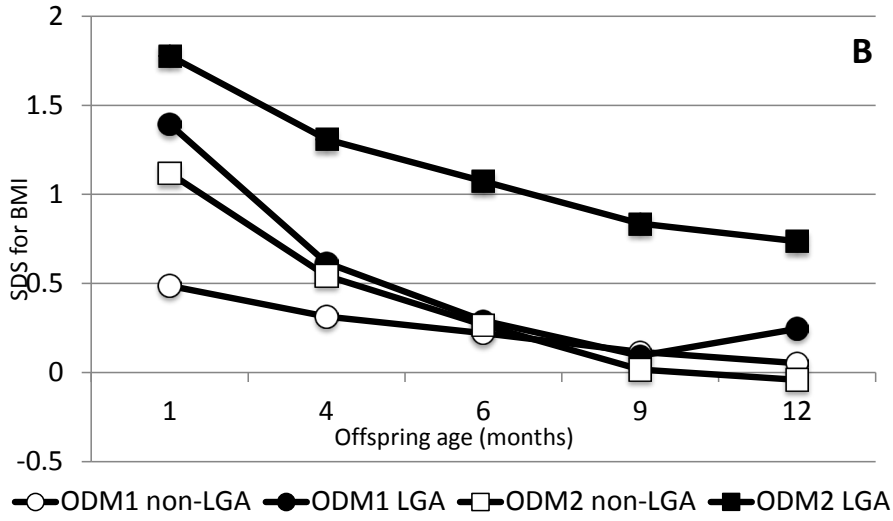


Figure 5.1 Mixed model for mean BMI SDS for offspring at the age of 1 to 12 months for ODM1 and ODM2 (A); (non)-LGA ODM1 vs. ODM2 (B); mean BMI SDS from 1 to 14 years for ODM1 vs. ODM2 with reference values from the 2009 growth study (C); (non)-LGA ODM1 vs. ODM2 with values from the 2009 growth study (D);
Reference values from Dutch boys and girls were adapted from Schonbeck et al [24], based on values from Cole & Roede [23].
White triangle = ODM1, black triangle = ODM2; white circle = non-LGA ODM1; black circle = LGA ODM1; white square = non-LGA ODM2; black square = LGA ODM2; dotted line = Dutch Boys 2009; dashed line = Dutch Girls 2009.



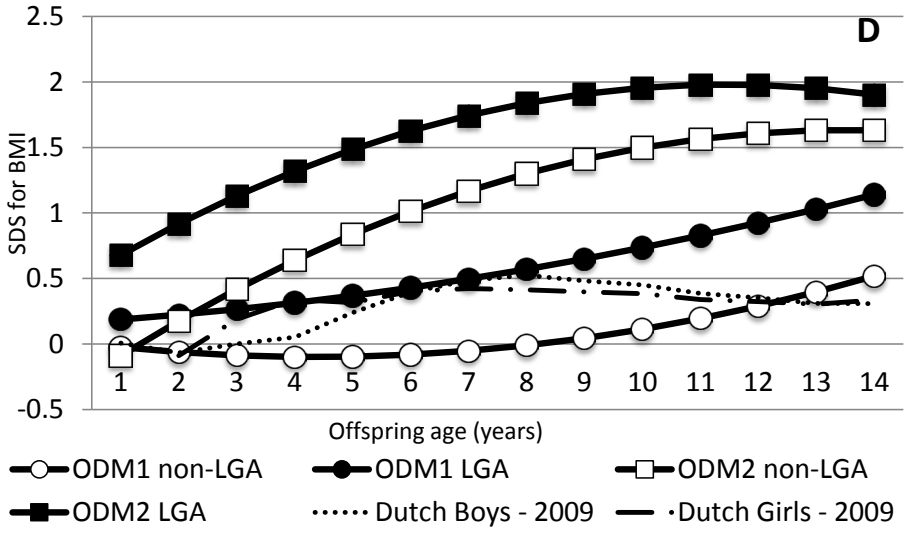


Figure 5.1 Continued

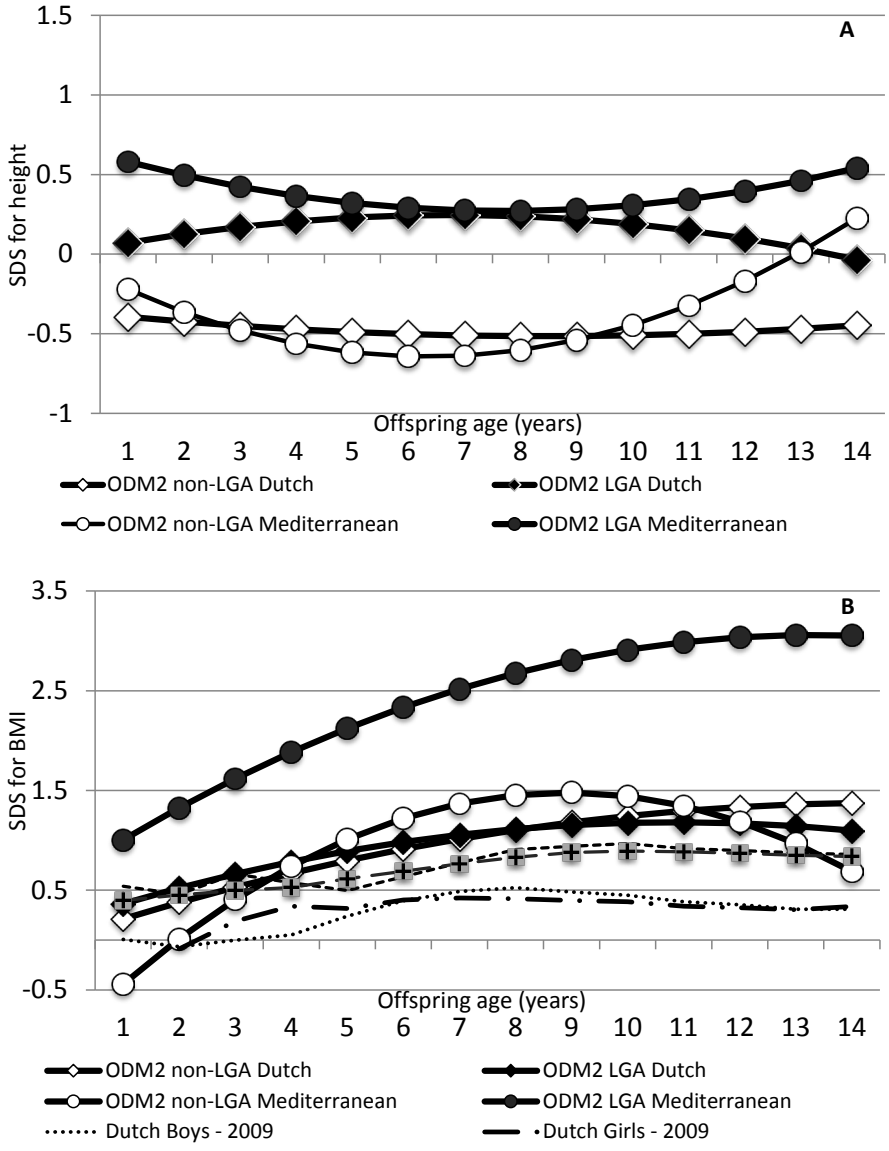


Figure 5.2 Mixed model for only ODM2 with mean height SDS of Dutch and Mediterranean (non)-LGA ODM2 (A); and BMI SDS of Dutch and Mediterranean (non)-LGA ODM2 and the 2009 growth study (reference population) (B);
Reference values from Dutch boys and girls adapted from Schonbeck et al [24], Mediterranean data from van Dommelen et at [25]; based on values from Cole & Roede [23].
White diamond = non-LGA Dutch ODM2; black diamond = LGA Dutch ODM2; white circle = non-LGA Mediterranean ODM2; black circle = LGA Mediterranean ODM2; white triangle = ODM2 Mediterranean; black triangle = ODM2 Dutch; dotted line = Dutch Boys 2009; dashed + dot line = Dutch Girls 2009; dashed line = Mediterranean Boys 2009; cross = Mediterranean girls 2009

Figure 5.1D shows BMI SDS trajectories in non-LGA and LGA subgroups. LGA ODM2 infants had the highest BMI SDS in early childhood with a gradual increase and subsequently the highest BMI SDS in early adolescence, possibly showing a pathway to paediatric overweight. LGA ODM1 showed a steady increase in BMI SDS with lower values than LGA ODM2, with a significantly different BMI SDS trajectory (p=0.04). The trajectories of non-LGA ODM1 and non-LGA ODM2 followed the same pattern as that of their LGA counterparts, albeit at a lower level. The BMI SDS trajectory of non-LGA ODM1 was significantly lower than that in non-LGA ODM2 (p=0.01). The same analysis was performed in primiparous women, thus including only one infant of each woman, which showed similar results (supplementary table 1).

Comparison to 2009 (Fifth) Dutch Growth Study

It was not possible to calculate statistically significant differences between offspring of diabetic pregnancies and the 2009 nation-wide study. However, visual comparison of the growth trajectories was possible as the mean BMI SDS values for the 2009 Dutch study are plotted in the graphs. In infancy, length of ODM1 was slightly below and ODM2 was slightly above the Dutch nation-wide study, which is represented as SDS 0. Up to age 14, height SDS was similar to the 2009 nation-wide growth study in both ODM1 and ODM2 (figure 5.1C, SDS 0).

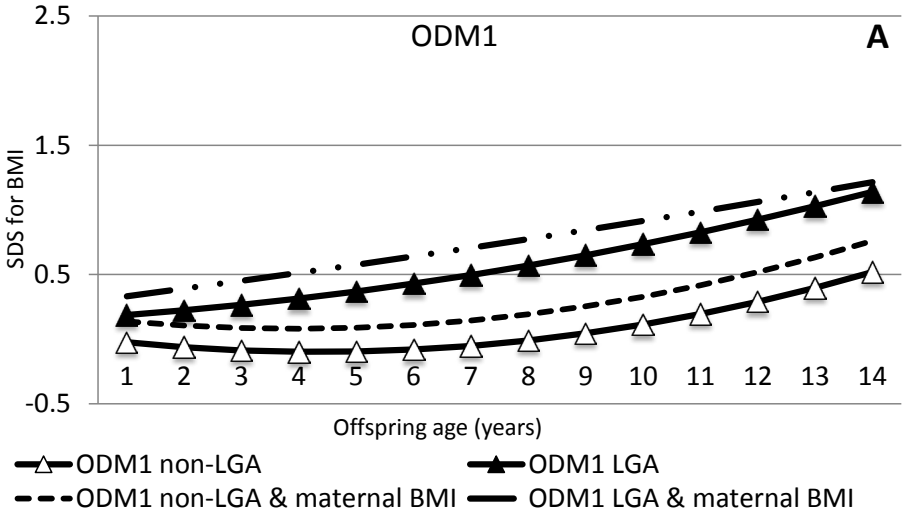
BMI SDS of ODM1 was close to that of the Dutch growth study population in early childhood and showed a gradual increase from mid–childhood onwards, slightly above the 2009 growth study. ODM2 showed a gradual increase in BMI SDS from the first year onwards, resulting in a BMI SDS in early adolescence that was higher than the 2009 growth study (figure 5.1C).

The BMI SDS trajectory of non-LGA ODM1 was lower than the 2009 growth study. LGA ODM1 was slightly above the 2009 growth study in early childhood with a continuing increase and reaching higher values than Dutch children. Both non-LGA and LGA ODM2 have higher values than the Dutch growth study (figure 5.1D).

Covariates maternal age at delivery, parity, educational level, employment hours, marital status, ethnicity, breast feeding, preconceptional HbA1c, mean pregnancy HbA1c, paternal BMI, paternal ethnicity or paternal diabetes did not influence any of the models and were therefore excluded as confounders.

Ethnicity in ODM2

Even though maternal ethnicity was a non-significant confounder in the mixed model for the whole group, we performed a subgroup analysis in ODM2 because of a heterogeneity of ethnicities within this group and known differences between Dutch and Dutch-Mediterranean offspring [25, 27].



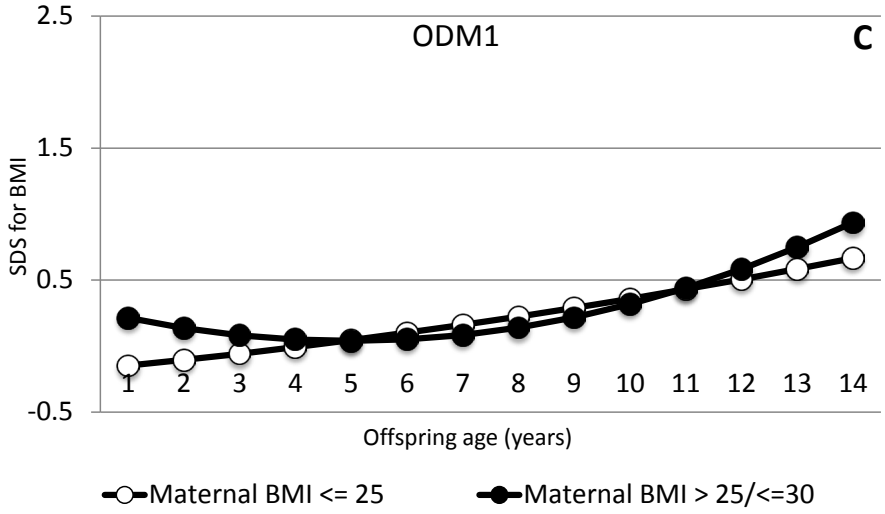
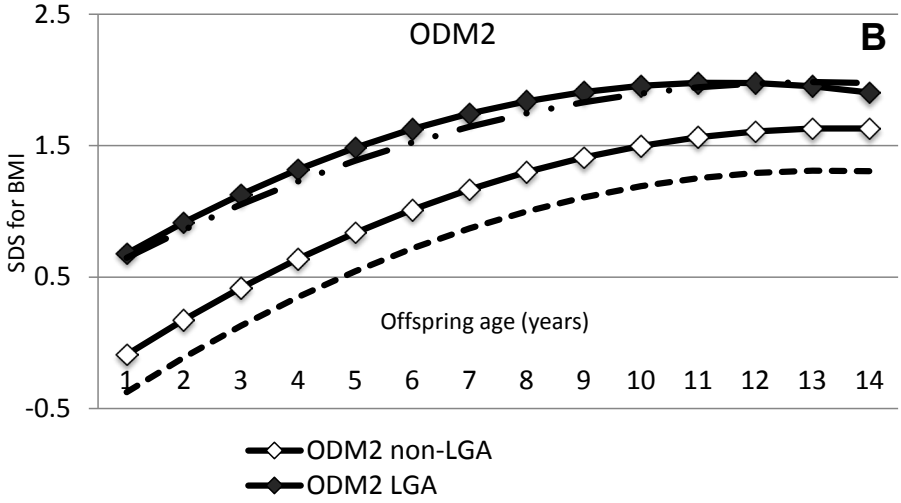


Figure 5.3 Mixed model for offspring mean BMI SDS for non-LGA vs. LGA ODM1 and the effect of maternal BMI on the growth trajectories (A); similar for non-LGA vs. LGA ODM2 (B). Offspring mean BMI SDS for ODM1 for mothers with a BMI <=25kg/m2 and 25-30kg/m2 (C); similar for ODM2 according to a maternal BMI of BMI 25-30kg/m2 and > 30kg/m2(D);
White triangle = ODM1 non-LGA; black triangle = ODM1 LGA*; white diamond = ODM2 non-LGA*; black diamond = ODM2 LGA*; dashed line = ODM1 or ODM2; white circle = ODM1 and mothers with BMI <= 25kg/m2; black circle = ODM1 and mothers with BMI >25/<=30kg/m2; white square = ODM2 and mothers with BMI >25/<=30kg/m2; black square = ODM2 and mothers with BMI >25kg/m2*
**corrected for maternal BMI*



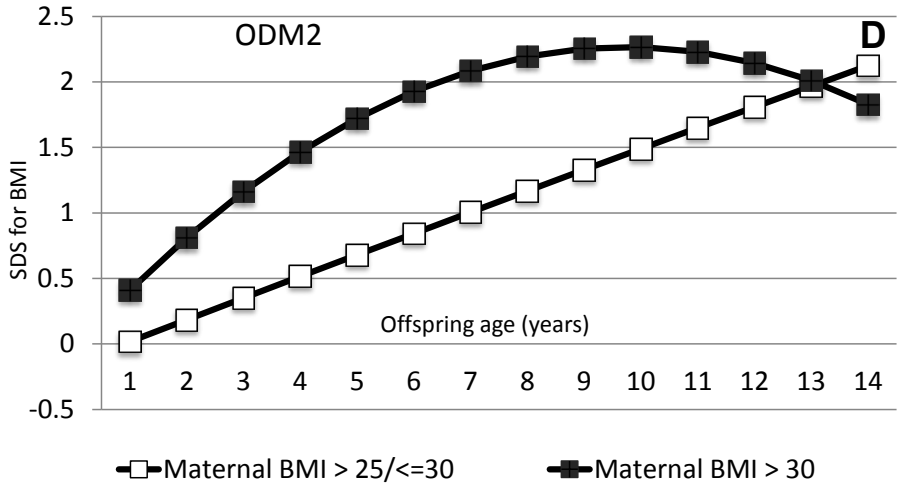


Figure 5.3 Continued

There were no differences in height for Dutch and Dutch-Mediterranean ODM1 and ODM2 (figure 5.2A).

LGA Dutch-Mediterranean ODM2 showed the highest increase in BMI SDS from early childhood until early adolescence, however there were no statistically significant differences in BMI SDS trajectories between LGA and non-LGA Dutch and Dutch-Mediterranean ODM2 (figure 5.2B). Even non-LGA Dutch-Mediterranean children have a BMI SDS trajectory slightly above their nation-wide counterparts. Values from the nation-wide studies are all lower in their mean BMI SDS trajectories, indicating that ODM2 have a risk of becoming overweight with BMI SDS reaching up to +3SDS in adolescence.

Maternal BMI

Addition of maternal BMI to the models of growth trajectories in ODM1 and ODM2 resulted in an increase of BMI SDS trajectories in the non-LGA and LGA ODM1 and in a decrease in the non-LGA ODM2 subgroups (figure 5.3A/B).

A separate subgroup analysis of ODM1 from mothers with a prepregnancy BMI below 25 kg/m2 or above 25 to 30 kg/m2 is shown in figure 5.3C and a similar analysis of ODM2 from mothers with a BMI from 25 to 30kg/m2 or above 30kg/m2 is shown in figure 5.3D. The growth trajectories according to maternal BMI did not differ much in the ODM1, but ODM2 from a mother with a BMI>30kg/m2 had a considerable higher BMI SDS than those from a mother with a BMI 25-30kg/m2.

Height and length

Length SDS plateaued in the first year of life (supplementary figure 5.1A/1B). Differences between ODM1 and ODM2 were not significant (NS, supplementary figure 5.1B).

Height of ODM1 and ODM2 were similar (supplementary figure 5.1C). LGA offspring in both ODM1 and ODM2 were slightly taller than the non-LGA groups, although differences were small (NS; supplementary figure 5.1D).

Discussion

This is the first exploratory study comparing growth trajectories of BMI and height SDS of offspring of women with type 1 and type 2 diabetes mellitus. At birth almost 50% of neonates in both groups were LGA but thereafter growth trajectories differed significantly with highest BMI SDS in ODM2. While non-LGA ODM1 showed a BMI pattern similar to the 2009 nation-wide study, BMI SDS increased steadily in LGA ODM1. Highest values were found in ODM2 that were LGA at birth, which is in line with current literature [17, 18]. There were no significant difference in glucose control during pregnancy between the two types of maternal diabetes (HbA1C), but maternal BMI was significantly higher in women with type 2 diabetes. Subgroup analyses of ODM2 based on ethnicity showed the highest BMI SDS values for Dutch-Mediterranean ODM2 who were born LGA. Height SDS for both ODM1 and ODM2 were comparable to those of the 2009 Dutch Growth Study, which indicates that only weight in these infants is increased and not height.

Previous studies on the growth of offspring of women with pregestational diabetes either analysed only ODM1[17, 18] or combined different types of diabetes [28]. There are a number of cross-sectional studies, but these lack a uniform definition for overweight/obesity and differences in statistical methodology preclude adequate comparison[8, 11, 12, 29-33]. There are only two longitudinal growth studies in infants of women with pre-existing diabetes: in one study it was found that maternal BMI and being LGA at birth were predictors of childhood overweight in ODM1[17]. The other longitudinal study was performed in children who were born to First Nation Canadian inhabitants with paediatric-onset type 2 diabetes. In this diabetes-prone population 89% of infants were already overweight or obese at an early age and remained so until the age of 19 years [14]. Our longitudinal data expressed in growth trajectories could be a first step in providing parents and health care workers with a gross estimation of when they should provide special attention to offspring from pregestational diabetic women in order to possibly prevent adiposity.

Addition of maternal BMI to the model did not change the BMI SDS trajectories, but it did shift the intercept slightly upwards in LGA and non-LGA ODM1 and resulted in a downwards shift in the non-LGA ODM2, suggesting that maternal BMI does influence offspring growth in this population Subgroup analyses according to maternal BMI did not reveal major differences in growth profiles in ODM1, but obese women with type 2 had children with a higher BMI SDS. In other words, a normal or slightly increased BMI (25-30kg/m2) in women with diabetes, results in an offspring growth trajectory that is relatively close to the Dutch 2009 reference group [24]. In contrast, maternal obesity, which was the case in about half of ODM2, results in a higher growth trajectory with more childhood obesity.

Developmental Origins of Health and Disease (DOHaD) states that intrauterine overnutrition programs adaptations of the fetal metabolism to cope with an adverse postnatal environment; which is enriched with suitable nutrients [1, 34, 35]. These adaptations cause accumulation of adipose tissue and (relative) hyperglycemia leading to pathological changes in appetite and energy regulation in offspring [5]. These epigenetic changes affect both ODM1 and ODM2, because not only genetic susceptibility to overweight, but also epigenetics and parental lifestyle habits may echo into the child and influence growth trajectories in their development. Environmental factors might possibly have a larger effect in ODM2 because of a higher maternal BMI. Unfortunately, there are no studies investigating lifestyle and eating habits in nurturing of ODM2 and subsequent development of overweight/obesity.

Preventive strategies that might battle childhood obesity in this population should include striving for a lower maternal prepregnancy BMI , especially in women with type 2 diabetes. To pursue normal maternal prepregnancy BMI might also contribute to prevent childhood obesity, given that families are better accustomed to a healthier lifestyle. Mothers with a higher maternal BMI are, for example, known to impose less

dietary restrictions on offspring [36]. Another important aspect is the prevention of LGA at birth. This seems difficult at present and data indicate an increase rather than a decrease in LGA infants in these women [37-39]. This may among others be explained by the better periconceptional glucose control of the present resulting in better placentation [40-43], increased maternal weight gain during pregnancy [44, 45] and poorer glucose control in the third trimester of pregnancy, since women are not routinely admitted to hospital anymore [42]. Strict dietary and maternal weight gain monitoring during pregnancy is likely to be the most effective preventive measure at this moment. Follow-up studies have shown that accelerated weight gain in young infants is strongly related to development of obesity and metabolic syndrome in later life [10]. Given the relationship between maternal diabetes and overweight/obesity in their offspring, child welfare centers and pediatricians should monitor the weight trajectories in these infants closely, including dietary and lifestyle advices. Priority should be given to infants of (obese) women with type 2 diabetes and –in the Netherlands- especially to those of Dutch-Mediterranean background.

Strengths and Limitations

Our data on growth trajectories of offspring of pregestational diabetic pregnancies could not be compared with a control group (data from uncomplicated pregnancies from the same institution). We were, however, able to compare our growth trajectories with those obtained from data dating before the obesity epidemic, namely the 1980 Dutch population study (SDS of 0) and these served as the basis for SDS calculation. Also, we could visually compare our data to the 2009 Dutch Growth Study on healthy children of Dutch and Mediterranean origin [22, 24, 25]. It was not possible to calculate whether differences between our mixed model trajectories were statistical significantly different from the Dutch nation-wide study.

Growth trajectories in the current study were based on measurements at several ages with differences in the number of available measurements at the different ages. However, the mixed model technique builds the curve based on the available values, which gives a custom model that fits all available values. Although the growth trajectories as depicted in the figures were all different, statistical significance was not always reached which may probably be due to the low numbers of infants included. Furthermore, Tanner stages and the onset of puberty was unknown in our study population. Correction for the onset of puberty was therefore not possible. The parental informed consent for offspring growth charts was 52-63% of all women contacted, which is comparable to that in retrospective cross-sectional studies (response rate of 46 to 66%; [46-49]. Due to the respective nature of this study, with children born up to 14 years earlier, such a relatively low response rate might be inevitable. The response regarding the supplementary questionnaires was low. This may possibly be due inadequate knowledge of the Dutch language in women with type 2 diabetes and/or a busy lifestyle of working parents. We did not include women with gestational diabetes in this study given the relatively short duration of gestational diabetes during pregnancy. This group will be subject of a subsequent study.

In conclusion, BMI SDS trajectories of offspring of women with type 1 or type 2 diabetes born in a single tertiary centre, differed despite a similar percentage of LGA infants at birth. Risk factors a higher BMI SDS profile were: type 2 diabetes of the mother (especially in those of Dutch-Mediterranean background), maternal obesity and being LGA at birth. Some of these risk factors (type 2 diabetes and maternal obesity) are likely to be interrelated. Prevention of childhood obesity in these offspring might be achieved by prepregnancy prevention of overweight in women with type 2 diabetes, prevention of excessive weight gain in pregnancy and by close follow-up of weight gain of the infants during childhood with dietary and lifestyle advices. The latter seems especially important in infants of women with type 2 diabetes who were LGA at birth. Studies on lifestyle and nutrition in offspring of women with diabetes are thus far lacking, but are important to further unravel the causes of childhood obesity in this population.

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Disclosure statements

The authors have nothing to disclose

Contribution to Authorship

N.H. wrote manuscript, researched data; L.R. researched data, reviewed/edited manuscript; H.V, G.V., J.M. reviewed/edited manuscript, contributed discussion, D.B. contributed to discussion.

Details of Ethics Approval

Ethics approval was granted by the Medical Ethics Committee at the University Medical Center, Utrecht in the Netherlands (application number 13/179, reference number WAG/om/13/053639) on the 09th of April 2013.

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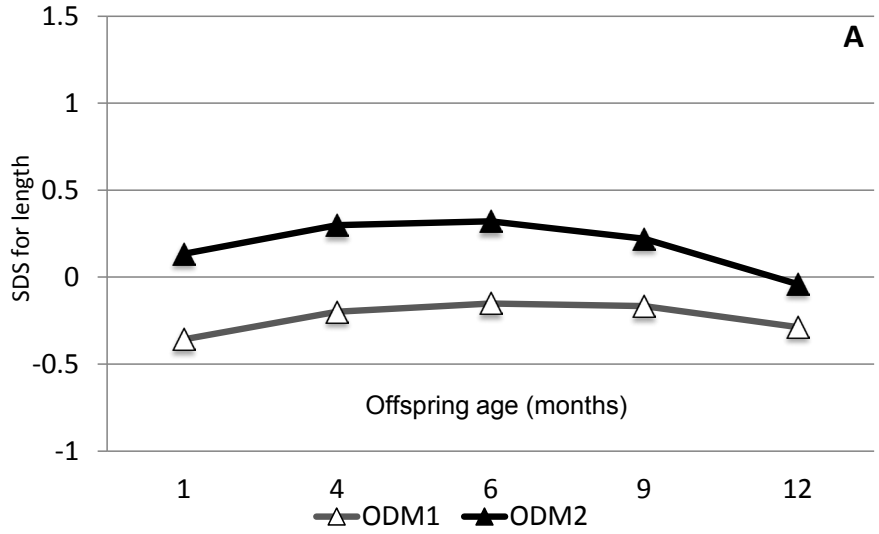
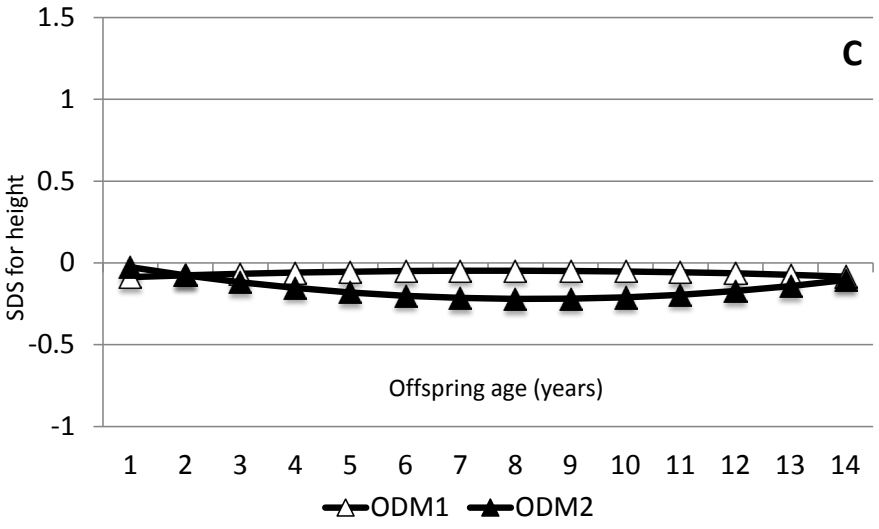
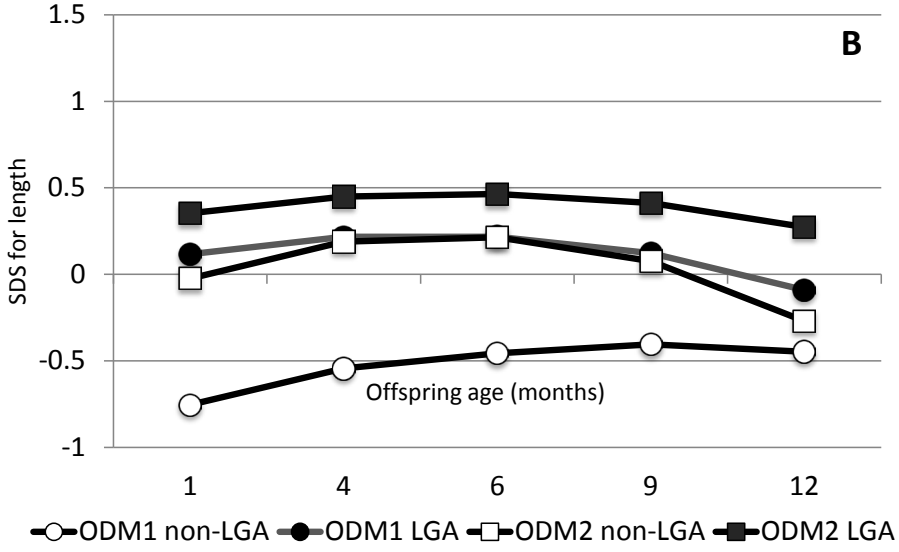
Supplementary table 5.1 Regression equation (mixed model) for offspring BMI SDS in time expressed as age, (β = intercept; A = coefficient for linear component, B = coefficient for square component; CI = confidence interval for the intercept)

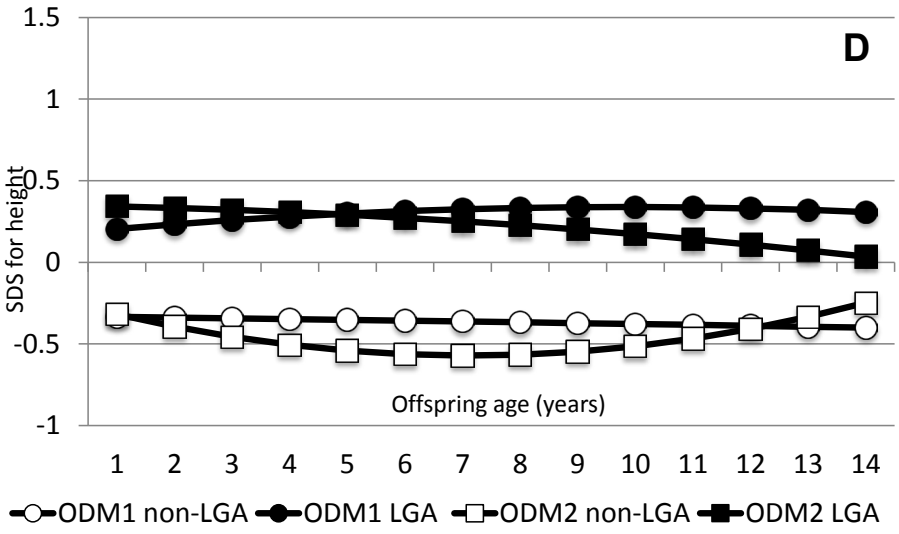
All offspring of diabetic mothers					
Age category	**Diabetes type**	**β**	**β 95% CI**	**A**	**B**
M1 - M12	ODM 1	1,09	-1,0--0,06	-2,406	1,470
M1 - M12	ODM 2	1,62	1,25- 1,989	-2,680	1,350
Y1 - Y14	ODM1	0,08	-0,21- 0,38	-0,017	0,005
Y1 - Y14	ODM2	-0,02	-0,45- 0,40	0,280	-0,011
M1 - M12	ODM1 non-LGA	0,55	-2,06--0,76	-0,83	0,331
M1 - M12	ODM1 LGA	1,73	-0,91- 0,44	-4,275	2,790
M1 - M12	ODM2 non-LGA	1,35	-1,312- 0,092	-2,953	1,558
M1 - M12	ODM2 LGA	1,96	1,43- 2,5	-2,340	1,111
Y1 - Y14	ODM1 non-LGA	0,01	-0,38- 0,41	-0,058	0,007
Y1 - Y14	ODM1 LGA	0,16	-0,244- 0,57	0,028	0,003
Y1 - Y14	ODM2 non-LGA	-0,37	-0,898- 0,16	0,294	-0,011
Y1 - Y14	ODM2 LGA	0,45	- 0,18- 1,088	0,240	-0,009
Primiparous women (eldest ODM), ODM1 n = 52, ODM2 n = 32					
Age category	**Diabetes type**	**β**	**β 95% CI**	**A**	**B**
M1 - M12	ODM 1	0.98	0.65- 1.31	-2.187	1.287
M1 - M12	ODM 2	1.42	0.99- 1.86	-2.268	1.179
Y1 - Y14	ODM1	0.04	- 0.32- 0.40	-0.010	0.003
Y1 - Y14	ODM2	0.03	- 0.42- 0.49	0.245	-0.008
M1 - M12	ODM1 non-LGA	0.25	- 0.13- 0.63	0.234	-0.476
M1 - M12	ODM1 LGA	1.85	1.38- 3.48	-5.251	3.629
M1 - M12	ODM2 non-LGA	1.10	1.55- 0.05	-2.324	1.250
M1 - M12	ODM2 LGA	1.85	1.24- 2.54	-2.270	1.161
Y1 - Y14	ODM1 non-LGA	-0.13	- 0.62- 0.35	0.003	0.002
Y1 - Y14	ODM1 LGA	0.26	- 0.26- 0.77	-0.029	0.006
Y1 - Y14	ODM2 non-LGA	-0.29	- 0.90- 0.33	0.256	-0.009
Y1 - Y14	ODM2 LGA	0.47	- 0.20 – 1.15	0.220	-0.006





Supplemental figure 5.1 Mixed model for offspring mean length SDS in infancy for ODM1 vs. ODM2 at 1 to 12 months of age (A); (non)-LGA ODM1 vs. ODM2 (B); Mixed model for offspring length at 1 to 14 years of age for height SDS in ODM1 and ODM2 (C); (non)-LGA ODM1 vs. ODM2 (D).
White triangle = ODM1, black triangle = ODM2; white circle = non-LGA ODM1; black circle = LGA ODM1; white square = non-LGA ODM2; black square = LGA ODM2.





Supplemental figure 5.1 Continued


The secret of life,
though, is to fall seven times
and to get up eight
Paulo Coelho - The Alchemist

Chapter 6

Long term BMI and growth profiles in offspring of women with gestational diabetes

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Lenie van Rossem
Douwe Biesma
Jan M. Wit
Harold W. de Valk

Abstract

Background & objective

Gestational diabetes mellitus (GDM) is reported to be associated with childhood obesity, however the magnitude of this association and relation to intrauterine growth is uncertain. We studied the growth profiles of offspring of GDM (OGDM) up to the age of 14 years, with subgroup analysis comparing large for gestational age (LGA) with non-LGA at birth as a reflection of the intrauterine environment.

Methods

All mothers with GDM who delivered at UMC Utrecht between 1990 and 2006 were contacted; informed consent was received for 104 OGDM of 93 mothers. Offspring data were collected through Dutch infant welfare-centers. Recorded height and weight were converted to BMI and subsequent age- and gender specific SDS values for Dutch children. A random-effects model was used; a mean of 7.4±2 measurements per infant were available. Data were compared to those of offspring of women with type-1 and type-2 diabetes (ODM1 and ODM2).

Results

Height of OGDM was similar to the Dutch reference population. Twenty-five (24%) OGDM were LGA. Non-LGA OGDM showed a BMI SDS comparable to that of the reference population with a slight increase in early adolescence. LGA OGDM had a higher BMI SDS trajectory compared to non-LGA OGDM and the reference population, with a plateau around age 10 years. Comparison of these growth trajectories with ODM1 and ODM2, studied with the same methodology, showed the highest BMI SDS trajectories during adolescence in ODM2, followed by LGA offspring of women with ODM1, followed by the other categories.

Conclusion

Up until early adolescence OGDM have a BMI that is 0.5 SDS higher than that of the Dutch background population. LGA OGDM are at higher risk of becoming overweight compared to non-LGA OGDM. These results emphasize the importance of adequate recognition and timely treatment of maternal gestational diabetes to prevent fetal macrosomia.

Gestational diabetes (GDM) is defined as any degree of glucose intolerance that is diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes [1]. The prevalence of GDM is rising worldwide [2, 3], and the condition is associated with adverse pregnancy outcomes, such as an increased risk of large-for-gestational-age (LGA) neonates and birth complications [4]. These LGA infants have an increased fat mass and decreased lean body mass as compared to LGA infants from non-diabetic women [5], and their intrauterine growth is disproportionate with an increased abdominal circumference as compared to the head circumference (HC/AC ratio) [6]. In adolescence, offspring from gestational diabetic pregnancies (OGDM) have been shown to have an increased risk of abnormal glucose metabolism and hypertension [7, 8]. It is unknown whether intrauterine adiposity adds to postnatal adiposity and subsequent health issues.

In order to anticipate and formulate preventive strategies in the childhood obesity epidemic, longitudinal analysis of data on body mass index (BMI) are important. Studies on BMI of OGDM have mostly been cross-sectional in design [7-16] and only a few longitudinal studies have been done solely in GDM [17-20]. The cross-sectional cohorts have shown an increased risk for developing adiposity compared to children not exposed to intrauterine diabetes mellitus [7, 10, 12]; even mild GDM treated with no or only dietary intervention was associated with an increase in offspring obesity between the ages of 5 and 10 years [11]. Pooling the different cross-sectional studies is difficult due to different definitions of endpoints used: obesity, BMI or BMI z-score [7, 8, 10, 13]. Also, the definitions used for obesity differed [10, 13]. The available longitudinal data are unsuitable for comparison, due to differences in methodology: different age categories and follow-up periods (age 0.5 - 13 years) and different statistical methods and different assessments of body mass (BMI, BMI SDS, quintiles and skinfold thickness) [17-21]. Additionally, different types of maternal diabetes were included in most studies [14, 15, 21, 22]. The available evidence on longitudinal BMI data in OGDM show a higher childhood BMI up to 13 years compared to offspring of non-diabetic pregnancies [21], and a higher childhood BMI standard deviation score (SDS) up to 8 and 14 years compared to background reference populations [18, 20]. This indicates that OGDM does have an increased risk for higher BMI or frank obesity when reaching late childhood / early adolescence.

Little is known about the influence of being born LGA on postnatal growth although this is a commonly posed question by parents. Only a single longitudinal study investigated LGA neonates as a subgroup, and showed indeed that these infants have the highest BMI in children aged 4 to 7 years [16]. Unfortunately, there are no data available on height development of OGDM. Height trajectories are an indicator of growth and give an indication to which extent this parameter influences overall BMI.

The current study was performed to answer two questions. First, to assess whether the growth trajectories of LGA and non-LGA offspring are different up until early adolescence, with LGA as a reflection of intrauterine adiposity. Second to explore if growth trajectories of OGDM differ from those of offspring of women with type-1 or 2 diabetes (ODM1, ODM2).

Patients and methods

Patients

The study group consisted of offspring of women with GDM who delivered in the University Medical Center, Utrecht, the Netherlands between 1990 and 2006. All women who delivered in this period were contacted in 2013. After consent was obtained, individual offspring growth charts from the Dutch infant welfare-centers were retrieved. The parents were invited to complete a questionnaire by mail including questions regarding maternal and paternal height, weight, comorbidities and ethnicity. Parents were asked to provide the most recent height and weight of the child, measured either by health care workers or themselves.

Infant height and length were collected through Dutch infant welfare centers, which have a high coverage and record infant weight, supine length (until 2.0 years) and height (from 2.0 years onward) through standard protocols on specified dates between birth and 4 years (1, 4, 6, 9, 11, 14, 18, 24, 36, 45 months). Thereafter, children are measured in the school health service at 5.5, 11 and 13 years, with a variance of 1-2 years around these ages. Trained health care professionals perform the measurements. Infants' length and standing height was measured to the nearest 0.1 cm. Up to 15 months children were weighed naked. Older children were weighed wearing underwear only, on calibrated mechanical or electronic step scales. Weight was to the nearest 0.1 kg. The medical ethics committee of the University Medical Centre Utrecht approved this study.

Gestational diabetes was diagnosed using the 75-grams oral glucose tolerance test in 84% of cases; other patients were diagnosed through elevated fasting glucose levels or an abnormal glucose profile showing hyperglycemia.

Methods

Baseline maternal characteristics at pregnancy and pregnancy outcomes were retrieved from records of the UMC Utrecht. Parents provided information regarding their own current height and weight, educational status and current height and weight for each child when they completed the written questionnaire. Birthweight (BW) SDS was calculated as follows: (BW minus mean BW for gender, parity and gestational age)/SD for gender, parity and gestational age, based on Dutch reference data [23]. LGA was defined as a BW ≥90th percentile corrected for gestational age, gender, and parity [23]. Conditional target height (cTH) of offspring was calculated based on parental height according to Hermanussen & Cole [24] and adapted to Dutch growth standards [25]. Length and height of OGDM were expressed as SDS for age and gender based on the Fifth Dutch Growth Study performed in 2009 [26]. BMI was calculated from height and weight with the following formula: weight (kg)/(height(m))^2. BMI was expressed as a SDS for the 1980 nation-wide growth study, in which SDS 0 equals the age- and gender-specific mean of the 1980 Dutch reference population [27].

Values from the Fifth Dutch Growth Study and subgroup analyses

Since the BMI of Dutch children has increased from the 1980s onwards, we also calculated mean BMI SDS for children of Dutch origin participating in the 2009 (Fifth) Dutch Growth Study [28]. The values of the 2009 nation-wide study were plotted in the BMI SDS graphs for visual comparison of our offspring from the diabetic pregnancies, in order to show the effect of the obesity epidemic in a nation-wide cohort. A description of the ODM1 and ODM2 population from women with type-1 or 2 diabetes has been published previously (*Hammoud e.a., in revision Pediatric Reseach;* ***chapter 5***).

Statistical analysis

The longitudinal analyses fitted smooth, flexible curves with a random-effects model to estimate the growth trajectory of OGDM, and the subgroups non-LGA OGDM and LGA OGDM. Mixed model addresses the correlation of repeated height and BMI SDS measurements obtained within the same child, as well as time-independent variables (maternal age at delivery, parity, educational level, employment hours, marital status, ethnicity, breast feeding, preconceptional HbA1c, mean pregnancy HbA1c, paternal BMI, paternal ethnicity or paternal diabetes) and accommodates to the available values in the dataset. Fixed effects were the covariates maternal diabetes type (GDM), LGA (yes, no), time (age in years), and the interaction between time and maternal diabetes type to show increases or decreases in growth over time. Random effects were intercept and time. Potential confounders were the previously mentioned time-independent variables; there were labelled as covariates in a sensitivity analysis. If the addition of a covariate to the model changed the estimate with more than 10%, we considered this a confounder. In a next step, we checked whether these potential confounders changed the model by visual inspection of the graphs.

Given the known rapid decreases in BMI SDS during the first year of life in infants born LGA, both in (non)-diabetic populations [29-32], we separately analysed the growth trajectories in the first year of life and the years thereafter.

In a model with the factors as fixed effects and random effects (mentioned before), the models were examined using the Akaike information criterion (AIC) and Bayesian information criterion (BIC). The best model fit had the lowest AIC and BIC, which included a linear and square interaction of diabetes with age, with intercept and age as a random effect, in order to determine the trajectories for BMI and height SDS. Consequently, for the growth SDS points in the square model, the values of OGDM, non-LGA OGDM and LGA OGDM were modelled as

SDS=intercept+β_{0ij}+β_{1ij}(age)+β_{2ij}(age)^{**2}, where β_0 represents the intercept, β_i is the diabetes type (e.g. maternal GDM), β_j is LGA and age is offspring age in years (^{**2}=square). Data were analysed using IBM® SPSS Statistics version 23.0 for Mac and Microsoft® Excel® for Mac2011. Software prepared by the Dutch Growth Research Foundation was used to calculate height and BMI SDS (©Growth Analyser 3.5).

Results

From 1990 to 2006, 468 offspring and their 406 mothers were identified; efforts were made to contact all parents through mail, phone and email, but 58% of the mothers (n=235) were not traceable due to moving to an unknown address or disconnected phone. Another 78 (19%) women refused participation, resulting in informed consent for 104 children (22%) from 93 (23%) mothers. There were 6 dichorionic diamniotic twins in the study population; these infants were included. One infant with trisomy 21

Table 6.1 Baseline characteristics of the study populations
Values are n (%) or mean (±SD) or median (interquartile range) ¶;
** Eldest infant of the mother born our center (e.g. primiparous women);*
*** 10-20 missing values; *** 63 - 71 missing values*

	OGDM
***n* of infants**	**104**
Maternal BMI (kg/m^2)	25.8 (7.8)¶ **
Maternal age at delivery (years)	34±4
Multiparous (%)	66 (64)
OGTT performed in pregnancy (%)	82 (84)
Mean pregnancy A1C (%)	5.8±0.5 ***
Insulin treatment in pregnancy (%)	50 (48)
Pre-eclampsia (%)	7 (7)
Caesarean section (%)	43 (42)
Gestational age at delivery (weeks)	39 (2)¶
Female gender (%)	51 (49)
Birthweight (g)	3530 (725)¶
Large for gestational age (LGA) (%)	25 (24)
Birthweight Z-score	0.57 (1.3)¶
Neonatal admissions on medium or intensive care (%)	55 (53)
Breastfeeding at 1 week (%)	61 (63)**
Conditional target height boys (cm)	181.7±4.3
Conditional target height girls (cm)	169.7±3.9
n* of women	**93**
Maternal ethnicity Caucasian (%)	76 (82)
Paternal ethnicity Caucasian (%)	81 (87)
Current paternal BMI (kg/m^2)	25.5 (3.8) ¶ **
Maternal education (university of applied sciences)(%)	24 (33) **
Maternal fulltime job (%)	14 (19) **

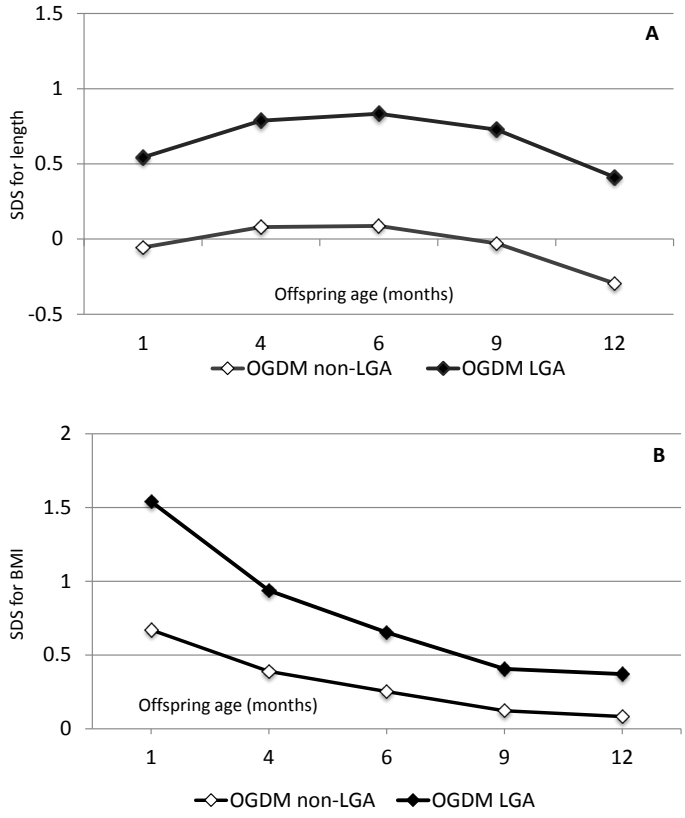

Figure 6.1 Mixed model for offspring length SDS for (non)-LGA OGDM ages 1 month to 12 months (A); BMI SDS for (non)-LGA OGDM from 1st month to 12 months (B);
SDS, standard deviation score for height; LGA, large for gestational age.
White diamond = non-LGA OGDM, black diamond = LGA OGDM

was excluded; there were no infants with major congenital malformations in the study population. Maternal BMI and age were not different between responders and non-responders. However, ethnicity was, with more (Dutch) Caucasians in the responders, and more women of Mediterranean descent in the non-responder group.

A total of 104 children were included from 93 mothers. The mean number of measurements of height and weight per child was 7.4±2 between birth and 14 years of age, with a total of 771 measurements. Median maternal BMI was 25.8 (7.8) kg/m^2 and 82% of women were of Caucasian descent; paternal BMI was 25.5 (3.8) kg/m^2 with 87% of Caucasian descent. Forty-nine percent of offspring was female. Median birthweight was 3530 (725) grams with 24% being LGA. Fifty (48%) women were treated with insulin during their pregnancy, the other half with dietary advice only. The baseline characteristics are displayed in Table 6.1. Five (4.8%) infants were small for gestational age (BW <10th percentile).

Growth trajectories: 1 to 12 months

During the first year of life length between non-LGA and LGA OGDM showed no significant differences, although LGA OGDM were slightly longer than non-LGA (NS; fig. 6.1A). BMI SDS decreased in both non-LGA as well as LGA OGDM in infancy, with LGA OGDM having a slightly higher BMI SDS than non-LGA (NS; fig. 6.1B).

Growth trajectories 1 to 14 years

Height

Height SDS was similar to the 2009 Dutch growth study (SDS 0) from age 1 to age 14 years with a slight decrease in early adolescence (fig. 6.2A). Although LGA OGDM were slightly taller than non-LGA OGDM, these differences were not statistically significant (fig. 6.2B).

BMI and comparison to 2009 (Fifth) Dutch Growth Study

In figure 6.2C and 6.2D the BMI SDS is depicted from age 1 to 14, together with that of the 2009 reference population. Up until late childhood (8-10 years) the BMI SDS for the total group was similar to that of the Dutch 2009 reference group, whereafter the BMI SDS increased (fig 6.2C).

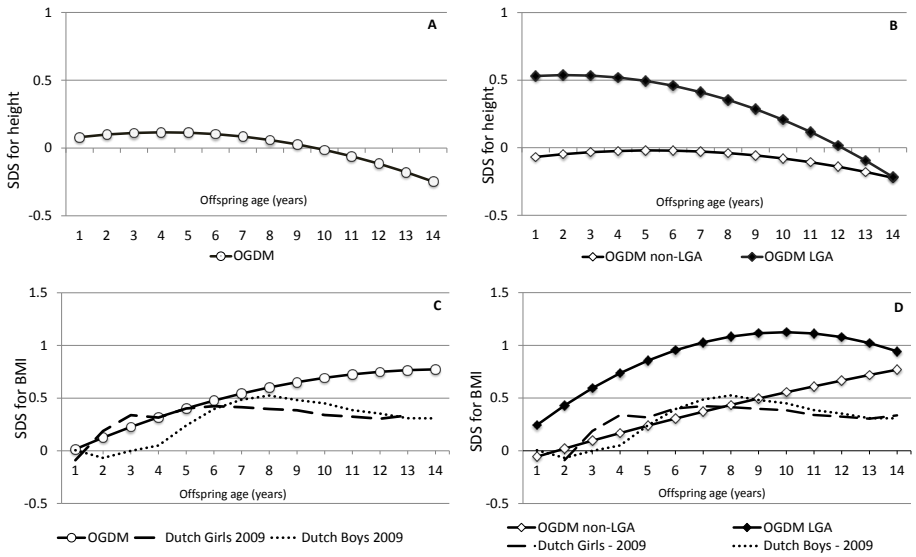

Figure 6.2 Mixed model for offspring height SDS for all OGDM ages 1 to age 14 years (A); and for (non)-LGA OGDM for age 1 to age 14 years (B); for BMI SDS for all OGDM ages 1 to age 14 years including reference values from 2009 reference population (C); and for (non)-LGA OGDM for age 1 to age 14 years including reference values from 2009 reference population (D);
SDS, standard deviation score for body mass index; BMI, body mass index; LGA, large for gestational age. Reference values from 2009 for Dutch boys and girls adapted from Schonbeck et al [28], based on values from Cole & Roede [27].
White circle = OGDM; white diamond = non-LGA OGDM, black diamond = LGA OGDM; dotted line = Dutch Boys 2009; dashed line = Dutch Girls 2009.

Subgroup analysis showed different growth trajectories between LGA and non-LGA OGDM, but the difference did just not reach statistical significance (fig 6.2D; p 0.07). LGA OGDM had a higher BMI SDS at 1 year of age and continued to increase in BMI SDS until late childhood (8-10 years) with a plateau afterwards; non-LGA OGDM showed a steady increase in BMI SDS up to age 14 years, a BMI trajectory that resembled that of Dutch boys and girls of the 2009 population.

The sensitivity analyses for the maternal age at pregnancy, parity, maternal educational level and employment type, maternal and paternal ethnicity, maternal prepregnancy BMI and current paternal BMI showed no factors that changed the slope of the models.

Analyses were also performed after excluding twins and in nulliparous women only, showing comparable results. Therefore all these infants were included in the final analyses. A subgroup analysis for Dutch Caucasian (82%) vs. non-Caucasian OGDM was not performed due to great ethnic heterogeneity in the non-Caucasian group.

Comparison to offspring of women with type-1 (ODM1) and type-2 diabetes (ODM2)
Figure 6.3 shows the growth trajectories of OGDM together with those of ODM1 and ODM2. The latter data were obtained before and studied with the same methodology (Hammoud et al, in revision Pediatric Research, **chapter 5**). ODM2, both LGA and non-LGA had the highest BMI SDS, both before the age of 1 years, as well as between 1 to 14 years. Both OGDM subgroups and non-LGA ODM1 showed comparable BMI SDS trajectories as the 2009 Dutch reference population, suggesting that the risk for obesity in these subgroups is limited. LGA ODM1 had a growth trajectory in between those of ODM2 and those of OGDM and non-LGA ODM1.

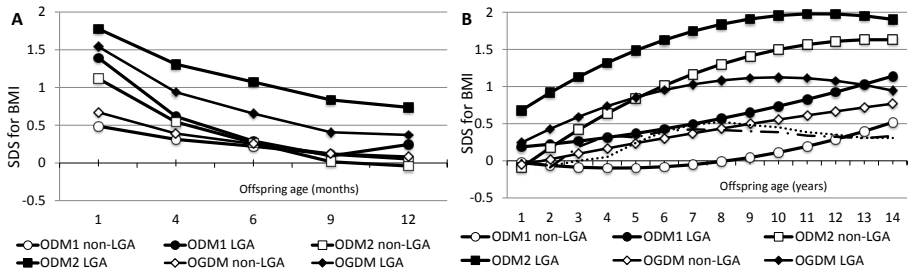

Figure 6.3 Mixed model for offspring BMI SDS for non-LGA and LGA ODM1, ODM2, OGDM from 1st month to 12th month (A); and year 1 to year 14 (B).
Reference values for ages 1 to 14 years adapted from the 2009 nationwide study for Dutch boys and girls; from Schonbeck et al [28], based on values from Cole & Roede [27].
White triangle = ODM1, black triangle = ODM2; white circle = non-LGA ODM1; black circle = LGA ODM1; white square = non-LGA ODM2; black square = LGA ODM2; white diamond = non-LGA OGDM, black diamond = LGA OGDM; dotted line = Dutch Boys 2009; dashed line = Dutch Girls 2009.

Discussion

This study showed that non-LGA and LGA OGDM show different BMI SDS trajectories during childhood, both reaching slightly higher values than the 2009 (Fifth) Dutch Growth Study, with LGA OGDM having highest values. Nevertheless, both subgroups of OGDM had a mean BMI SDS of less than +1 standard deviation at early adolescence, indicating that their risk for becoming overweight up to puberty is likely to be limited. Height SDS for non-LGA and LGA OGDM were comparable to that of the 2009 background population, implying that the higher BMI SDS in early adolescence is related to the weight component and not to differences in height. Both in the Dutch reference group and in the OGDM group, BMI SDS compared to the 1980 nationwide study was increased, suggesting a gradual shift in offspring BMI normative values, which indicates an increased incidence of overweight / obesity in both the reference group and the OGDM since the 1980s [28].

It is becoming increasingly clear that a hyperglycemic intrauterine environment is responsible for an increased risk of diseases in childhood and later adulthood. The relatively over-nourished offspring of GDM is prone to later development of obesity and diabetes not only due to genetic susceptibility [33], but also due to the exposure to the abnormal intra-uterine environmental with potential epigenetic changes in the fetal phenotype [34]. These intra-uterine phenomena contribute to childhood obesity and potentially to obesity and diabetes in adulthood with an increased risk for cardiovascular disease [35, 36]. Preventive strategies are needed. This matter is intuitively most relevant for those offspring likely to be most at risk: the ones born LGA. This is a frequently raised issue by the pregnant couple. Therefore we analyzed the growth trajectories of OGDM, analyzing non-LGA and LGA separately. Comparing our study with other studies proved to be difficult in view of widely differing definitions and methodology. Several cross-sectional studies on OGDM have found evidence for overweight / obesity [7, 9-13]. Although the available evidence on longitudinal BMI data in OGDM indicate a higher childhood BMI [17, 19, 20], with gender and maternal prepregnancy BMI as significant contributing factors [18, 21], results cannot be compared due to differences in methodology. In the only other longitudinal study in which LGA and non-LGA infants were studied separately a higher BMI for LGA OGDM was found and this was also higher as compared to LGA offspring from non-diabetic women at ages 4-7 years [16]. In a cross-sectional prospective cohort of 6-11 year old infants no difference in BMI was found between (non)-LGA OGDM and controls was found [37].

We did not find maternal BMI to be of influence on the BMI SDS trajectory of OGDM, which is in contrast to most studies in which maternal BMI was taken into account [8, 9, 17, 22, 38, 39]. This might be due to the low incidence of maternal obesity in our study group, with a mean BMI of 25.8. This is quite relevant given the higher BMI in most GDM studies from other countries. Apparently this profile of patients with GDM is common in our region and this may present a clinically different entity with a different outcome for the infants as compared to other studies. Other studies have shown that in 16-17 years old adolescents, the relation between maternal GDM and offspring BMI was attenuated

after correction for maternal prepregnancy BMI [38] and weight gain in pregnancy [8]. Furthermore, offspring of mothers with GDM and a normal BMI did not show an increase in obesity, in contrast to offspring of obese GDM mothers [9, 39]. Maternal obesity is, therefore, a strong predictor of childhood obesity [14] and a higher childhood BMI is related to maternal BMI [21] in pregnancies complicated by GDM. In our series, the relatively low maternal BMI may explain the limited effect of maternal BMI on childhood BMI.

In literature there are no studies comparing the growth trajectories of offspring of women with GDM as compared to those with type-1 and type-2 diabetes, separately. Such a comparison is essential when studying differences in genetic and epigenetic pathway to obesity. The comparison shown in Figure 6.3 suggests that offspring of women with type-2 diabetes have the highest risk of childhood obesity. The most outspoken difference between the 3 types of diabetes was the maternal BMI, being 31 kg/m^2 in women with ODM2, as compared to 24 kg/m^2 in women with type 1 diabetes and 26 kg/m^2 in the GDM group. This stresses the importance of maternal BMI in respect to their infant's growth.
A few studies are available with a heterogenic group with offspring from DM1, DM2 (ODM1/2) and GDM [15, 40-43]. In 2 studies ODM1 and OGDM have been compared as separate groups. Overweight rates in OGDM and ODM1 were twice that of the background population [44] with a higher risk for obesity at age 18-20 years in OGDM and only weakly for ODM1 [43].

Methodological considerations:
This study was performed in a single center, where pregnant women with gestational diabetes were diagnosed and treated according to the same protocol.

A simultaneous longitudinal control group was not available for comparison. We could, however, compare our data with nationwide data from the Dutch population [26-28]. The reported BMI and height SDS were calculated based on these population values, and the latter were plotted in the graphs for comparison [28]. Unfortunately it was not possible to calculate statistical significance between the OGDM subgroups and the nationwide population because the complete dataset of the Dutch reference group was not available for analysis.

GDM is most prevalent in ethnic subgroups of the population with a high incidence of type 2 diabetes, amongst others natives from Turkey, Morocco, Suriname and the Caribbean islands. These groups were underrepresented in the current study, because some populations are small in our region and secondly because traceability of parents and offspring in these groups is a difficult challenge. BMI is usually higher in these women, partly explaining the relatively low mean maternal BMI in our study. We only received informed consent from 23% of the eligible mothers. This response rate was lower than reported in literature, which ranges from 46 to 66% [10, 18, 20, 38], and with response rates not reported in most studies. It does show, however, that this group is hard to trace

and recruit. This is an issue present explicitly or implicitly in many studies. A prospective cohort study would be the best way to include and follow-up this offspring.

Given the lack of heterogenetic ethnicities of our study population, a subgroup analysis was not performed. Our OGDM BMI SDS might have been higher if more Mediterranean-Dutch children would have participated in our study [45]. Although the growth trajectories as depicted in the figures were different, statistical significance between (non)-LGA OGDM was not always reached. The small number of patients probably contributed to this.

Tanner stadia and onset of puberty were not available; therefore the impact of this natural process is unknown for the current group. By using SDS from the nationwide study, where children are included with onset of puberty at different ages, the effect of puberty on height and BMI SDS trajectory is smoothed in the graphs.

In conclusion, this is the first study to analyze longitudinal growth trajectories in offspring of women with GDM up to the age of 14 years with separate height- and BMI SDS for LGA and non-LGA offspring. Growth trajectories were only slightly above those of the Dutch reference population, indicating that their risk of becoming overweight in adolescence seems limited, at least in a population with a low incidence of maternal obesity. Compared to offspring from pregestational diabetic pregnancies, we showed that ODM2 are at highest risk of becoming overweight in early adolescence, followed by that of LGA ODM1. Non-LGA ODM1 had a growth trajectory comparable to that of the reference population. This study gives a broad view on the intrauterine origins of adult disease in offspring of women with diabetes. Parents and health workers should have extra consideration of the risks of offspring obesity in diabetic pregnancies, especially for those born LGA and take preventive measures, where necessary.

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Disclosure statements

The authors have nothing to disclose

Contribution to Authorship

N.H. wrote manuscript, researched data; L.R. researched data, reviewed/edited manuscript; H.V, G.V., J.M. reviewed/edited manuscript, contributed discussion, D.B. contributed to discussion.

Details of Ethics Approval

The ethical approval was granted by the Medical Ethics Committee at the University Medical Center, Utrecht in the Netherlands (application number 13/179, reference number WAG/om/13/053639) on the 09th of April 2013.

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We zijn een volk van
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tot een regiment

Boeli van Leeuwen
– Geniale Anarchie

Chapter 7

Lifestyle, diet and body mass index in offspring of women with pregestational and gestational diabetes

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Abstract

Objective

Offspring from diabetic pregnancies show an increased risk for childhood obesity, which may be related to the abnormal intrauterine environment, genetic imprinting or current diet and lifestyle. We analyzed whether diet and lifestyle differ between offspring from different diabetic pregnancies. We hypothesize that offspring from type 2 diabetic pregnancies are more prone to more unhealthy diet and lifestyle habits.

Research Design and Methods

All women with a pregnancy complicated by type 1, type 2 or gestational diabetes, who delivered in UMC Utrecht between 1990 and 2006, were contacted to participate in this study. Parents filled a questionnaire regarding offspring diet, lifestyle and childhood and parental anthropometric measurements.

Results

We received a completed questionnaire regarding offspring of 51 type 1 (ODM1), 21 type 2 (ODM2) and 87 gestational diabetic pregnancies (OGDM), at an average age of 10 years. Prevalence of overweight/obesity in ODM2 was twice as high compared to OGDM and ODM1. Maternal BMI was highest in mothers with type 2 diabetes. ODM2 skipped breakfast more often and were less frequently a member of a sports club compared to ODM1 and OGDM, but consumed less snacks. The intake of fruit, vegetables and sugar containing drinks were comparable between the groups. ODM2 parents judged their offspring as being more vulnerable and less healthy as compared to peers, whilst ODM1 and OGDM parents report their children's health comparable to peers.

Conclusion

ODM2 show a less healthy diet and lifestyle compared to ODM1 and OGDM; This may play a role in the higher incidence of obesity in ODM2 and provides a possible target for prevention of childhood overweight/obesity in these children.

Children of women with type 1, gestational and especially type 2 diabetes mellitus during pregnancy are at increased risk of developing obesity during childhood [1-4]. Recently we showed that this risk is highest for children of women with type 2 diabetes born large-for-gestational age (LGA), followed by non-LGA infants of type 2 diabetic women. Childhood obesity is lower in offspring of women with GDM or LGA-offspring from mothers with type 1 diabetes while the growth trajectory of non-LGA offspring of women with type 1 diabetes and gestational diabetes is comparable to that of the general population (Hammoud et al). Childhood obesity in these children is hypothesized to be due to genetic imprinting, effects of an abnormal intrauterine environment (with a relatively overnourished fetus and subsequent changes in adipose tissue as well as energy regulation that echoes throughout their lives [5, 6]), or current diet and lifestyle. Also, maternal BMI has been shown to be a significant determinant of childhood BMI [7-12], with hyperglycemia as further contributing factor [3, 4, 10, 11]. In our previous study, women with type 2 diabetes had by far the highest BMI compared to offspring of type 1 diabetic mothers, mothers with gestational diabetes or the Dutch reference population (Hammoud e.a. submitted).

In the postnatal period, nutritional and other lifestyle habits from parents are easily transmitted to children, which may contribute to the development of childhood adiposity, together with overweight parents not recognizing adiposity in their offspring [13]. Other lifestyle habits also contribute to offspring BMI, such as physical activity, sleep and screen time [14-19].

To the best of our knowledge there is no previous literature on diet and lifestyle in offspring of diabetic pregnancies. The aim of this study was to assess differences in diet and lifestyle between offspring from women with type 1 (ODM1), type 2 (ODM2) and gestational diabetes (OGDM). Furthermore, we studied the overall health perception in these groups as judged by their parents as an indication of their wellbeing.

Methods

Study design and population

All women with a pregnancy complicated by type 1, type 2 or gestational diabetes mellitus who gave birth in the University Medical Center (UMC), Utrecht, the Netherlands, between 1990 and 2006 were contacted to participate in the study. Parents were asked to complete a questionnaire by (e)mail including questions regarding their offspring diet, lifestyle, anthropometric data, parental health and ethnicity. All women with type 1 and type 2 diabetes had a singleton pregnancy, whereas in the GDM group 4 dichorionic diamniotic twin pairs were included. One infant with trisomy 21 was excluded from the OGDM subgroup, because of the known shorter stature and parental influence in lifestyle [14]. There were no infants with major structural malformations in the study population. Gestational diabetes was diagnosed using a 75-g oral glucose tolerance test in 67 (77%) of cases; the other patients were diagnosed through elevated fasting glucose levels or

an abnormal glucose profile. All women with type 1 and type 2 diabetes mellitus were treated with insulin during their pregnancy; 46 (54%) of women with gestational diabetes were treated with insulin. Maternal characteristics during pregnancy and pregnancy outcome were retrieved from their medical records. The medical ethics committee of the University Medical Center Utrecht approved this study.

Anthropometrics

Birthweight (BW) Z-score was calculated as (BW minus mean BW for gender, parity and gestational age)/SD, based on Dutch reference data [15]. Large for gestational age (LGA) was defined as a BW ≥90th percentile corrected for gestational age, sex, and parity [15]. BMI was calculated as weight (kg)/(height (m)^2 and expressed as SDS (standard deviation score) according to age and gender specific Dutch reference data [16, 17]. Overweight and obesity were calculated based on the International Obesity Task Force (IOTF) cut-off values [18]. Conditional target height (cTH) was calculated from parental heights according to Hermanussen & Cole [19] adapted to Dutch growth standards [20]. Software available from the Dutch Growth Research Foundation was used to calculate BMI SDS (©Growth Analyser 3.5).

Dietary and lifestyle assessment

The questionnaire was adapted from The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study [21, 22] and included 46 different questions on overall health perception, food intake, physical activity and school grades of offspring. Additionally, questions included parental information regarding their own current height and weight, chronic diseases, educational status, ethnic origin, current full-/or part-time job and duration of breast-feeding in the neonatal period for each infant.

For diet 7 questions were included in the questionnaire, which inquired on the frequency of consumption of breakfast, fruits, vegetables, snacks, sugar containing juice and fruit juice in offspring. There were five answering categories (ranging from “never” to “more than 2 or 3 servings a day”), the answer to the questions on the number of weekdays that breakfast, fruits and vegetables were consumed could range from “never” to “every day of the week”. For the analyses, these answer options were translated to 3 scale categorical variables for breakfast, fruits, vegetables: never (1), 1-3 days a week (2), ≥4 days a week (3). The amount of servings of juice and snacks a day were also categorized into the following 3 categories: none (1), ½ - 1 ½ servings per day (2), ≥ 2 servings per day (3).

For physical activity in offspring 5 questions were included, which inquired on how many days a week children would walk or cycle to school and play outside (ranging from “never” to “every day of the week”). Also, information on the hours spent playing outside per day and screen time on a daily basis was included (ranging from “30 minutes or less” to “4 hours or more”). Membership of a sports club was included and categorized (“yes” or “no”). For analyses, the answers were translated to a 3 scale categorical variable for

walking/cycling to school and playing outside: never (1), 1-3 or 1-2 days a week (2), >3 or ≥3 days a week (3), respectively. Hours spent playing outside and screen time were also translated into the following 3 or 4 categories: ≤1 hour or ≤ 30 minutes per day (1), 1-2 hours per day or ½ hour – 1 hour /day (2), ≥ 3 or 1-2 hours per day (3), >2 hours screen time per day (4).

We asked the parents for the overall impression of their offspring's health and vulnerability compared to their peers. Response options included 5 categories (ranging from "excellent to generally healthy or vulnerable perception" to "moderate to unhealthy or not vulnerable perception"). For the analyses, the answer options were recoded to 2 categories: (1) healthy (if always or mostly healthy) or (2) less healthy; the same 2 categories were applied to vulnerability. Finally, the impression of stressfulness of the offspring's life as judged by their parent was scaled from 0 to 10 (with "10" being most stressful).

Statistical analysis

For analysis of categorical variables the Chi-square test was used, for continuous variables the Student's t-test, and for non-parametric variables the Mann–Whitney U test. Data were analyzed using IBM® SPSS Statistics version 23.0 for Mac.

Results

One hundred and fifty ODM1, 70 ODM2 and 478 OGDM were identified and contacted. A completed questionnaire was received from 51 (34%) ODM1; 21 (30%) ODM2 and 87 OGDM (21%) from 33 mothers with type 1, 13 mothers with type 2 and 72 mothers with gestational diabetes during pregnancy due to some mothers having multiple children in the study. Age and BMI at baseline from mothers with type 1 or type 2 diabetes mellitus who participated were comparable to those of the women who did not. For mothers with gestational diabetes the ethnicity was different between responders and non-responders, with more Dutch women in the responders group, and more women from non-native Dutch (mainly Mediterranean) origin in the non-responder group. ODM and parental characteristics are summarized in table 7.1. Mean offspring age of ODM1, ODM2 and OGDM was 10.9, 9.2 and 9.7 years, respectively ($p < 0.05$). The prevalence of overweight/obesity in ODM2 was twice as high as compared to OGDM and ODM1 (NS). Two children were diagnosed with type 1 diabetes, one in the ODM1 group and one in the OGDM group. Psychiatric comorbidity was diagnosed in 4 OGDM: ADHD in 3 (3%), Asperger in 1 (1%). Breastfeeding rates were comparable between the 3 groups; however, more ODM1 were breastfed up to 6 months whilst ODM2 and OGDM were breastfed for a longer period ($p < 0.05$; table 7.1).

Mothers of ODM2 had the highest pre-pregnancy BMI, while BMI in type 1 diabetic and gestational diabetic women was comparable. Educational level did not differ significantly between the groups. Significantly more women with type 2 or gestational diabetes were of non-Caucasian origin. Twenty mothers, who had gestational diabetes in their pregnancy

(23%), were diagnosed with diabetes at the time of the questionnaire. Current paternal BMI was comparable between the groups, although fathers of ODM2 had a slightly higher BMI.

Table 7.1 parental and offspring characteristics
Values are n (%) or mean ± SD or median (interquartile range) in skewed data ¶;
** Eldest infant of the mother born our center (e.g. primiparous women);*

	ODM1	ODM2	OGDM	P	# Missing values
	n = 51	*n = 21*	*n = 87*		
ODM characteristics					
Age at follow-up (years)	10.9 ± 2.6	9.2 ± 3.7	9.7 ± 3.0	< 0.05	
Female (%)	28 (55)	10 (48)	41 (47)	0.66	
BMI (kg/m^2) ¶	17.4 (3.7)	17.1 (5.7)	17.0 (3.3)	0.14	
BMI SDS	0.6 ± 1.25	1.2 ± 1.47	0.6 ± 1.32	0.12	
Overweight or obese (%)	8 (16)	8 (38)	17 (20)	0.10	
Height (cm)	149 ± 19	138 ± 25	141 ± 20	< 0.05	
cTH (cm)	176 ± 7.8	175 ± 7.3	176 ± 7.3	0.10	
Neonatal characteristics					
Gestational age at birth (weeks) ¶	38 (2)	38 (1)	39 (2)	< 0.05	
Birthweight (gr) ¶	3535 (915)	3730 (545)	3555 (738)	0.63	
Birthweight Z-score	0.98±1.5	0.85±1.1	0.6±1.2	0.17	
Large for gestational age (%)	24 (47)	7 (33)	23 (26)	< 0.05	
Breastfed (%)	38 (75)	12 (57)	53 (61)	0.20	13 (DM1); 9 (DM2); 34 (GDM)
Breastfed up to 6 months (%)	31 (82)	8 (67)	35 (66)	< 0.05	
Breastfed > 6 months (%)	7 (18)	4 (33)	18 (34)	0.24	
Paternal characteristics					
Caucasian (%)	50 (98)	14 (67)	78 (90)	< 0.05	
Current BMI (kg/m^2) ¶	24.7 (5.0)	27.2 (5.2)	25.8 (3.7)	0.11	
Diabetes (currently, any type) (%)	2 (4)	0	1 (1)	0.41	1 (DM1) ; 3 GDM
	n = 33	*n = 13*	*n = 72*		
Maternal characteristics*					
Age at child birth (years)	33.3±3.4	32.6±5.4	33.6±4.3	0.82	
Multiparous (%)	6 (18)	7 (54)	42 (58)	< 0.05	
Caucasian (%)	33 (100)	10 (77)	62 (86)	< 0.05	
Education university of applied sciences (%)	17 (52)	3 (23)	23 (32)	< 0.05	2 (GDM)
Employment (yes; %)	24 (73)	6 (50)	54 (75)	0.21	1 (DM2)
BMI before pregnancy					
BMI (kg/m^2) ¶	24.0 (3.8)	29.4 (7.8)	26.2 (7.6)	< 0.05	
BMI classification (%)				< 0.05	
Normal weight	22 (67)	2 (15)	29 (40)		
Overweight (BMI >25/<= 30)	8 (24)	5 (39)	24 (33)		
Obese (BMI > 30)	3 (9)	6 (46)	19 (27)		
Insulin use in pregnancy (%)	33 (100)	13 (100)	45 (54)	< 0.05	

Table 7.2 Dietary and lifestyle assessment
Values are n (%)

	ODM1	ODM2	OGDM	P	# Missing values
	n = 51	*n = 21*	*n = 87*		
Diet					
Breakfast				< 0.05	
Never	1 (2)	0	0		
1-3 times a week	0	4 (19)	1 (1)		
>3 times a week	50 (98)	17 (81)	86 (98)		
Vegetables				0.37	
Never	0	0	0		
1-3 times a week	0	1 (5)	2 (2)		
> 3 times a week	51 (100)	20 (95)	85 (98)		
Fruit intake				0.35	
Never	3 (6)	1 (5)	2 (2)		
1-3 times a week	6 (12)	4 (19)	6 (7)		
> 3 times a week	42 (82)	16 (76)	79 (91)		
Amount of fruit				0.43	
None	3 (6)	1 (5)	3 (3)		
½-1 ½ per day	40 (78)	13 (62)	69 (79)		
=> 2 per day	8(16)	7 (33)	15 (17)		
Fruit juice				0.57	
None	21 (41)	8 (38)	38 (44)		
1-2 servings per day	30 (59)	12 (57)	48 (55)		
> 2 servings per day	0	1 (5)	1 (1)		
Sugar containing drinks				0.67	
None	5 (10)	2 (10)	4 (5)		
1-2 servings per day	34 (67)	12 (57)	59 (67)		
> 2 servings per day	12 (23)	7 (33)	24 (28)		
Snacking between meals				< 0.05	
Sometimes (<1 / day)	2 (4)	6 (28)	10 (12)		
Once or twice a day	43 (84)	13 (62)	63 (72)		
More than twice a day	6 (12)	2 (10)	14 (16)		
Lifestyle					
Walking/cycling to school				0.44	
Never	3 (6)	2 (10)	13 (15)		1 (DM2)
2/5 times per week	1 (2)	1 (5)	4 (5)		2 (GDM)
≥ 3/5 times per week	47 (92)	17 (85)	68 (80)		
Play outside				0.18	
< 1 day a week	7 (14)	2 (10)	4 (5)		
1-3 times a week	11 (21)	8 (38)	20 (23)		
> 3 times a week	33 (65)	11 (52)	63 (72)		

Table 7.2 Continued

	ODM1	ODM2	OGDM	P	# Missing values
	n = 51	*n = 21*	*n = 87*		
Hours spent outside				0.38	
Max. 1 hour	3 (6)	3 (14)	11 (13)		1 (GDM)
1-2 hours	36 (71)	14 (67)	48 (56)		
Three hours or more	12 (24)	4 (19)	27 (31)		
Screen time hours				0.09	
Max. 30 minutes/day	7 (14)	7 (35)	26 (30)		1 (DM2)
½ hour – 1 hour /day	26 (50)	7 (35)	31 (36)		
1-2 hours / day	8 (16)	3 (15)	22 (25)		
> 2 hours / day	10 (20)	3 (15)	8 (9)		
Member of sports club (yes)	46 (90)	14 (67)	73 (84)	< 0.05	

Causes of possible adiposity

In table 7.2, the results of the questionnaire are shown. Significantly more ODM2 had breakfast less than 4 times a week, as compared to ODM1 and OGDM. Vegetable, fruit, sugar containing drinks or fruit juice consumption were comparable between the groups. ODM2 consumed significantly less snacks between meals (62%) compared to ODM1 (84%) and ODM2 ((72%, $p<0.05$)). Walking or cycling to school, the amount of hours playing outside and screen time per day were comparable between the groups (NS). Significantly less ODM2 (67%) were member of a sports club compared to ODM1 (90%) and OGDM (84%).

Consequences of possible adiposity

The impression of health and vulnerability of the child, as judged by their parents, is presented in table 7.3. Parents of ODM2 were less positive about their child's health and compared to parents of ODM1 and OGDM. Most parents of ODM1 and OGDM judged their children to be generally resistant (i.e. judging their offspring as less vulnerable), whereas only 75% of the parents of ODM2 judged their children as generally resistant. There were no significant differences between the groups regarding the degree of stressfulness of life.

Given the relatively low number of cases included we were unable to assess relationships between BMI of the children and their diet and lifestyle.

Table 7.3 impression by parent
Values are n (%) or mean ± SD

	ODM1	ODM2	OGDM	P	# Missing values
	n = 51	*n = 21*	*n = 87*		
Normal health impression by parent	50 (98)	17 (85)	86 (99)	< 0.05	1 (DM2)
Less vulnerable as judged by parent	47 (92)	12 (75)	78 (94)	< 0.05	5 (DM2); 4 (GDM)
Stressful life as judged by parent	3.4 ± 2.3	4.2 ± 2.9	3.1 ± 2.5	0.17	1 (DM1); 3 (DM2)

Discussion

To the best of our knowledge, this is the first study on lifestyle and diet in offspring of diabetic pregnancies. We found some interesting differences in lifestyle and diet between offspring of women with type 2 diabetes and type 1 / gestational diabetes. Prevalence of childhood overweight/obesity was twice as high in ODM2 as compared to ODM1/OGDM, and ODM2 more often skipped breakfast, snacked less and were less often a member of a sport club and their parents were less positive about their health.

We found a high prevalence of childhood overweight/obesity in ODM2, which is in line with previous studies [1, 2] and our previous longitudinal study on ODM1, ODM2 and GDM, in which we found that the BMI trajectory of the ODM2 group was significantly different from that of the other groups with a higher BMI SDS at age 14 years with 2SDS higher than the 1980 national Dutch growth study [16], and 1.5 SDS above that of the Fifth Growth Study [17] (Hammoud et al, submitted; **chapter 5 and 6**).

Several findings may explain this high prevalence of overweight/obesity in ODM2. The prevalence of maternal overweight/obesity, which was highest in the ODM2 group, may be one factor. Preexisting maternal obesity has previously been related to the differences in the offspring's BMI SDS trajectories [7, 9, 10, 23]. Unfortunately, there are no studies on diet and lifestyle of diabetic offspring, but considerable knowledge regarding non-diabetic offspring, which might help explain the differences in BMI, lifestyle and diet in this group. In ODM2 there was a lower attendance of sport clubs (as a proxy for less physical activity), and a higher percentage of skipping breakfast as a reflection of a non-balanced diet. The latter has previously been related to a higher prevalence of childhood obesity in children of elementary school age [24-26]. Moreover, participation in school breakfast programs, in which children regularly consume (school) breakfast, is associated with a lower BMI [27]. Interestingly however, in ODM2 a lower consumption of snacks was reported. This is in line with previous studies that showed less snacking in overweight/obese children [21, 28], suggesting that sports activity is more important than total caloric intake, but it may also reflect that (obese) mothers do not adequately recall their infant's diet and could therefore be the result of underestimation by parents. Additionally, regarding consumption of snack, the Netherlands Nutrition Centre encourages a maximum of 4 snacks a day, to reduce overeating. Copying of parental habits could also play a part in offspring obesity, and it has been shown that intake of fruit and vegetables is correlated between children and mothers, with obese children often consuming less of these products [29]. Studies on parental restriction of offspring diet have shown conflicting results, with a desirable effect in parental restriction leading to less consumption of 'unhealthy food-items' in toddlers and adolescents regarding soft drink consumption with a decrease in BMI SDS of offspring [30-32], whilst other studies showed a paradoxically increased consumption of the restricted items and a higher BMI SDS associated with strict parental regulation of healthy items [33, 34]. Higher maternal BMI is associated with less dietary restriction [34]. On the other hand, higher maternal educational status stimulates physical activity in offspring, restricts sedentary time and stimulates healthy intake in children [34]. It

may be that restrictive parental feeding practices have played a role in our study, but questions relating to this issue were not included in the questionnaire.

Also other lifestyle factors are known to be associated with an the risk of overweight, such as screen time [21] and short sleeping time [35]. The hours of daily screen time are associated with childhood BMI between the ages of 5 – 10 years and video games are associated with elevated blood pressure and lipids in obese children aged 14-18 years [21, 36-38]. Children who spend more time viewing TV appear to have a poorer diet, with higher intakes of sugar, fast food, snacks and processed meats with lower intakes of fruit and vegetables [39]. It has been estimated that > 1 hour screen time per day contributed approximately 17% to being overweight [21]. In contrast, an active lifestyle stimulates physical activity and fewer parental restrictions in sedentary time [34] and this would likely prevent overweight/obesity. Interestingly, we did not find a difference in screen time or active lifestyle (walking/cycling to school, play outside) between ODM2 and ODM1/OGDM, suggesting that maternal obesity and the lack of regular breakfast may be of greater importance in the onset of childhood overweight/obesity.

Previous findings regarding the effects of breast-feeding on the offspring's BMI in diabetic women are inconclusive [40, 41]. Given the fact that the rate and duration of breast-feeding did not differ between ODM2 and GDM (in contrast to childhood overweight/obesity), it seems unlikely that breast-feeding is of major influence on the development of overweight in these children.

Methodological considerations

Although a considerable number of children were born in our tertiary center during the study period, the traceability of parents was difficult. Even though maximum efforts were made to contact all parents, a response rate of only 20% was reached for the ODM. Therefore, the numbers in this study are relatively small and this hampers precision of the results and additional analysis of for example the effects of diet and lifestyle on BMI SDS growth patterns. A prospective cohort study might improve inclusion and follow-up of these children. Furthermore, when using questionnaires one cannot rule out some degree of information or recall bias. Attendance of child-care could attribute to a great variance in intake. Toddlers attending child-care have an energy intake in the upper ranges of the recommended intake [42]. Unfortunately, we do not know how many children in our population attended child-care.

Recommendations and summary

Our finding of a higher prevalence of childhood overweight/obesity in ODM2 necessitates the need for preventive strategies. It has been shown that parental feeding practices are linked to dietary habits and food intake, not only during childhood, but also in adult life [43]. Early intervention could consist of for example family-based behavioral treatments to reduce total energy intake [32], or increasing parental concern on offspring diet through intensive counseling of obese parents [13]. Parents should stimulate towards

an active lifestyle, because this also stimulates physical activity in offspring [34] and a reduction of reduction of restrictive parental feeding practices is advised [32].

In summary, this is the first study on lifestyle and diet in offspring of diabetic women. ODM2 show almost twice as much childhood overweight/obesity compared to ODM1 and GDM, which was related to maternal overweight, skipping breakfast, less snacking and lower membership of a sports club. These results indicate that the higher prevalence of overweight / obesity in ODM2 may partly be due to parental lifestyle influences, which enables the design of preventive strategies.

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Conflict of Interest

None.

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Life can only be
understood backwards;
but it must be lived
forwards
Søren Kierkegaard

Chapter 8

Summary and general discussion

Summary in Dutch (Nederlandse samenvatting)

Summary and general discussion

Outcome of pregnancies complicated by maternal diabetes mellitus remains impaired despite modern treatment possibilities. This is likely to be due to the fact that truly normal physiological glucose profiles have remained out of reach. Moreover, women with type 2 diabetes (DM2) or with gestational diabetes mellitus (GDM) generally are overweight, which has an independent adverse effect on outcome. And lastly, GDM is usually only diagnosed sometime after the actual onset of disease, which may hamper timely treatment.

In this thesis we have addressed several issues related to the pathophysiological alterations, causes and consequences related to diabetes during pregnancy (Chapter 1):

1. Do pregnancy outcomes differ, when GDM is diagnosed through screening or is based on symptoms (Chapter 2).
2. How are the fetal growth trajectories in women with type 1 diabetes (DM1), DM2 and GDM and is disproportionate growth restricted to fetuses being born LGA or not? (Chapter 3)
3. Is intrauterine adiposity, defined as an abnormal fetal head-to-abdomen circumference ratio (HC/AC ratio), related to childhood obesity, and is this relation similar for the three distinct types of diabetes during pregnancy (Chapter 4)
4. How is the relationship between birthweight (centile) and postnatal growth in offspring of women with diabetes during pregnancy, and which factors affect this relationship (Chapter 5 and 6)
5. Are there differences in nutrition and lifestyle during childhood between offspring from women with DM1, DM2 and GDM during pregnancy (Chapter 7).

The diagnosis of GDM (Chapter 2).

Currently in the Netherlands, GDM is usually diagnosed by second trimester screening at around 24-28 weeks of gestation. However, when doing so in an at risk population screened with the ADA-criteria [1], we found that over 30% of fetuses already had an abdominal circumference above the 90th centile as a consequence of hitherto undetected maternal hyperglycemia (**Chapter 2**). When waiting for maternal symptoms or signs of fetal overgrowth in a low risk and generally lean population, diagnosis was made 4 weeks later and at that time twice as many fetuses had an abdominal circumference >90th centile and more were large-for-gestational age (LGA) at birth (**Chapter 2**). Therefore, universal screening for GDM seems better than waiting for symptoms, at least as far as short-term perinatal outcome is concerned.

Recently it has been found that fetuses of women who developed GDM at/or after 28 weeks of gestation had a normal weight estimate at 20 weeks but showed a twofold increased relative risk of 'abdominal obesity' at 28 weeks. This risk was 4.5 fold higher when GDM was accompanied by maternal obesity [2]. Thus, apparently in women developing GDM accelerated fetal growth starts shortly after 20 weeks of gestation.

These data, together with our findings of fetal overgrowth in case of GDM detected at 24-28 weeks, indicate that risk assessment and diagnosis of GDM should in fact be made during the first trimester of pregnancy, to start preventive measures/treatment early (i.e. dietary counseling). First trimester risk assessment for GDM based on maternal characteristics may identify 52% of women who develop GDM later in pregnancy at a 10% false positive rate and combined with measurement of maternal serum adiponectin and sex hormone binding globulin (SHBG), detection rate may increase to 58% (Syngelaki A.; 'Diabetes and obesity in pregnancy', PhD thesis, University of Utrecht, July 4, 2016). Further improvement in such a first trimester risk assessment may enable early detection and treatment in the near future.

Disproportionate fetal growth (Chapter 3)

In **chapter 3** we showed that disproportionate fetal growth, with an abdominal circumference that is relatively larger than that of the fetal head (HC/AC ratio), is present in fetuses of women with DM1 and DM2 but also in GDM and both in fetuses that were non-LGA at birth and those that were born LGA. Disproportionate fetal growth was more prominent in LGA fetuses and especially when the mother had DM1. These data clearly show the effects of an abnormal intrauterine environment on fetal development. Maternal hyperglycemia results in fetal hyperglycemia and fetal hyperinsulinism with a subsequent glycogen storage in the fetal liver and fat storage in the subcutaneous tissues. According to the Pedersen-Freinkel paradigm, not only increased transplacental transfer of glucose but also of lipids and amino acids contribute to this process [3].

So, fetuses of women with diabetes are not only frequently LGA, but they also show a disproportionate growth, which indicates an altered development. Nowadays fetuses of women with DM1 and DM2 diabetes seem larger at birth than during the past [4-6], which is strange given modern treatment modalities. It can, however, be explained by an increase in maternal obesity [7], better control in early pregnancy with improved placentation [8-11], a lower incidence of maternal vascular complications, increased maternal weight gain during pregnancy [12] and poorer third trimester glucose control than in the past since these women are hardly being admitted to hospital anymore [10]. Last but not least, one should not forget that glucose levels in women with DM1 are still about 2 mmol/l higher during pregnancy than in women without diabetes, also if their fetuses were appropriate-for-gestational-age (AGA) at birth [13, 14].

Being born AGA or LGA seems partly to be determined by glucose control in early pregnancy, with poorer placentation and smaller fetuses in case of poor periconceptional glucose control [8-11] and bigger babies in case of poor third trimester control [10].

Intrauterine adiposity and birthweight in relation to postnatal growth and adiposity (Chapter 4-6).

In **chapter 4** we studied the relationship between intrauterine adiposity (HC/AC ratio) and birthweight with the body mass index (BMI) at 4 to 5 years of age, in a subgroup of offspring

from women with DM1, DM2 and GDM. Only in offspring of women with DM1 there was an association between HC/AC ratio and BMI-SDS at the age of 4-5 years with a lower HC/AC ratio (more fetal adiposity) being related to a higher childhood BMI. In contrast, in offspring of women with DM2 or GDM, there was no association between HC/AC ratio and childhood BMI SDS but BMI SDS was positively associated with the birthweight (centile). Women with DM2 themselves had the highest BMI and also their children had the highest incidence of overweight. Women with DM1 had the lowest BMI and also their children had the lowest BMI. Data from women and children in the GDM group were in between those of DM1 and DM2. These data suggest that in case of maternal diabetes, the BMI of the mother has the strongest predictive value regarding offspring BMI.

There are many studies that have shown that offspring of women with diabetes have an increased rate of overweight/adiposity. However, when correcting for maternal BMI most of these associations disappear, suggesting again that maternal obesity is the most important factor related to childhood obesity and/or metabolic syndrome [15-18]. In one follow-up study in offspring aged 16, it was clearly shown that maternal BMI was the driving factor behind childhood obesity in offspring of women with GDM [16]. The presence of maternal GDM did not affect outcome, but in combination with maternal obesity it resulted in the highest incidence of overweight in offspring. In other words, maternal obesity seems the most important factor, with diabetes as an additional risk factor. It may be speculated that intrauterine adiposity as a consequence of diabetes during pregnancy will only be seen in offspring of non-obese women with diabetes (i.e. those with DM1), whereas in the other women maternal factors related to obesity obscure such a relationship. This study was performed in a relatively small population, due to a small sample size of data regarding the HC/AC ratio during the third trimester of pregnancy; the number of included cases was 27, 22 and 24 for DM1, DM2 and GDM, respectively. Larger studies are necessary to validate our findings.

The relationship between maternal diabetes, size at birth, and growth trajectories of their offspring till the age of 14 years, was studied in the **chapters 5** (DM1 as compared to DM2) and **6** (GDM). For this study we obtained follow-up data from infant welfare centers from 78 offspring of women with DM1 (ODM1), 44 of women with DM2 (ODM2) and 104 of women with GDM (OGDM). All these infants were born in the University Medical Center Utrecht, the Netherlands, between 1990 and 2006. BMI SDS was calculated based on the 1980 nation-wide growth study, which is the current Dutch reference population [19]. Height SDS was calculated based on the 2009 (Fifth) nation-wide growth study [20]. BMI was also compared to values from the 2009 (Fifth) Dutch Growth Study, since the BMI of Dutch children has increased from the 1980s onwards [21].
The women with DM1 had a mean prepregnancy BMI of 24 kg/m^2 and those with DM2 had a mean BMI of 31 kg/m^2. At birth 47% and 43%, respectively of the newborns of these women were LGA. There were no significant differences in the height of the study populations between 0 and 14 years of age as compared to the nationwide data. The BMI SDS trajectories from 1-14 years, are shown in Figure 8.1.

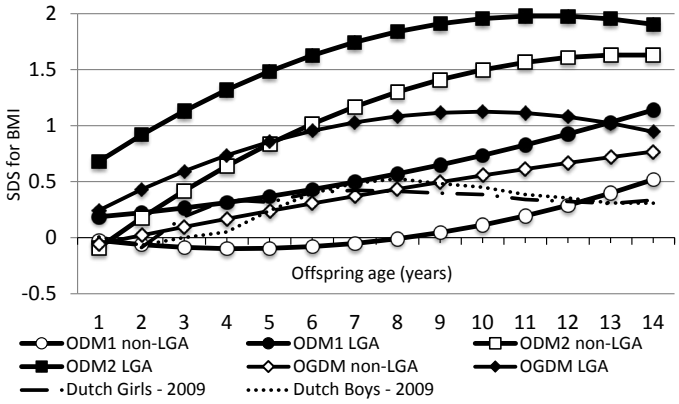

Figure 8.1 Mixed model for offspring from age 1 to age 14 years for mean BMI SDS in subgroups according to (non)-LGA at birth and maternal diabetes types (DM1 and DM2); with values from the 2009 growth study [21].

Offspring of women with DM2 showed the highest BMI SDS values and had on average a BMI of + 1.6 till +2 SD at the age of 14. Children that were LGA at birth had the highest BMI SDS values. The BMI SDS values of offspring of women with DM1 were significantly lower than those of the offspring of women with DM2. The BMI SDS values of LGA offspring from women with DM1 were higher than those of the 2009 growth study, but non-LGA infants of these women had similar BMI SDS values as those of the 2009 study [21].

The follow-up data from offspring of women with GDM are given in **chapter 6**. These women had a prepregnancy BMI of 26kg/m^2 and 25% of their infants were LGA at birth. The growth trajectories of their offspring were generally in between those of women with DM1 and DM2, with a higher BMI SDS in offspring born LGA. These results indicate that that their risk for becoming overweight up to puberty is likely to be limited. Height was not different from the Dutch reference values [20].

Maternal age at delivery, parity, educational level, employment hours, marital status, ethnicity, breast feeding, preconceptional HbA1c, mean pregnancy HbA1c, paternal BMI, paternal ethnicity or paternal diabetes did not influence the BMI or height SDS trajectories in the different populations. Within the 3 distinct diabetes populations maternal prepregnancy BMI did, however, have an effect on the BMI growth trajectories, in line with the literature. Addition of maternal BMI in ODM1 and ODM2 to the mixed model resulted in an increase in BMI SDS trajectories in the non-LGA ODM1 and in a decrease in the non-LGA ODM2 subgroups. In other words, in offspring of women with DM1 that were non-LGA at birth, a low maternal BMI was associated with a growth rate similar to that of the overall Dutch population. The high growth trajectory in non-LGA offspring of women with DM2 could be due to a high maternal BMI. Within the 3 groups of maternal diabetes, there was generally not a wide range in maternal BMI. However, between the

groups there were large differences, with women with DM2 having by far the highest BMI and those with DM1 having the lowest maternal prepregnancy BMI. These inter-group differences concur nicely with the differences in offspring growth trajectories.

Our longitudinal studies were performed using the mixed modeling technique, which is a statistical method that builds a custom model based on the available measurements. This method does not utilize imputation and allows on a custom model even though at each gestational age or postnatal age, not all measurements were taken at the same time. With this method, we have been able to compare intrauterine growth trajectories and postnatal BMI and height SDS trajectories between offspring of women with DM1, DM2 and GDM, which is a novelty in current literature. Other studies have either analyzed fetal or offspring data from a single or combined types of maternal diabetes; additionally, most studies were cross-sectional in nature. In literature, different definitions for childhood obesity were used and studies were performed are at different ages, which hampers comparison with our data. A strength of our studies is that the infants were born in the same center, in the same time period with maternal prenatal care being given in that center.

A limitation of our studies might be the possibility of selection bias given the fact that response rates were lower than two-thirds of the mothers contacted. For ODM1 and ODM2 a response rate of 52-63% was reached, which seems relatively good for a retrospective study dating back almost 1.5 decades after children were born. This may be due to the fact that all women received and continued to receive medical care in our hospital. However, the response rate for OGDM was only 22%. This might be due to the fact that a considerable part of the women with gestational diabetes were first generation immigrants with insufficient knowledge of the possible Dutch language; moreover, young families move often and change phone-numbers, which hampers tracing them after several years. And lastly, gestational diabetes is not a chronic disease, so contacts through the diabetes outpatient clinic ceased to exist. Response rates for the questionnaire were lower than the informed consent for the infant welfare data, possibly due to lack of time to complete the questionnaire and/or lack of competency in Dutch. Future prospective studies may obtain higher compliance.

When summarizing the findings of the **Chapters 4-6**, it appears that whereas a high incidence of infants of especially women with DM1 and DM2 were LGA at birth, the BMI SDS trajectories of their children differed considerably. In utero growth was most abnormal for fetuses of women with DM1 (**Chapter 3**), but growth after birth was almost normal in this population; in any case for those born non-LGA. It seems most plausible that differences in maternal BMI underlie the differences in postnatal growth, as we have discussed before. Accelerated growth after birth is strongly associated with the development of (type 2) diabetes and metabolic syndrome at later life, and this holds both for infants that were either LGA or small-for-gestational age (SGA) at birth [22]. Prevention of accelerated growth after birth is therefore of utmost importance.

The effect of nutrition and lifestyle during childhood (Chapter 7)

Postnatal growth of offspring of women with diabetes is dependent on the maternal BMI and on being LGA or otherwise at birth, but differences in growth trajectories may also be explained by differences in nutrition and lifestyle during childhood. Such studies on offspring of women with diabetes are lacking in literature. This issue was therefore explored in **chapter 7**. We send questionnaires to the parents of children who had participated in the previous studies and received 51, 21 and 87, respectively, completed questionnaires back from women with DM1, DM2 and GDM. The mean age of their children at that time was 10 years. Offspring of women with DM2 had the highest incidence of obesity (NS). These children of mothers with DM2 skipped breakfast more often, had less snacks during the day and were less often a member of a sport club than the children of the other two diabetes categories. Their parents were also less positive about their health. Although skipping breakfast and fewer snacks suggest less food intake, they are a sign of altered lifestyle, which – together with less physical activity - may result in obesity [23-27].

Summing up and perspectives

This set of studies has highlighted a number of important issues in the prognosis of offspring from women with a pregnancy complicated by diabetes. We do know that achieving normal glucose and insulin physiology is still not attainable despite revolutionary development in insulin preparations, insulin administration methodology and monitoring techniques. Unless we are able to deliver insulin into the portal vein in contrast to the peripheral subcutaneous tissue and can measure intravascular glucose frequently or continuously instead of subcutaneously and unless we will be able to match glucose levels and insulin infusion more intimately, normal glucose levels during the whole of pregnancy remain a phantom. Nevertheless, our possibilities have increased dramatically, far beyond the expectations at the time of the first St Vincent declaration [28].

Acknowledging current shortcomings, this set of studies does provide some new considerations and possibilities covering pre- and postnatal issues. The attention of pregnancy outcome has extended in the last two decades into the era of offspring prognosis. LGA is a major short-term adverse pregnancy outcome and is related to glycemic control (as assessed by HbA1C levels) in pregnancies complicated by diabetes [10, 14]. Screening and diagnosis in GDM is a hot issue, which causes much debate, with the focus centering on the population to screen (universal or on the basis of maternal risk factors), test types and cut-off values. We have shown that in the setting of the Dutch approach using selective screening, a considerable number of women are detected late in the course of pregnancy on the basis of fetal growth acceleration (diagnosis, not screening) who might have been found earlier if they were screened. This implies that also women without risk factors may develop GDM. Given the perinatal consequences of being LGA, this is a worthwhile issue to take into consideration when discussion screening procedures. Intra-uterine events cast their shadows in the postnatal years of development.

Disproportionate growth (assessed by the HC/AC ratio) is an indicator of fetal hyperinsulinism in a setting of sufficient metabolic substrates and here we see a sharp dichotomy between offspring of women with DM1 vs. offspring of women with DM2 or GDM in the first years of life. Disproportionate intrauterine growth is positively associated with childhood BMI in offspring of women with DM1 in contrast to those of women with DM2 or GDM. BMI in offspring of women with DM2 and GDM, but not in offspring of women with DM1, is related to birthweight. These findings, if corroborated by larger studies, indicate that regarding future child development, offspring of women with DM1 differ from those of women with DM2 and GDM. This is not illogical because the pathophysiology of DM2 and GDM are much alike. Fetal hyperinsulinism may be more prominent in pregnant women with DM1 because of a much larger maternal glucose variability compared to DM2 and GDM [29].

Collecting follow-up data up to 14 years after birth, we were able to analyze growth trajectories for a longer period than is usually done in literature and compare LGA- and non-LGA offspring. These data are important because long-term outcomes in addition to short-term outcomes are important for parents and health care professionals; and interventions may be necessary to prevent adverse long-term outcome. Non-LGA offspring of women with DM1 have a normal BMI SDS profile, but LGA offspring remain heavier that their non-LGA counterparts. A similar pattern is seen with non-LGA offspring of women with DM2 and LGA offspring albeit at a higher BMI SDS. Likewise, non-LGA offspring of women with GDM and LGA offspring of these women showed similar trends, in between those of DM1 and DM2. These patterns concur with that of intrauterine growth, although quite suggestive, this doesn't proof causality. Finally, lifestyle differences were observed between offspring of the different types of maternal diabetes, indicating a relevant topic of research.

What can we do to improve intra-uterine and postnatal life in the obesity epidemic? A number of possibilities come to mind:

1. Assuming the role of maternal obesity in increasing the risk of childhood and adolescent obesity, every attempt must be made to achieve weight loss in obese women before conception. Life style interventions targeted to this specific group are required. In women with Poly Cystic Ovary Sydrome (PCOS) and infertility, weight loss may normalize the menstrual cycle and solve the infertility problem, which may improve pregnancy outcome at the same time.
2. Reducing excessive weight gain during pregnancy. This issue was not touched upon in our studies due to lack of data since those measurements were abandoned in the Netherlands during the last decades. Weight gain during pregnancy shows a strong correlation to fetal birth weight (for instance in case of maternal DM1 [30] and to postnatal growth [31, 32]. Again, targeted nutritional counseling is indicated. There are (American) guidelines on optimal weight gain during pregnancy in relation to prepregnancy BMI [33]. Adequate nutritional counseling during pregnancy is of great importance and obstetricians should start to weigh the pregnancy women again at regular intervals.

3. Prevention of macrosomia (LGA) at birth. In women with diabetes glucose levels play an important role in the pathogenesis of fetal macrosomia. At present it is difficult to reduce the incidence of fetal macrosomia since there are several reasons why these infants are more likely to be LGA nowadays than in the past, as has been outlined before: real ''normoglycemia'' cannot yet be achieved, and almost good is not good enough. However, Murphy et al. have shown that application of offline continuous glucose monitoring (Offline CGM) by a dedicated multidisciplinary team in a single center can reduce the incidence of LGA in a mixed population of women with DM1 and DM2 [34]. In trials with real time CGM, patient groups were too small or compliance was too low (insufficient wearing of glucose sensors) to provide meaningful results [35]. The current CONCEPTT trial in women with DM1 employs real time CGM before or after conception, and will provide meaningful information [36, 37]. A recent trial in China using Offline CGM together with strict dietary measures reduced significantly the incidence of LGA infants in women with GDM [38], which underlines –again- the additive value of an adequate and strict diet. Regarding GDM, an early diagnosis before the occurrence of fetal macrosomia may decrease the incidence of LGA in this condition. Universal screening of GDM is therefore indicated and first trimester identification of women at high risk for developing GDM should further be investigated.
4. Genetics and epigenetics are more difficult issues. Knowledge of the genetics of DM2 has evolved over the past years. Several genes have been identified through pooling of data of multiple individual cohorts in case–control genome-wide associations study (GWAS) analyses with researchers being able to indicate the individual effect size of an allele on the risk for DM2 [39]. With this knowledge, it would be possible to identify individuals at high risk for developing DM2 and targeted intervention could be employed to promote personal healthful behavioral changes. Exposure to diabetes in the intrauterine environment could induce epigenetic modifications, through DNA methylation and/or histone modifications. Those epigenetic modifications may progress with aging during postnatal life, resulting in a 'metabolic phenotype' and an increased risk for development of obesity and DM2 [40, 41]. With all current knowledge, adequate lifestyle and nutrition coupled with optimal glycemic control are here also the only tools we have.
5. Prevention of accelerated growth of children after the age of 2 years should receive more attention. This does not only hold for children from women with diabetes, but for the whole population. In this issue, there is a very important role for infant welfare centers. Offspring of women with DM2, should be prioritized, given the fact that they are more at risk for childhood obesity and have a more "unhealthy" dietary and lifestyle habits.

In conclusion, these follow-up studies are a valuable addition to previous literature, as it provides important developmental data of concise cohort of children from pregnancies complicated by diabetes. It could mean a first step to provide parents and health workers with a gross estimation of when they should provide special attention to offspring from

(pre)gestational diabetic pregnancies in order to possibly prevent adiposity. This research provides a glimpse into how intrauterine environment translates into postnatal growth and that different factors influence postnatal development. Furthermore, we suggest a prospective cohort on this group of offspring to provide more insight into diet and lifestyle and its effects on offspring BMI.

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Summary in Dutch (Nederlandse samenvatting)

Diabetes mellitus, ook wel bekend als suikerziekte, ontstaat als er relatief of absoluut tekort is aan insuline en daardoor de bloedsuikerspiegels stijgen. Ondanks verbeteringen in de medische zorg, is de uitkomst van zwangerschappen die gecompliceerd worden door diabetes mellitus nog steeds slechter dan die van zwangerschappen zonder diabetes. Dit wordt waarschijnlijk veroorzaakt doordat daadwerkelijk normale glucosewaarden niet behaald worden. Een verder complicerende factor bij vrouwen met type 2 diabetes (DM2; "ouderdomssuikerziekte") en diabetes gravidarum (GDM; zwangerschaps suikerziekte) is dat deze vrouwen vaak overgewicht hebben, wat eveneens bijdraagt aan de slechtere zwangerschapsresultaten. Het veelal pas laat ontdekken van zwangerschapssuikerziekte, in het verloop van de zwangerschap, staat bovendien een tijdige behandeling in de weg.

In dit proefschrift wordt getracht op de volgende vragen een antwoord te geven (hoofdstuk 1):

1. Zijn de zwangerschapsresultaten verschillend, wanneer zwangerschapssuikerziekte gediagnosticeerd wordt door middel van screening van vrouwen met risicofactoren of wanneer gewacht wordt op symptomen van de aandoening? (hoofdstuk 2).
2. Hoe zijn de foetale groeiprofielen bij vrouwen met type 1 diabetes (DM1), DM2 en GDM? Is onevenredige groei in de baarmoeder, waarbij de foetale buikomtrek relatief te groot is in vergelijking met de hoofdomtrek, voorbehouden aan neonaten die te zwaar zijn bij de geboorte, of komt dit ook voor bij foetussen die een normaal geboortegewicht hebben? (hoofdstuk 3).
3. Is intra-uteriene obesitas, gedefinieerd als een abnormale verhouding tussen hoofd- tot buikomtrek, gerelateerd aan zwaarlijvigheid op kinderleeftijd? En is deze relatie vergelijkbaar tussen de drie verschillende typen diabetes in de zwangerschap? (hoofdstuk 4).
4. Wat is de relatie tussen geboortegewicht en groei na de geboorte van de kinderen van moeders met diabetes en welke factoren beïnvloeden deze relatie? (hoofdstuk 5 en 6)
5. Zijn er verschillen in voeding en levensstijl tussen kinderen van moeders met DM1, DM2 en GDM in de zwangerschap? (hoofdstuk 7).

De diagnose van zwangerschapssuikerziekte (GDM) (hoofdstuk 2).

In Nederland wordt bij vrouwen met bepaalde risicofactoren zwangerschapssuikerziekte veelal in het 2e trimester van de zwangerschap gediagnosticeerd, bij 24-28 weken, door middel van een glucose belastingstest [1]. Wanneer hiermee zwangerschapssuikerziekte wordt gediagnosticeerd, blijkt meer dan 30% van de foetussen al een te grote buikomtrek te hebben. Dit is het gevolg van al eerder opgetreden hoge glucosegehaltes bij de moeder (**hoofdstuk 2**). Wanneer wordt gewacht tot de zwangere vrouw symptomen vertoont van een te hoog bloedsuikergehalte of wanneer pas getest wordt als de foetus te groot lijkt te zijn, dan wordt de diagnose GDM gemiddeld 4 weken later vastgesteld

dan wanneer de vrouw met risicofactoren wordt opgespoord. Op dat moment hebben tweemaal zoveel foetussen al een te dikke buikomtrek en zijn meer kinderen te zwaar bij de geboorte (**hoofdstuk 2**).

Het is dan ook beter om alle zwangere vrouwen te screenen op zwangerschapssuikerziekte, in plaats te wachten op symptomen. Recent is gebleken dat foetussen van vrouwen met zwangerschapssuikerziekte die bij ongeveer 28 weken zwangerschapsduur werden gediagnosticeerd, bij 20 weken nog een normaal gewicht hadden maar bij 28 weken al frequent te zwaar waren, zeker als hun moeder overgewicht had [2]. Het lijkt er dus op dat foetussen van vrouwen die GDM ontwikkelen een versnelde foetale groei vertonen die kort na 20 weken zwangerschap begint. Samen met onze bevindingen van foetale overgroei wanneer zwangerschapssuikerziekte, opgespoord wordt bij 24-28 weken, geven deze gegevens aan dat de risicobeoordeling en diagnose van zwangerschapssuikerziekte in feite al tijdens het eerste trimester van de zwangerschap gedaan zou moeten worden om vroegtijdig met preventieve maatregelen (dieetadvisering)/behandelingen te beginnen. Een risico-analyse in het eerste trimester op basis van kenmerken van de zwangere vrouw zou 52% van de vrouwen die later in de zwangerschap zwangerschapssuikerziekte ontwikkelen, kunnen identificeren. Slechts 10% van de zo geïdentificeerde vrouwen zou foutief positief uit de test komen. Gecombineerd met bepaalde metingen in het bloed van de moeder (namelijk serum adiponectine en sex hormone binding globulin (SHBG)), zou de detectie verhoogd kunnen worden tot 58% (Syngelaki A.; '*Diabetes and Obesity in Pregnancy*', PhD thesis, Universiteit Utrecht, 4 juli, 2016). Een verdere verbetering van een dergelijke eerste trimester risicobeoordeling kan vroegtijdige opsporing van GDM en behandeling in de nabije toekomst wellicht mogelijk maken.

Onevenredige (disproportionele) foetale groei (hoofdstuk 3)

In **hoofdstuk 3** vonden we dat onevenredige foetale groei met een buikomtrek die relatief groter is dan de hoofdomtrek vaak voorkomt bij foetussen van vrouwen met zwangerschapsdiabetes. Door middel van echoscopisch onderzoek bij een groot aantal foetussen van vrouwen met DM1 en DM2 en GDM konden we dit ook aan tonen bij alle vormen van diabetes in de zwangerschap. Disproportionele foetale groei kwam het vaakste voor bij kinderen die ook de zwaar waren bij de geboorte en dan vooral bij moederlijke type-1 diabetes. Echter, ook bij kinderen met een normaal geboortegewicht was de groei in de baarmoeder vaak afwijkend. Deze gegevens tonen duidelijk de effecten van een abnormale omgeving in de baarmoeder op de ontwikkeling van het kind in de baarmoeder. Te hoge bloedsuikers bij de zwangere vrouw resulteren in te hoge suikerwaarden en insulinespiegels bij de baby. Dit zorgt voor meer suiker- en vetopslag in de lever en het onderhuidse vetweefsel van de baby. Volgens het Pedersen-Freinkel-paradigma draagt niet alleen het transport van suiker van moeder naar baby via de navelstreng bij aan dit probleem, maar ook het transport van vetten en eiwitten [3].

Tegenwoordig zijn pasgeborenen van vrouwen met DM1 en DM2 diabetes vaak zwaarder dan in het verleden [4-6]. Dit bevreemdt, omdat momenteel de bloedsuikerregulatie bij vrouwen met diabetes sterk verbeterd is. Dit fenomeen kan echter verklaard worden door 1) een toename van zwaarlijvigheid van moeders [7], 2) een betere controle van bloedsuikerspiegels rondom de bevruchting waardoor de placenta zich beter ontwikkelt en de foetus meer voeding krijgt [8-11], 3) minder hart- en vaatziekten door betere bloedsuikerregulatie bij deze (relatief) jonge vrouwen, 4) meer gewichtstoename van de moeder tijdens de zwangerschap [12] 5) en een slechtere controle van de suikers aan het einde van de zwangerschap doordat deze vrouwen tegenwoordig nauwelijks meer worden opgenomen in het ziekenhuis [10]. Tenslotte moet men niet vergeten dat de glucosespiegels bij vrouwen met DM1 tijdens de zwangerschap nog steeds een stuk hoger zijn dan bij vrouwen zonder diabetes [13,14]. Bijna goede bloedsuikerspiegels zijn nog niet goed genoeg.

Obesitas in de baarmoeder en geboortegewicht in relatie tot groei en obesitas op de kinderleeftijd (Hoofdstuk 4-6).

In **hoofdstuk 4** bestudeerden wij de relatie tussen foetale groei en geboortegewicht met het gewicht, de body mass index (BMI), van de kinderen op de leeftijd 4 tot 5 jaar, in een subgroep van kinderen van vrouwen met DM1, DM2 en GDM. Bij kinderen van vrouwen met DM1 was er een relatie tussen een dikke foetale buikomtrek en de BMI waarbij een relatief dikke buikomtrek geassocieerd was met een hogere BMI. Deze relatie werd niet gevonden bij de kinderen van vrouwen met DM2 of GDM. Echter, bij deze kinderen was de BMI op 4-5 jarige leeftijd wel gerelateerd aan hun geboortegewicht. Vrouwen met DM2 hadden zelf de hoogste BMI en ook hun kinderen hadden het vaakste overgewicht op de leeftijd van 4-5 jaar. Vrouwen met DM1 hadden zelf de laagste BMI en ook hun kinderen hadden de laagste BMI. Kinderen van vrouwen met GDM hadden, evenals hun moeders, een BMI tussen die van DM1 en DM2 in. Deze gegevens suggereren dat bij maternale diabetes, de BMI van de moeder de sterkste voorspeller is van de BMI van de nakomelingen.

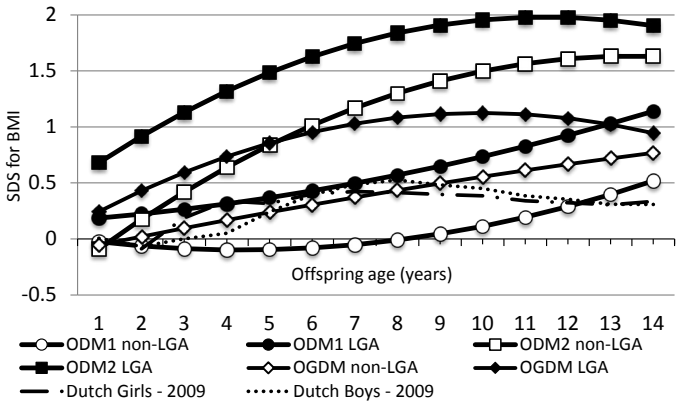
Er zijn veel onderzoeken die hebben aangetoond dat kinderen van vrouwen met diabetes een verhoogd risico hebben op het ontwikkelen van overgewicht/obesitas. Echter, indien een correctie wordt toegepast voor de BMI van de moeder, verdwijnen de meeste van deze associaties. Dit suggereert dat moederlijk overgewicht de belangrijkste factor is, met betrekking tot obesitas en / of hart- en vaatziekten bij hun nakomelingen [15-18].

In een vervolgstudie bij kinderen op 16 jarige leeftijd, werd duidelijk aangetoond dat de BMI van de moeder de bepalende factor is achter obesitas bij kinderen van vrouwen met zwangerschapssuikerziekte [16]. De aanwezigheid van zwangerschapssuikerziekte alleen, had geen invloed op de uitkomst van de nakomelingen. Echter de combinatie van zwangerschapssuikerziekte en maternale obesitas resulteerde in de hoogste incidentie van overgewicht bij deze kinderen. Met andere woorden, de belangrijkste factor voor obesitas op kinderleeftijd lijkt moederlijk overgewicht te zijn, waarbij diabetes als een additionele risicofactor beschouwd moet worden.

In ons onderzoek dat in dit hoofdstuk wordt besproken, werd een relatie tussen een te grote buikomtrek van de baby tijdens de zwangerschap, als gevolg van diabetes tijdens zwangerschap alleen waargenomen bij kinderen van vrouwen met type-1 diabetes, d.w.z. bij vrouwen zonder overgewicht. In de andere gevallen, waarbij de moeders ook zwaarder waren (namelijk DM2 en GDM), heeft moederlijk overgewicht deze relatie mogelijk overvleugeld. Dit onderzoek werd uitgevoerd in een relatief kleine populatie (27, 22 en 24 kinderen van vrouwen met respectievelijk DM1, DM2 en GDM). Grotere studies zijn nodig om deze bevindingen te valideren.

De relatie tussen maternale diabetes, geboortegewicht, en het postnatale groeipatroon van deze kinderen tot en met de leeftijd van 14 jaar, werd bestudeerd in de **hoofdstukken 5** (DM1 vergeleken met DM2) en **6** (GDM). Voor dit onderzoek kregen we follow-up gegevens van de GGD's van 78 kinderen van vrouwen met DM1 (ODM1), 44 van vrouwen met DM2 (ODM2) en 104 van vrouwen met GDM (OGDM), na instemming van de ouders. Al deze kinderen zijn geboren in het Universitair Medisch Centrum Utrecht, tussen 1990 en 2006. De standaard deviatie score (SDS) voor de BMI werd berekend op basis van gegevens van de Nederlandse referentiepopulatie uit 1980 (SDS = 0) [19]. De SDS voor de lengte van de kinderen werd berekend op basis van gegevens uit de vijfde landelijke groeistudie uit 2009 [20]. De BMI van de kinderen werd ook vergeleken met de waarden uit de vijfde landelijke groeistudie uit 2009, aangezien de BMI van alle Nederlandse kinderen sinds 1980 ook is toegenomen [21].

De vrouwen met DM1 hadden een normaal BMI voordat ze zwanger werden (24 kg/m^2) en vrouwen met DM2 waren over het algemeen obese (gemiddelde BMI 31 kg/m^2). Bij de geboorte waren respectievelijk 47% en 43% van de pasgeborenen van deze vrouwen



Figuur 8.1 Resultaten van het statistisch model voor kinderen uit zwangerschappen met diabetes vanaf de leeftijd van 1 jaar tot en met de leeftijd van 14 jaar voor het gemiddelde BMI-SDS, onderverdeeld in subgroepen te zwaar geboortegewicht (LGA) en niet te zwaar geboortegewicht (non-LGA) en maternale diabetes types (DM1 en DM2); vergeleken met de waarden van de 2009 groei studie [21].

te zwaar. Er waren geen verschillen in de lengte van deze kinderen tussen 0 en 14 jaar in vergelijking met de landelijke gegevens.

De BMI-SDS groeiprofielen van 1 tot en met 14 jarige leeftijd, zijn weergegeven in figuur 8.1.

Kinderen van vrouwen met DM2 hadden de hoogste BMI-SDS groeiprofielen en hadden gemiddeld een BMI die bijna 2 standaard deviaties hoger was dan die van Nederlandse kinderen op de leeftijd van 14 jaar. Kinderen die te zwaar waren bij de geboorte hadden het hoogste BMI. De BMI-SDS waarden van de kinderen van vrouwen met DM1 waren lager dan die van de nakomelingen van vrouwen met DM2. De BMI-SDS waarden van te zwaar geboren kinderen van vrouwen met DM1 waren hoger dan die van de vijfde landelijke groeistudie uit 2009, maar die met een normaal geboortegewicht hadden een vergelijkbare BMI-SDS als die van de vijfde landelijke groeistudie [21].

De groeiprofielen van kinderen van vrouwen met GDM worden besproken in **hoofdstuk 6**. Deze vrouwen hadden vóór hun zwangerschap gemiddeld een iets te hoge BMI (26kg/m^2) en 25% van hun kinderen was te zwaar bij de geboorte. De BMI-SDS groeiprofielen van deze kinderen lagen in het algemeen tussen die van kinderen van vrouwen met DM1 en DM2 met hogere waarden bij kinderen die te zwaar waren bij de geboorte. Deze resultaten tonen aan dat in deze groep kinderen, het risico op overgewicht tot aan de puberteit waarschijnlijk beperkt is, als je dit vergelijkt met de kinderen uit de vijfde nationale groeistudie uit 2009. De lengte-SDS van deze kinderen verschilde niet ten opzichte van de Nederlandse referentiewaarden [20].

De leeftijd van de moeder bij de bevalling, de hoeveelheid kinderen die ze gebaard heeft, haar opleidingsniveau, het aantal werkuren per week, haar burgerlijke status, haar etniciteit, of ze borstvoeding heeft gegeven, het gemiddelde suikergehalte (HbA1c) voor de bevruchting en tijdens de zwangerschap, de BMI van vader, etniciteit van de vader en of deze diabetes heeft, bleken factoren die geen beïnvloedende rol hebben gespeeld op de BMI-SDS groeiprofielen van de kinderen.

Binnen de 3 verschillende typen van moederlijke diabetes bleek de BMI van de moeder vóór de zwangerschap wel een effect te hebben op de BMI-SDS groeiprofielen van de kinderen, wat in lijn is met de huidige literatuur. Sterker nog, toevoeging van de BMI van de moeder in het statistische model resulteerde in een toename van de BMI-SDS groeiprofielen van kinderen van vrouwen met type-1 diabetes met een normaal geboortegewicht. Bij kinderen van vrouwen met type-2 diabetes resulteerde toevoeging van BMI van de moeder in een afname van de BMI-SDS groeiprofielen van de kinderen met een normaal geboortegewicht. Met andere woorden, bij nakomelingen van vrouwen met DM1 die niet te zwaar waren bij de geboorte, lijkt een lagere moederlijke BMI te zorgen voor een groei van de kinderen die gelijk is aan die van de Nederlandse populatie. De hoge BMI-SDS groeiprofielen van niet te zware kinderen

van vrouwen met DM2 kunnen worden veroorzaakt door een hogere BMI van deze moeders. Binnen de drie groepen van maternale diabetes afzonderlijk, waren er meestal geen grote verschillen in moederlijke BMI. Echter, tussen de drie groepen waren er wel grote verschillen waarbij vrouwen met DM2 veruit de hoogste BMI hadden en vrouwen met DM1 de laagste BMI. Deze verschillen corresponderen goed met de verschillen tussen de BMI groeiprofielen van hun kinderen.

Ons longitudinale onderzoek is met behulp van de '*mixed model*' statistisch model uitgevoerd, wat een statistische methode is die een aangepast model bouwt op basis van de beschikbare metingen. Dit statistisch model voegt zelf géén missende gegevens toe. Er komt een aangepast model op basis van de verschillende metingen bij elke zwangerschapsweek of op de verschillende leeftijden in de kindertijd, zelfs wanneer niet alle metingen op hetzelfde moment zijn uitgevoerd. Met deze methode zijn we in staat om groeitrajecten te vergelijken tussen kinderen van vrouwen met DM1, DM2 en GDM. Dit is uniek, in vergelijking met de beschikbare kennis. Andere studies hebben vaak of alleen één moederlijk diabetes type bekeken of verschillende typen diabetes tezamen beoordeeld, wat vergelijking tussen de verschillende typen diabetes bij moeders zeer lastig maakt. Ook is de meerderheid van onderzoeken op één tijdstip uitgevoerd, wat vergelijking met onze longitudinale gegevens lastig maakt. Bovendien worden in deze studies verschillende definities van overgewicht bij kinderen aangehouden en is op een scala aan leeftijden een enkele meting uitgevoerd; hierdoor kunnen we de gegevens uit de literatuur niet goed vergelijken met onze gegevens. Een groot voordeel van ons onderzoek is dat alle kinderen geboren zijn in hetzelfde centrum, in dezelfde periode, en met dezelfde verloskundige en internistische begeleiding.

Samengevat kan uit de bevindingen van de **hoofdstukken 4-6** geconcludeerd worden dat de BMI-SDS groeiprofielen van kinderen van vrouwen met type-1 en type-2 diabetes aanzienlijk verschilden. De groei in de baarmoeder was het meest afwijkend bij foetussen van de vrouwen met DM1 (**hoofdstuk 3**), terwijl hun groei na de geboorte bijna normaal was; in ieder geval voor de kinderen met een normaal geboortegewicht. Het lijkt het meest aannemelijk dat verschillen in moederlijk BMI ten grondslag liggen aan de grote verschillen in de groei op de kinderleeftijd. Versnelde groei na de geboorte is sterk geassocieerd met de ontwikkeling van (type 2) diabetes en hart- en vaatziekten op latere leeftijd. Dit geldt zowel voor zuigelingen die ofwel te zwaar zijn bij de geboorte of een te laag geboorte gewicht hebben [22]. Preventie van versnelde groei na de geboorte is daarom van groot belang.

Het effect van voeding en leefstijl tijdens de kindertijd op de ontwikkeling van overgewicht op die leeftijd (hoofdstuk 7)

De groei van kinderen van vrouwen met diabetes is afhankelijk van de BMI van hun moeder en van hun geboortegewicht, maar verschillen in groeiprofielen kunnen (deels) ook worden verklaard door verschillen in voeding en leefstijl tijdens de kindertijd. Dergelijke studies bij kinderen van vrouwen met diabetes ontbreken in de literatuur.

Dit werd daarom in **hoofdstuk 7** onderzocht, met vragenlijsten aan ouders van kinderen die hebben deelgenomen aan de eerdere onderzoeken. Van 51 kinderen van vrouwen met DM1, 21 met DM2 en 87 met GDM, werden ingevulde vragenlijsten ontvangen. De gemiddelde leeftijd van de kinderen was op dat moment 10 jaar. Kinderen van vrouwen met DM2 had het hoogste percentage van obesitas. Deze kinderen sloegen het ontbijt vaker over, aten minder vaak tussendoortjes en waren minder vaak lid van een sportclub in vergelijking met kinderen van de andere twee diabetes categorieën. Hun ouders waren ook minder positief over hun gezondheid. Hoewel het overslaan van het ontbijt en minder tussendoortjes minder voedselinname suggereert, zijn ze een uiting van een veranderde levensstijl, die - samen met minder lichamelijke activiteit - op termijn kan leiden tot obesitas [23-27].

Samenvatting en perspectieven

Het bereiken van een normale glucose en insuline huishouding is nog niet haalbaar bij patiënten met diabetes, ondanks de revolutionaire ontwikkeling in insulinepreparaten en manieren van toediening en van controles van bloedsuikerwaarden. Tenzij we in staat zijn insuline direct toe te dienen in de holle ader in tegenstelling tot het onderhuidse vetweefsel van de buik en in staat zijn het suikergehalte in het bloed continue en direct te meten, in plaats van met een vingerprik en tenzij we in staat zijn om suiker en insuline toediening beter op elkaar af te stemmen, zullen normale glucose waarden gedurende de hele zwangerschap een illusie zijn. Toch zijn onze mogelijkheden inmiddels aanzienlijk verbeterd [28].

De onderzoeken gepresenteerd in dit proefschrift hebben een aantal patho-fysiologische mechanismen bloot gelegd met betrekking tot het leven in de baarmoeder en de invloed van die periode op het leven daarna. Een te zwaar geboortegewicht is een belangrijk korte termijns zwangerschapsresultaat en is bij vrouwen met diabetes gerelateerd aan bloedsuikerwaarden tijdens de zwangerschap [10,14]. Opsporen van vrouwen met risicofactoren en de diagnose in zwangerschapssuikerziekte is een *hot issue*, die veel discussie doet oplaaien, met nadruk op de groep vrouwen die gescreend moet worden (universeel of alleen op basis van risicofactoren), welke diagnostische test gehanteerd moet worden en welke afkap-waarden moeten worden gebruikt. We hebben aangetoond dat in de Nederlandse benadering met behulp van selectieve screening bij alleen risico zwangeren, zwangerschapssuikerziekte vaak te laat in de zwangerschap gediagnosticeerd wordt, met als gevolg te veel dikke kinderen. Ook vrouwen zonder risicofactoren kunnen GDM ontwikkelen. Gezien de gevolgen van een te zwaar geboortegewicht op de latere groei, is dit een belangrijk aspect om rekening mee te houden bij de discussie over screeningsprocedures. Gebeurtenissen in de baarmoeder werpen hun schaduw vooruit op de ontwikkeling op kinderleeftijd en daarna.
Onevenredige (disproportionele) groei in de baarmoeder is een indicator van een te hoog insuline gehalte, maar relaties met latere uitkomst verschillen tussen nakomelingen van vrouwen met DM1 vs. nakomelingen van vrouwen met DM2 of GDM in de eerste jaren van het leven. Onevenredige groei is gerelateerd aan de BMI bij kinderen

van vrouwen met DM1 in tegenstelling tot die van de vrouwen met DM2 of GDM. BMI bij nakomelingen van vrouwen met DM2 en GDM is juist gerelateerd aan hun geboortegewicht. Deze bevindingen, indien bevestigd door grotere studies geven aan dat nakomelingen van vrouwen met DM1 verschillen van die van de vrouwen met DM2 en GDM. Dit is niet onlogisch, omdat de oorzaak van DM2 en GDM veel op elkaar lijkt. De grotere variabiliteit in suikerspiegels bij DM1 verklaart waarschijnlijk de hogere incidentie van disproportionele foetale groei, in vergelijking met DM2 en GDM [29].
Door het verzamelen van de groeigegevens van kinderen tot 14 jaar na de geboorte, waren we in staat om de groeiprofielen te analyseren over een langere periode dan meestal gebeurt en hebben we kinderen met een normaal geboortegewicht kunnen vergelijken met kinderen met een te zwaar geboortegewicht. Deze gegevens zijn belangrijk omdat de lange termijn resultaten in aanvulling op korte termijn resultaten belangrijk zijn voor ouders en beroepsbeoefenaren in de gezondheidszorg; en om interventies te initiëren om ongewenste resultaten op de lange termijn te voorkomen. Nakomelingen van vrouwen met DM1 met een normaal geboortegewicht hebben ook een normaal groeiprofiel na de geboorte, maar te zware pasgeborenen blijven zwaarder dan hun tegenhangers met een normaal geboortegewicht. Een soortgelijk patroon wordt gezien bij nakomelingen van vrouwen met DM2, zij het met hogere BMI groeiprofielen. De profielen van nakomelingen van vrouwen met GDM liggen tussen die van DM1 en DM2 in. Tenslotte blijken levensstijlen te verschillen tussen nakomelingen van de vrouwen met type-2 diabetes en de die met DM1 en GDM, wat een zeer relevant onderwerp is voor verder onderzoek.

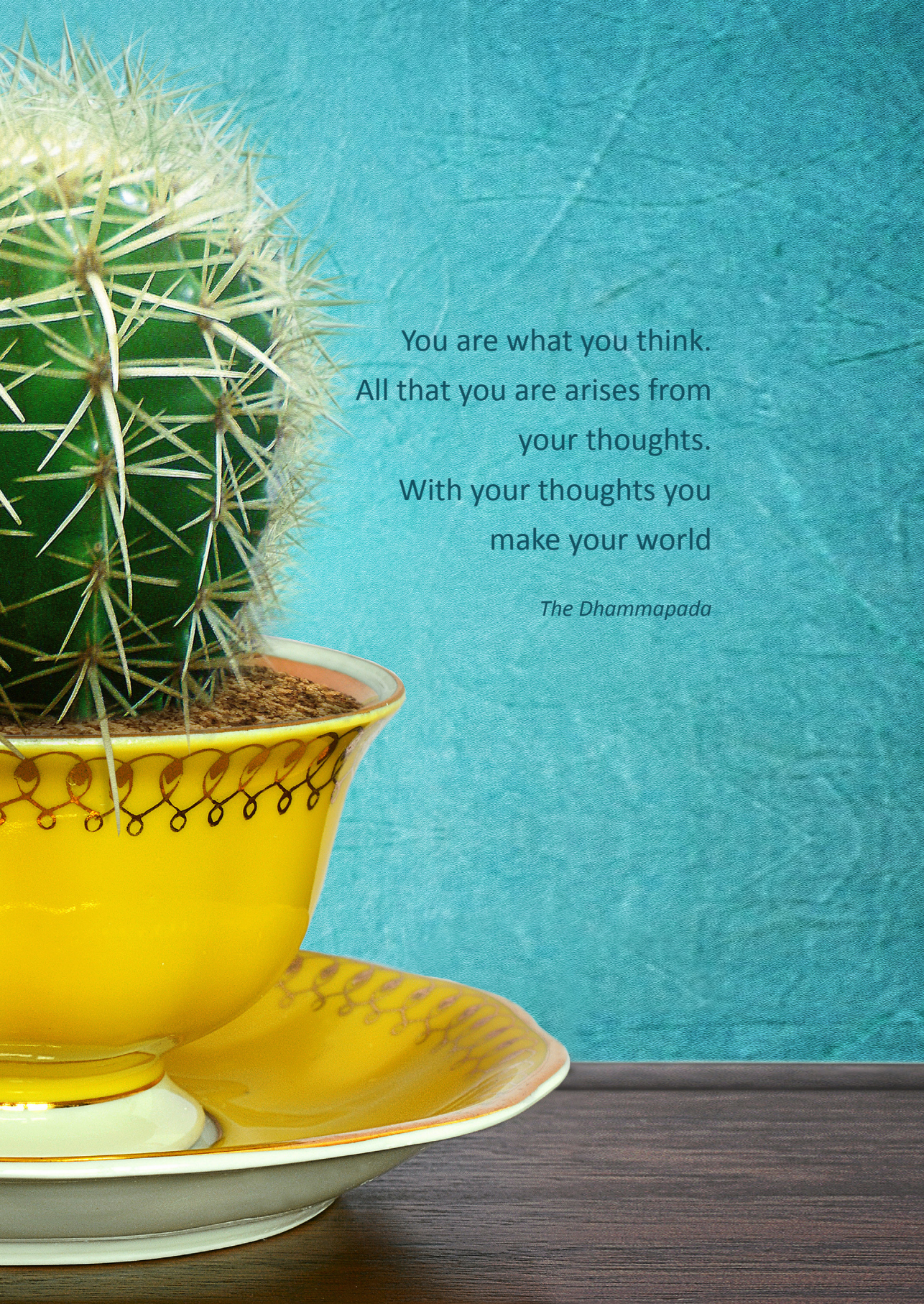
Wat kunnen we doen om het leven in de baarmoeder en op de kinderleeftijd te verbeteren in het licht van de huidige obesitas-epidemie? Een aantal mogelijkheden komen voor de geest:

1. Obesitas. Ervan uitgaande dat moederlijke obesitas een grote rol speelt bij het risico op obesitas van hun kinderen, is het bereiken vaan een normaal gewicht voor de zwangerschap van groot belang. Levensstijl interventie gericht op deze specifieke groep is vereist. Bij vrouwen met polycysteus ovarium sydroom (PCOS) en onvruchtbaarheid kan gewichtsverlies de menstruatiecyclus doen normaliseren en wordt het onvruchtbaarheidsprobleem vaak verholpen en zullen de zwangerschapsresultaten tegelijkertijd verbeteren.
2. Beperking van buitensporige gewichtstoename tijdens de zwangerschap. Deze kwestie werd niet bestudeerd in onze studies, vanwege het ontbreken van deze gegevens. Gewichtstoename tijdens de zwangerschap toont een sterke correlatie met het geboortegewicht (bijvoorbeeld bij maternale DM1 [30] en postnatale groei [31,32]). Gerichte voedingsadviezen worden daarom aangeraden. Er zijn (Amerikaanse) richtlijnen over optimale gewichtstoename tijdens de zwangerschap in relatie tot de BMI vóór de zwangerschap [33]. Adequate voedingsadvisering tijdens de verloskundige controles dient weer geactiveerd te worden evenals gewichtscontroles .

3. Preventie van een te zwaar gewicht van de baby bij de geboorte. Bij vrouwen met diabetes zijn hoge glucosespiegels een belangrijke oorzaak van een te zwaar geboortegewicht. Het is moeilijk om het percentage te zwaar geboren kinderen te verlagen omdat er verschillende redenen zijn waarom momenteel deze zuigelingen vaker zwaarder geboren zijn dan in het verleden, zoals eerder beschreven: echte normale suikerwaardes kunnen nog niet worden bereikt, en bijna goed is niet goed genoeg. Toepassing van offline continue glucosemonitoring (Offline CGM) door een toegewijd multidisciplinair team in één enkel centrum, zou echter de incidentie van te zwaar geboren neonaten in een gemengde populatie van vrouwen met DM1 en DM2 kunnen doen verminderen [34]. Onderzoeken met real-time continue glucosemonitoring (CGM), waren tot dusverre te klein of werden onvoldoende door de vrouwen gebruikt om zinvolle resultaten te leveren [35]. De huidige CONCEPTT trial bij vrouwen met DM1, waarbij real-time CGM gestart wordt voor of na de bevruchting zal mogelijk wel zinvolle informatie opleveren [36,37]. Een recente studie in China bij vrouwen met GDM, die gebruik maakte van Offline CGM samen met strikte dieetmaatregelen, toonde een flinke daling in het aantal kinderen dat te zwaar was bij de geboorte [38], waarin – opnieuw – wordt onderstreept wat de additionele waarde is van een adequaat en streng dieet. Vroege diagnose van zwangerschapssuikerziekte vóór het optreden van een te grote buikomtrek in de baarmoeder zou de incidentie van te zwaar geboren kinderen kunnen verminderen. Universele screening van GDM is daarom geïndiceerd en identificatie van vrouwen met een hoog risico voor het ontwikkelen GDM in het eerste trimester van de zwangerschap moet nader worden onderzocht.
4. Genetica en epi-genetica zijn lastige kwesties. Kennis van de genetica van DM2 is in de loop van de afgelopen jaren toegenomen. Verschillende genen zijn geïdentificeerd die het risico op type-2 diabetes beïnvloeden [39]. Met deze kennis is het mogelijk om personen met een hoog risico voor het ontwikkelen van DM2 te identificeren en gerichte preventieve maatregelen te nemen. Blootstelling aan diabetes in de baarmoeder kan epi-genetische veranderingen veroorzaken door veranderingen in activering/inactivering van bepaalde genen. Deze epi-genetische veranderingen kunnen op de lange termijn resulteren in een verhoogd risico op het ontwikkelen van obesitas, DM2 en hart- en vaatziekten [40,41]. Ondanks al deze nieuwe kennis, blijven vooralsnog alleen een adequate leefstijl en voeding, in combinatie met een optimale bloedsuikercontrole de enige instrumenten die we hebben.
5. Preventie van versnelde gewichtsstijging van de kinderen na de leeftijd van 2 jaar moet meer aandacht krijgen. Dit geldt niet alleen voor kinderen van vrouwen met diabetes, maar voor de gehele populatie. Hierin is een zeer belangrijke rol weggelegd voor de GGD's. Nakomelingen van vrouwen met DM2 dienen voorrang te krijgen, gezien het feit ze een hoger risico op het ontwikkelen van overgewicht hebben en doordat zij er vaker een 'ongezond' eet- en leefpatroon op na houden.

Referenties

Zie Summary and general discussion, pagina 127.


You are what you think.
All that you are arises from
your thoughts.
With your thoughts you
make your world
The Dhammapada

Addendum

List of abbreviations
List of co-authors
List of publications
Acknowledgements
Curriculum vitae

List of abbreviations

AC	= abdominal circumference
AGA	= appropriate for gestational age
BMI	= body mass index
BW	= birthweight
CGM	= continuous glucose monitoring
CS	= caesarean section
cTH	= conditional target height
DM1	= type 1 diabetes mellitus
DM2	= type 2 diabetes mellitus
FAC	= Fetal abdominal circumference
GA	= gestational age
GCT	= Glucose challenge test
GDM	= gestational diabetes mellitus
HC	= head circumference
HC/AC ratio	= head circumference to abdominal circumference ratio
IOTF	= International Obesity Task Force
LGA	= Large for gestational age
NICU	= neonatal intensive care unit
NS	= not significant
ODM1	= offspring of type 1 diabetes pregnancies
ODM2	= offspring of type 2 diabetes pregnancies
OGDM	= offspring of gestational diabetic pregnancies
OGTT	= Oral glucose-tolerance test
SD	= standard deviation
SDS	= standard deviation score
SGA	= small for gestational age
SHBG	= sex hormone binding globulin

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Curriculum vitae

Nurah Hammoud was born 2 days late, on a Monday night - October 29th 1984 - in St. Elisabeth Hospital (SEHOS) on Curaçao after an uncomplicated pregnancy. Her birthweight was 2750g and her apgar score was not recorded. She grew up under the Caribbean sun and was intrigued to study medicine in The Netherlands, inspired by her father who is a general practitioner on the island. After finishing her athenaeum, she moved to Utrecht in 2002 to get her medical degree at the University of Utrecht. Her internship gynecology was abroad in Hospital Virgen Macarena in Sevilla, Spain and she immediately knew that this was a very interesting field of medicine. When she returned, she started a student research project with professor Visser and Dr. de Valk, which was the start of this doctorate thesis. During her studies, she also participated in several committees, such as in the medical student association MSFU Sams. After finishing her 5th year in medical school, she decided to take a sabbatical of a year and a half to focus even more on student organizations. She joined the board of Dutch Antillean student association Passaat and was a committee member of the international student platform AIESEC, in the Make a Move project. All the while her research continued. After her sabbatical she did an internship in gynecology at the Queen Elisabeth Hospital in Malawi, and she finished her medical degree in 2010. She went on to work as a resident OB/GYN not-in-training in the Sint Franciscus Gasthuis Rotterdam and St. Antonius Hospital Nieuwegein, and continued her work in the scientific field under the supervision of professor Visser, professor Biesma and Dr. de Valk. In 2011 she was admitted to the residency program for OB/GYN and was transferred to St Elisabeth hospital Tilburg, and in 2012 she continued her residency in the UMC Utrecht under supervision of professor Franx. She joined the board of the Consultative Body on Integration matters on behalf of the Dutch Caribbean in the Netherlands (OCaN) and was active for almost 5 years. In 2014 she joined the board of De Jonge Specialist, which is the representative organization for Dutch registrars; in 2015 she became treasurer of the board. In 2015 she started her last couple of years as resident OB/GYN and returned to St. Antonius Hospital Nieuwegein, under supervision of Dr. Schagen van Leeuwen, where she enjoys her work. She lives in Amsterdam, together with her life-partner Juan-Carlos Goilo.