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CLINICAL SCIENCES, LUND | FACULTY OF MEDICINE | LUND UNIVERSITY

Pregnancy characteristics as risk factors for future maternal diabetes and other diseases

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LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Abstract

In Sweden approximately 2-3% of all preganncies are affected by Gestational Diabetes (GDM). Hyperglycemia during pregnancy is a riskfactor for adverse pregnancy outcome. GDM causes an increased risk for Caesarean section, large for gestational age infants (LGA) and preeclampsia. In addition, women with previous GDM have a high risk of developing type 2 diabetes (T2D) and also an increased risk of cardiovascular disease later in life.

Aims

    I.   investigate if women diagnosed with diabetes later in life had hyperglycemia related complications of previous pregnancies.

    II.   analyse the impact of BMI and gestational weight gain on the risk of developing T2D and other metabolic disesaes later in life.

    III.   analyse the pregnancy outcome in relation to a predisposition for diabetes (defined as onset of T2D later in life), with or without elevated BMI during pregnancy.

    IV.   analyse glucose control and pregnancy outcome in GDM pregnancies in regard to treatment modality in two different time periods.

Methods:

We used the populationbased MISS-cohort (Melanoma in Southern Sweden). It was established in 1990, with o follow up in 2000 and consists of almost 30000 women in the ages 25-65 years. Self-reported data regarding social status, medication, previous illnesses etc. is included in the data base. Data regarding current medication is retrieved from the Swedish Prescribed Drug Register. From the Swedish Medical Birth Register (SMBR) we collected data from 1973-2005 regarding pregnancy outcome. A novel database from the Specialized Maternity Care Unit in Lund included women with GDM pregnancies 2012-2013 and 2016-2017 was used. Additional data regarding the pregnancy was retrieved from Obstetrix and data regarding the woman´s glucose values was retrieved from Diasend.

Results:

Women who later in life developed T2D had hyperglycemia-related adverese outcomes during previous pregnancies. They had higher BMI, a lower Gestational Weight Gain (GWG), higher frequency of macrosomia and caesarean section compared to women without diabetes later in life. Women with over weight during pregnancy had more than six fold increase in the risk of developing diabetes and more than two-fold risk of developing cardiovascular disease 10-17 years after pregnancy. Being overweight during pregnancy and having a predispostion for diabetes was equal riskfactors for macrosomia. If the women had both riskfactors there was an almost eight times higher frequency of LGA. The mean glucose values have improved among women with GDM 2016-2017 compared to 2012-2013,with less frequenct use of insulin and more use of metformin. There is more heredity for diabetes and non-Scandinavian origin among the women with GDM.

Conclusion:

Having a predisposition for diabetes impacts the pregnancy outcome and increases the risk of hyperglycemia related adverse events during pregnancy and delivery. Having a high BMI at the beginning of pregnancy increases the risk of future T2D and cardiovascular disease. Having a predisposition for T2D and being overweight synergistically increases the risk of macrosomia. Despite changing demographics, improved metabolic control can be achieved and favorable pregnancy outcome maintained, while using more metformin and less insulin.

Key words Gestational Diabetes Mellitus, Pregnancy outcome, overweight, cardiovascular disease,	
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LUND UNIVERSITY

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For John, Elin, Abbe and Edit

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I. Moll, U., Olsson, H. and Landin-Olsson, M. (2014) Women who develop diabetes later in life have diabetes-associated complications during preceding pregnancies. Journal of Diabetes Mellitus, 4, 341-349.

II. Moll U, Olsson H, Landin-Olsson M (2017) Impact of Pregestational Weight and Weight Gain during Pregnancy on Long-Term Risk for Diseases. PLoS ONE 12(1):e0168543.doi:10.1371/journal.pone.0168543

III. Moll, U, Olsson, H, Landin-Olsson, M (2019) Women with a predisposition for diabetes have an increased risk of pregnancy complications, especially in combination with pregestational overweight (submitted to BMC Pregnancy and Childbirth)

IV. Moll, U, Nilsson, C, Ursing, D, M Landin-Olsson, Strevens, H (2019) Pregnancy outcome in women with gestational diabetes – a longitudinal study of changes in demography and treatment modalities (submitted to Acta Obstetricia et Gynecologica Scandinavica)

Abbreviations

ACOG	The American College of Obstetricians and Gynaecologists
ADA	American Diabetes Association
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring system
CVD	Cardiovascular Disease
EASD	European Association for the Study of Diabetes
GDM	Gestational Diabetes Mellitus
GLUT	Glucose Transporters
GWG	Gestational Weight Gain
HAPO	Hyperglycaemia and Adverse Pregnancy Outcome Study
HbA1c	Haemoglobin A1C
IADPSG	International Association of Diabetes and Pregnancy Study Groups
IOM	Institute of Medicine
LGA	Large for Gestational Age
MAGE	Mean Amplitude of Glucose Excursions
MISS	Melanoma in Southern Sweden
NICE	National Institute for Health and Care Excellence
OAD	Oral Anti Diabetic Drugs
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
SD	Standard Deviation
SMBG	Self Monitoring Blood Glucose
SMBR	Swedish Medical Birth Register
T2D	Type 2 Diabetes
WHO	World Health Organisation

Abstract

In Sweden approximately 2-3% of all pregnancies are affected by Gestational Diabetes (GDM). Hyperglycaemia during pregnancy is a risk factor for adverse pregnancy outcome. GDM is a well known risk factor for caesarean section, large for gestational age infants (LGA) and preeclampsia. In addition, women with previous GDM have a high risk of developing type 2 diabetes (T2D) and also an increased risk of cardiovascular disease (CVD). Signs of these conditions can often be diagnosed within the first decade after a GDM pregnancy.

The aim of this thesis was to

I. investigate if women diagnosed with diabetes later in life had hyperglycaemia related complications during previous pregnancies.

II. analyse the impact of BMI and gestational weight gain on the risk of developing T2D and other metabolic diseases later in life.

III. analyse the pregnancy outcome in relation to having maternal predisposition for diabetes, with or without elevated BMI during pregnancy.

IV. analyse glucose control and pregnancy outcome in GDM pregnancies in regard to treatment modality in two different time periods.

In paper I-III we used the population based MISS-cohort (Melanoma in Southern Sweden). The cohort consists of almost 30000 women in the ages 25-65 years. The cohort was established in 1990 for the study of risk factors of malignant melanoma and a follow up of the cohort10 years later is included in the database. Self-reported answers regarding social status, medication, previous illnesses etc. is included in the data base. Data regarding current medication was retrieved from the Swedish Prescribed Drug Register. From the Swedish Medical Birth Register (SMBR) we collected data regarding the pregnancy outcome. A novel database from the Specialized Maternity Care Unit in Lund was compiled and included women with GDM pregnancies 2012-2013 and 2016-2017. Additional data regarding the pregnancy and delivery was retrieved from Obstetrix and data regarding the woman´s glucose values was retrieved from Diasend, a telemedicine solution for sharing blood glucose values.

Women who later in life developed T2D had hyperglycaemia-related adverse outcomes of their pregnancies earlier in life. They had higher BMI and a lower Gestational Weight Gain (GWG) compared to women without diabetes later in life. They also had a higher frequency of macrosomia and caesarean section. Women with overweight during pregnancy had a more than six-fold increase in the risk of developing diabetes and more than two-fold risk of developing cardiovascular disease 10-17 years after pregnancy. Being overweight during pregnancy and having a predisposition for diabetes were equal risk factors for macrosomia. If the women had both risk factors there was

almost an eight times higher frequency of LGA. The mean glucose values have improved among women with GDM 2016-2017 compared to 2012-2013, despite less frequent use of insulin and more use of metformin. There is more heredity for diabetes and more non-Scandinavian origin among the women with GDM.

Conclusion:

Having a predisposition for diabetes impacts the pregnancy outcome and increases the risk of hyperglycaemia related adverse events during pregnancy and delivery. Having a high BMI at the beginning of pregnancy increases the risk of future T2D and cardiovascular disease. Having a predisposition for T2D and being overweight synergistically increases the risk of macrosomia. Despite changing demographics, an improved metabolic control can be achieved and favourable pregnancy outcome maintained while using more metformin and less insulin. Neglecting to diagnose GDM and neglecting to start treating risk factors have negative impact on pregnancy outcome. To reduce the risk of future disease, it is beneficial for the woman to be of normal weight before pregnancy. If intervention during or after pregnancy can reduce the risk of diabetes or cardiovascular disease for these women will hopefully be thoroughly studied in the future.

Introduction

In pregnancy the female body go through many changes. One of these changes are the great hormonal changes that occur. These changes contribute to an increasing insulin resistance that peeks during the third trimester. A pregnancy might be considered a stress test for the body´s capacity to respond to the increasing demand for insulin. When this demand is not sufficiently met, the blood glucose increases, and hyperglycaemia and gestational diabetes (GDM) develops.

Women with obesity or a family history of diabetes have a higher risk of developing gestational diabetes. The current trend is an increasing prevalence of obesity or overweight in young women of childbearing ages in the world. Thus follows, that the prevalence of GDM is increasing worldwide.

Gestational diabetes has implications for the health of both the woman and the foetus during pregnancy and delivery. If the hyperglycaemia is untreated there is an increased risk of an unfavourable pregnancy outcome. Having gestational diabetes also has implications for the future health of both the woman and the child. Women with gestational diabetes have a considerable risk of developing diabetes mellitus in the future. Gestational diabetes is also a strong risk factor for cardiovascular disease. For the child there is an increased risk of developing diabetes and obesity. Interestingly it seems that even the father is at an increased risk of diabetes, overweight and obesity if the mother of his child has GDM. All of this implies that GDM is strongly influenced by lifestyle and environment and that prevention and treatment of GDM and prevention of future disease should include the whole family.

Diabetes Mellitus and Obesity

The prevalence of diabetes mellitus is increasing in the world as well as in Sweden. In Sweden it is estimated that 500 000 (7%) subjects have diabetes mellitus (1). The risk for diabetes mellitus type 2 (T2D) is increasing with increasing overweight and obesity and a more sedentary lifestyle. Since the initial symptoms of diabetes mellitus type 2 are often insidious and the mean blood-glucose slowly rises over time, it is a challenge to diagnose the disease early. There are benefits for the patient of early and appropriate treatment, to reduce the risk of complications in the future(2). These complications are

predominantly cardiovascular disease and a future risk of nephropathy, retinopathy, angiopathy and neuropathy. Life style interventions (and oral anti diabetic drug OAD) can reduce the risk of diabetes in over weight patients with pre diabetes (3)

In addition, obesity is a risk factor for diabetes as well as cardiovascular diseases, such as coronary heart disease and stroke. Obesity is also a risk factor for cancer (4).

The prevalence of obesity in younger women of childbearing ages is increasing (5). The prevalence of women with overweight and obesity during pregnancy in Sweden is reported to be around 40% (6).

Diagnose of Diabetes Mellitus

The diagnose of diabetes mellitus can be made by using a 75g Oral glucose Tolerance Test (OGTT) or by analysing plasma glucose (7). It is also possible to analyse HbA1C (8), where HbA1c ≥ 48 mmol/mol is used as a cut off level and is diagnostic for diabetes mellitus together with clinical symptoms of diabetes or another confirming test (Table 1).

Table 1.
Criteria for the diagnoses of Diabetes Mellitus

	mmol/L
Fasting plasma-glucose	≥ 7.0
2 hour plasma-glucose post 75g OGTT (venous/capillary)	≥11.1/≥12.2
Symptoms + random plasma-glucose (venous/capillary)	≥11.1/≥12.2
HbA1c (mmol/mol)	≥48

Gestational Diabetes Mellitus

Introduction

It is estimated that 16.2% (21.3 million) of all live births worldwide (2017) is affected by gestational diabetes each year (1). In Sweden the prevalence of gestational diabetes mellitus (GDM) is 1.9% (9, 10). In Europe the estimated prevalence of GDM is 5.4% (11), but the incidence of GDM is increasing, in line with increasing BMI among young women of childbearing ages(12).

Risk factors for Gestational Diabetes

The risk factors for developing GDM are similar to risk factors for diabetes mellitus type 2, i.e. overweight or obesity and a family history of diabetes, combined with a sedentary lifestyle. Pregnancy related risk factors include a previous pregnancy affected by GDM and previous birth of a macrosomic infant.

The increased risk of GDM depending on prepregnancy weight and diet habits have come into recent focus, A high potato consumption and overall a "Western diet" that tends to consist of processed meat, fried products and sodas and be low in vegetables and fibres, increases the risk of GDM (13-15)

The incidence of diabetes mellitus is more common in some Non-Scandinavian populations and the maternal prepregnancy weight and pregnancy weight gain can differ in different ethnic groups(16, 17). In some ethnic groups from different regions of the world there is a remarkably high risk for gestational diabetes (as well as type 2 diabetes), for example in south east Asia, India and the Middle East. Many indigenous populations, such as native Americans, Aborigines, Maori and Torres Strait islanders, have higher risk for GDM, than the western population in the same country (18, 19). In addition, the prevalence of type 2 diabetes is high in these populations. In the participating centres of the global HAPO study, the frequency of GDM (diagnosed with IADPSG (International Association of Diabetes and Pregnancy Study Groups)-criteria) varied between 9.3-25.5%. This indicates that there is a large differences in the frequency of GDM in different populations and ethnicities (20).

In Sweden there has been an increase in the incidence of GDM during the last 10-15 years. This increase is mainly due to increasing age, increasing BMI and non-Scandinavian Ethnicity among the pregnant women(10, 21). Since the immigration to Sweden during 2015-2016 was unprecedented, this supposedly had an impact on the demographics in our region(22).

Gestational Diabetes and pregnancy

Pregnancy is a condition with many hormonal changes. The hormone production of the placenta includes prolactin, progesterone, human placental lactogen and growth hormone. These hormones cause successively increasing insulin resistance during pregnancy. The insulin production increases during pregnancy in response to the increased insulin resistance. There is emerging evidence of an increase in the pancreatic β-cell mass and the is also studies that show development of new islets in the pancreas (23). Gestational diabetes develops, as the insulin resistance increases and the need for insulin is insufficiently met. Taking this into account, the pregnancy might be looked at as a stress test and pregnancy can unmask incipient diabetes mellitus. For the mother there is an increased risk for hypertension and preeclampsia during pregnancy (24-26).

The increased availability of nutrients in the circulation during pregnancy, causes more nutrients to cross the placenta, and causes hyperinsulinemia in the foetus. This leads to an increased glucose absorption and accelerated growth. GDM is a risk factor for macrosomia (birthweight ≥4000g) and Large for Gestational Age infants (LGA). It is well known that the risk for caesarean section and birth trauma is increased The hyperinsulinemia also can decrease the gene expression for surfactant and thus inhibit lung maturation and cause respiratory distress syndrome in the new-born infant (27). In pregnancies with GDM the placenta is often larger than normal and there is evidence of morphological changes in the placenta, such as increased concentration in GLUT-transport proteins and a proportionally higher glucose uptake in the placenta in a GDM pregnancy(28, 29). The macrosomic foetus is in a hyper insulinemic state and has an increased metabolism and thus an increased need for oxygen. This can account for the increased risk of hypoxia during gestation and labour. Malformations and especially heart malformations are not as common in GDM pregnancies as in pregnancies affected by type 1 diabetes, since organogenesis occurs during the first trimester and since the hyperglycaemia-induced oxidative stress rarely occurs during the first trimester in GDM pregnancies. However, there are structural differences measured by echocardiogram in the heart of a foetus in a pregnancy affected by GDM. The reason for this is speculative but might be due to other intrauterine metabolic changes and oxidative stress that affect organogenesis in a GDM pregnancy (30)(Figure 1).
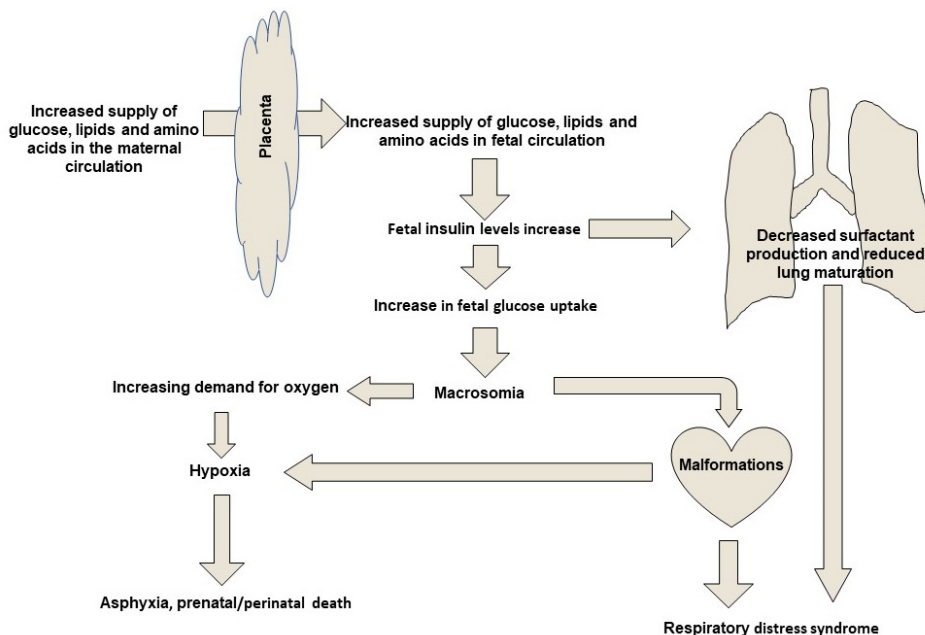

Figure 1.
A simplified description of metabolic changes and physiological changes in the foetus.

After birth, the hyperinsulinemia in the infant might cause significant hypoglycaemia, as the supply of nutrients is abruptly cut off. Hypoglycaemia occurs during the first days of life, before breastfeeding is established. Severe hypoglycaemia may affect the infant´s neurodevelopment. Additional feeding with supplements/formula are often needed. Thus, the infants should be observed in a neonatal unit, with frequent glucose measurements and feeding, to avoid severe hypoglycaemia, often defined as p-glucose ≤2.0mmol/L, and risk adverse effect on the infant.

Future risk

Women with previous GDM have an increased risk of developing diabetes mellitus type 2 (31). There is also an increased risk for obesity and cardiovascular disease (32-34) The incidence of diabetes after GDM varies in different studies depending on the characteristics of the population, such as ethnicity, but also differences in diagnostic criteria for GDM and differences in time to follow-up (35, 36). Approximately 60% of women with GDM will develop T2D within 10 years after pregnancy (37).

For the infant there is a risk of being overweight later in life and there is also reports on effects on cognition and motor skills in the child. (33, 38-45). The child has a 4-8 times higher risk of developing T2D if the mother had GDM compared to children born to mothers without GDM (46).

Screening for T2D after a GDM pregnancy is advocated and uncontroversial (32, 47). Screening for T2D within 3-6 months of delivery is recommended. In many settings the follow up is 6 weeks postpartum and thereafter annually (48).

Diagnose of Gestational Diabetes

Gestational Diabetes Mellitus (GDM) is a medical condition that can be diagnosed during pregnancy. O´Sullivan introduced the term "gestational diabetes" instead of the previously used "carbohydrate intolerance in pregnancy" and proposed different cut off levels from diabetes for diagnosing gestational diabetes with oral glucose tolerance test (49). Historically the condition was defined as "carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy" and the medical risk of disease was focused on the pregnancy outcome and the risk of developing diabetes after pregnancy. In the 1999 report from WHO the diagnostic thresholds for GDM equalled the threshold for Impaired Glucose Tolerance (IGT) outside of pregnancy (7). There has historically been a lack of clinical studies of OGTT and diagnostic criteria of GDM in relation to the benefit of treatment on pregnancy outcome. In addition, there have been different treatment traditions and differences in health care organization that have contributed to the great differences in prevalence and treatment of GDM in different regions of the world.

In 2008 the HAPO-study was published (50). It was a large multi-centre randomized study that showed that there is a continuously increasing risk for several adverse outcomes of pregnancy with increasing elevations of plasma glucose during OGTT. Based on the HAPO-study from 2008 the IADPSG published recommendations for general screening for GDM in all pregnant women and proposed diagnostic criteria based on fasting glucose and/or 1 hour or 2 hour blood glucose after a 75g OGTT (51). In an OGTT, the pregnant woman is in a fasting state and drinks 75g of glucose. The woman remains in a resting state for 2 hours. Glucose measurements are made with venous sampling in the fasting state and/or 1 and 2 hours after glucose consumption. The diagnostic values are presented in Table 2.

Table 2.
Criteria for the diagnose of Gestational Diabetes

Diagnostic values for Gestational Diabetes (IADPSG and WHO criteria) during 75g OGTT	
Fasting plasma venous glucose	≥ 5.1 mmol/L
1 hour plasma venous glucose	≥ 10.0 mmol/L
2 hour plasma venous glucose	≥8.5 mmol/L

These diagnostic levels are now adopted by WHO and ADA(48, 52). They are also adopted by the Swedish National Board of Health and Welfare (Socialstyrelsen) (53). There is, however, no current guideline regarding general screening of pregnant women and therefore the number of women who are screened with OGTT and diagnosed with GDM differ greatly in different regions in Sweden. There are currently several screening methods for GDM in use and different countries and diabetes associations have advocated for different screening methods. There is internationally still a controversy regarding screening procedures and diagnostic thresholds. For example, the American College of Obstetricians and Gynaecologists (ACOG) recommend a 2-step approach with initial universal screening with a non-fasting 50g 1 hour Oral Glucose Challenge test (OGCT) and a following diagnostic 100g 3 h OGTT(54). NICE (National Institute for Health and Care Excellence) recommend a 75g OGTT in women with risk factors, and have different diagnostic thresholds (55). Overall, there is still no universal screening method for GDM in the world. It has been advocated that different screening methods should be used, depending on differences in clinical settings, economic resources and infrastructure, population characteristics and prevalence of type 2 diabetes in that specific country or region (56). In Europe there are, to date, several different screening methods and cut off levels being used (11).

During pregnancy there is an increase in blood volume and a high turnover of red blood cells, and during the third trimester the HbA1c-value usually decreases. The use of HbA1c as a diagnostic method for GDM is not recommended as a stand-alone test, since HbA1c has a low sensitivity during pregnancy (57-59).

To differentiate gestational diabetes from diabetes that exist prior to pregnancy, but with first recognition during pregnancy, different diagnostic criteria to diagnose "overt diabetes in pregnancy" is proposed, but not universally endorsed. These diagnostic thresholds are presented in Table 3.

Table 3.
Proposed criteria for the diagnose of overt diabetes during pregnancy

Diagnostic values for Overt Diabetes in pregnancy	
Fasting plasma-glucose	≥ 7 mmol/L
Random plasma glucose	≥ 11.1 mmol/L + confirming test[1]
HbA1c	≥ 48 mmol/mol

[1]or capillary p-glucose ≥12.2 mmol/l. Confiriming test = fasting plasma glucose or HbA1c ≥48 mmol/mol

Treatment of Gestational Diabetes

Several studies have shown that treatment of GDM improves pregnancy outcome (60-63). The positive effects consist of reduced risk of LGA infants and macrosomic births. There is also a reduced risk of shoulder dystocia (where there is failure to deliver the shoulders of the infant) and caesarean section. For the mother there are beneficial effects, with reduced risk of preeclampsia and hypertension during pregnancy.

To organize the optimal care is challenging in many cases and for many clinics. Women are instructed to do self-monitoring blood glucose measurements (SMBG) fasting and before and after meals and it is often difficult to achieve good adherence to these instructions (64, 65).

Lifestyle advise is considered the foundation of the treatment of GDM. All women should also be counselled, preferable by a dietician, to keep a healthy diet, with sufficient calorie intake during pregnancy, but without nutrients that contribute to glucose excursions above treatment targets (52). When pharmacological treatment is warranted to keep the blood-glucose within the desired range, insulin is often the first line of treatment. Insulin does not cross the placenta and is easily titratable, which is convenient as the insulin resistance often increases rapidly in the latter half of pregnancy. Traditionally, fast-acting insulin with meals have been used to treat postprandial blood glucose elevations. NPH-insulin at bedtime is used in cases with high fasting glucose(66).

There are many studies reporting on safety using oral antidiabetic drugs (OAD) such as metformin and glyburide during pregnancy(67-70). Metformin seems to have a more preferable effect than glyburide (71) It is reported that metformin reduces the risk of LGA infants, neonatal hypoglycaemia and reduces maternal weight gain (72, 73). However, there are still concerns regarding OAD and the long-term effect on the foetus, since metformin and sulfonylureas are transferred over the placenta. There are

studies showing that there is an increased risk of overweight and obesity in the child, if the mother was treated with metformin during pregnancy (70, 74, 75).

Women receiving metformin are additionally treated with insulin as step-up approach, if they do not meet glycaemic targets. Treatment failure with Metformin with the need for supplementary insulin occurs in 10-46.3% of the cases (76). When comparing metformin to insulin treatment there are no major differences, but there seems to be a small benefit for Metformin, regarding the risk for neonatal hypoglycaemia, but there is evidence of shorter gestational length. When metformin is compared to insulin treatment there are lower GWG and lower birthweight achieved, but also a reduction in preeclampsia compared to insulin. (77).Furthermore, women who are treated with Metformin gain less weight during pregnancy compared to insulin treated women (69, 77, 78). In a clinical setting, it is often the women with the highest glucose values, that receives insulin-treatment or need add-on insulin to Metformin.

The novel treatment regimens with GLP-1 receptor agonists, DPP-2 receptor antagonist and SGLT-2 inhibitors have not been sufficiently studied during pregnancy and is currently not recommended during pregnancy. There is however some data regarding sitagliptin and liraglutide, with some positive results regarding reduced insulin resistance in GDM pregnancy and increased pregnancy rate in IVF pregnancy among women with PCOS, but there is still insufficient data regarding pregnancy outcome and long-term effect on women and foetus (79, 80).

Preventing Gestational Diabetes during pregnancy

Diet- and exercise-intervention in early pregnancy has limited effect on preventing gestational diabetes and LGA infants (81, 82). However in some populations, for example in a Chinese study, lifestyle intervention was shown to have an effect on preventing GDM in an overweight or obese pregnant population (83). In a recent metanalysis there is some evidence that diet in combination with exercise has some effect on reducing the risk of GDM and caesarean section, in addition to an effect on limiting GWG(84). There is some evidence that diet with low glycaemic index (low GI) is beneficial in early pregnancy for preventing GDM (85).

Preventing GDM by means of OAD is also an investigated solution. Metformin seems to have a significant effect on reducing the risk of GDM in women with PCOS (86, 87), however the same promising results were not seen in an obese population (88).

Gestational Weight and Gestational Weight Gain

Being overweight increases the risk of developing GDM, but it is also an independent risk factor for several adverse pregnancy outcomes, such as hypertension in pregnancy and preeclampsia. Both GDM and obesity are associated with adverse pregnancy

outcomes, and a combination of these two risk factors has a greater impact than either one alone (89, 90).

Overweight and a high GWG increases the risk of caesarean section (91). However, a high prepregnancy BMI is a stronger predictor of caesarean delivery than high GWG (92, 93).

Because of the large impact of GWG on pregnancy outcome, different desirable intervals of weight gain during pregnancy, depending on the woman´s prepregnancy BMI is proposed. The guideline from the Institute of Medicine (IOM), is the most referred to guideline regarding weight gain during pregnancy (Table 4) (94). These guidelines aim to achieve better pregnancy outcome, but also improve the future health of the mother.

Table 4.
IOM recommendations for weight gain during pregnancy according to prepregnancy BMI

Prepregnancy BMI (kg/m2)	Recommended weight gain (kg)
< 18.5	12.5-18
18.5-24.9	11.5-16
25.0-29.9	7-11.5
≥30	5-9

Women with obesity or overweight before pregnancy is at risk of delivering an infant with high birth weight (95, 96). Maternal overweight leads to increased foetal growth, increased risk for large for gestational age (LGA) infants and for caesarean section(97-107). A low GWG among obese women is beneficial and reduces the risks of complications during pregnancy and delivery. It is known that women with obesity and T2D who gain less than 5 kg during pregnancy have less perinatal morbidity and fewer LGA-infants (108). On the other hand, excessive GWG, outside the IOM recommendations is associated with an independent risk of LGA infants and caesarean section (109).

Despite the IOM recommendations it is often difficult to achieve a GWG within the proposed limits. A recent study showed that the majority of overweight and obese women in the US gain above the recommended levels (110). With this said, women with obesity often gain less weight during pregnancy, than normal weight women, and weight loss during pregnancy is more common in obese women, with the highest occurrence in women in the highest BMI classes (BMI≥35kg/m^2)(111).

In addition to the immediate complications during delivery, some studies have shown that a high GWG have negative impact on long term maternal health, with increased risk of post-partum weight retention and obesity related diseases (112-114). Gestational

weight gain has a larger impact compared to pregestational BMI, on the risk for obesity late in life (115).

Large for Gestational Age infant and Macrosomia

GDM as well as a high maternal BMI is a risk factor of macrosomia (116, 117). A high GWG increases the risk of LGA and macrosomia (118). Macrosomia is defined as a birthweight >4000g, however there are medical associations that propose a higher limit of 4500g, because the medical risks rapidly increases when the infant has a birth weight of 4500g or more(119, 120). LGA is defined as birth weight above the 90th percentile for the specific gestation period. In a Swedish material the weight intervals for Small for Gestational Age (SGA), Appropriate for Gestational Age (AGA) and LGA according to both gestation period and sex of the infant is reported (121).

For a macrosomic infant there is an increased risk of caesarean section, trauma during delivery and shoulder dystocia (122). The baby of a mother with uncontrolled hyperglycaemia during pregnancy, can be both macrosomic and LGA. Often the infant is also inappropriately large over the shoulders and torso, which can attribute to the increased risk of shoulder dystocia. There is also a higher risk for clinically significant hypoglycaemia after birth in the macrosomic infant(123).

Caesarean Section

Overall, in the Swedish population with GDM, the frequency of caesarean section is 25.9% (6). As previously stated, a high maternal BMI is a stronger predictor of caesarean delivery than gestational weight gain (92, 93, 101, 124-126). Even women with a slightly elevated BMI have an increased risk of caesarean section, increased birth weight and malformations (127). Some studies have also noticed the even higher risk in the women who at the same time have GDM (89, 90).

Glucose excursions

There are contradicting reports regarding the impact of glucose excursions in gestational diabetes on adverse pregnancy outcomes, such as macrosomia and caesarean section. One study reports no correlation between glucose excursions and adverse pregnancy outcomes in diet treated GDM (128). However, when using CGM and analysing the glucose levels more carefully, there is an improvement of pregnancy outcome in the group with the lowest MAGE (mean amplitude of glucose excursions) and lowest SD of glucose measurements (129)

After GDM - Future risk for disease

After delivery the placental hormones are immediately cleared from the woman´s circulation and the insulin sensitivity is restored to prepregnancy levels. Therefore, the glucose levels normalize and pharmacological treatment for GDM is immediately discontinued after delivery.

As previously stated, the risk of T2D after GDM is elevated. Women with GDM are reported to have a seven-fold increase in the risk of developing T2D (31, 37). However, depending on the timing of postpartum testing and the characteristics of the population, there are different reports regarding the incidence of T2D post GDM pregnancy. The frequency of T2D after GDM is reported to 3.5%- 70% in European cohorts(130, 131) and 10-20% in Australian and American cohorts (36, 132). The indigenous people of Australia have a more than four-fold higher risk of diabetes after GDM, compared to non-indigenous Australians (18), demonstrating the impact of ethnicity on the risk of developing diabetes. Women of non-European origin, especially Asian origin or black ethnicity also have a higher risk of developing diabetes after GDM (37). In populations in southeast Asia and India the frequency of T2D after GDM is reported to be 9-90% depending on region and follow up period (133-135).

There are several predictors for development of T2D. The risk is greater in women with GDM who had a higher OGTT value at screening during pregnancy, higher fasting glucose and women with medical treatment for GDM (136, 137). Several metabolic factors including a higher fasting glucose and higher HbA1c during pregnancy and higher triglycerides during pregnancy indicates a higher risk for diabetes after a GDM pregnancy. Maternal characteristics that predict T2D after GDM are older maternal age and non-Caucasian ethnicity, but also a high BMI prior to pregnancy, PCOS and a family history of diabetes (59, 132, 138-140). Women with multiparity with short intervals between pregnancies are also at a higher risk of developing T2D (141).

The time period between GDM and development of T2D is often relatively short. Already within a few years of pregnancy, a large proportion of women have developed T2D. In a Swedish study, as much as one third of the women are found to have impaired fasting glucose, impaired glucose tolerance or T2D at one year follow up (142). Another study reports that 10 years after gestational diabetes, more than two thirds of the women were diagnosed with glucose intolerance or T2D in a Swedish population (143).

The metabolic syndrome is a combination of risk factors for cardiovascular disease. It includes glucose intolerance or T2D, hyperlipidaemia, hypertension and increased waist circumference The prevalence of metabolic syndrome is up to three times higher after GDM than in the normal population (144, 145). Women with GDM have an almost two-fold increased risk of developing cardiovascular disease compared to women without GDM, independent of their BMI. The cardiovascular disease is often diagnosed early in life, within the first 10 years after a GDM pregnancy(32, 34, 146-

148). In the Nurses' Health II Study, a prospective analysis over more than 15 years, the risk of myocardial infarction and stroke in women with previous GDM, was increased by 43% compared to women who did not have GDM. However, the risk is augmented when adjusting for weight gain after pregnancy and an unhealthy lifestyle. In addition to this, the women had an increased risk of hypertension, independent on the development of T2D (149, 150).

The risk for CVD is increased in women with GDM even if the women do not develop T2D. Retnakaran et al reported that the risk for CVD is continuously increasing with elevated glycaemia in pregnancy, even in women with mild hyperglycaemia after a 50 g Glucose Challenge Test (GCT) and even in the glycaemic range below diagnostic values for GDM (151).

There are some studies regarding the future health of the infants. Recently the HAPO follow up study reported on the effects of maternal hyperglycaemia on the future health of the offspring and it is concluded that increasing levels of maternal glycemia has increasing impact on the child´s glucose metabolism. Offspring to mothers with the highest levels of glycemia in the HAPO study had the highest risk of impaired glucose tolerance (152). Children born to mothers with GDM, have an increased risk of several conditions, including obesity and T2D (153). However, this will not be further explored in this thesis.

Screening for diabetes after pregnancy remains a challenge in many cases. Since attendance to post-partum follow up visits are low, different efforts are made to increase the number of women who are tested for diabetes after pregnancy. During recent years these efforts have included improved patient information and SMS-reminders for postnatal follow up (142, 154).

There is a large proportion of women who do not receive any evaluation of metabolic control in the postpartum period. In some studies the frequency of women who are screened for diabetes after GDM pregnancy is as low as 34%, but is some studies as high as 73%(142, 155, 156). Women who are older, with higher income and education are more likely to be tested postpartum (142) On the contrary, the frequency for postpartum testing decreases in women with multiple pregnancies, caesarean deliveries and macrosomic births (155). The reasons for the low frequency of postpartum glucose testing are often lack of information from health care providers and education regarding the risk for future diabetes and other diseases. Some women assign procrastination as the major reason for not attending postpartum follow up (156-160).

The optimal period for postpartum testing has also been debated. Many advocate testing within 3 month postpartum and a follow up testing during the 6 week postpartum visit and thereafter annually, is often recommended (47, 52, 55, 161). The role of HbA1c testing at regular intervals is also discussed. HbA1c testing in the early postnatal period is not recommended, since the HbA1c levels might be affected by the

recent pregnancy and delivery. Even after one year of pregnancy, there is still a low sensitivity compared to OGTT, but might be recommended as an additional test for diabetes after GDM (48, 162, 163).

For the woman with GDM there is also a risk of developing type 1 diabetes after GDM, especially if there are autoantibodies present during pregnancy (12, 164-166). Interestingly, there seems to be an increased risk of diabetes, overweight and obesity even for the father, if the mother of his child have GDM (167). Socioeconomic and ethnical factors probably contribute to this effect.

Treatment to reduce the risk of future disease

Treatment during pregnancy

There is a lack of studies regarding long term effects of GDM treatement for the mother with previous GDM. There are a small number of studies reporting only a limited effect of treating GDM on metabolic risk factors and the risk of obesity or development of diabetes in the future (168). This is perhaps expected, since the development of diabetes after GDM is mostly facilitated by prepregnancy BMI and by maternal weight and weight gain after pregnancy (169, 170), and also by non-modifiable factors, such as ethnicity and heredity.

Treatment after pregnancy

There are, however, several studies regarding treatments to reduce the risk of future disease for women with previous GDM. In many intervention studies there has been an intent to optimize cardiometabolic risk factors and reduce the risk of diabetes. Lifestyle interventions with weight loss and specific nutrients have been shown to reduce cholesterol and triglycerides in the short term. While different intervention models with diet and life-style advice do have an effect on the treatment goals, there are significant reduction in cardiovascular risk factors in all women who lose weight or reduce their waist circumference independently on by which method this was achieved or if they were in a study treatment group or control group (171-173). These studies are often of short duration.

In longer prospective studies, there are benefits of increasing physical activity and reducing television watching and other collateral behaviours to reduce a sedentary lifestyle. A reduced risk of progression to T2D after GDM, independent of BMI is obtained (174). Adherence to a healthy diet has also proved to reduce the risk of progression to T2D, independently of diet regime (Alternate Mediterranean diet (aMED), Dietary Approaches to Stop Hypertension (DASH), or alternate Healthy Eating Index (aHEI)), and independently of BMI in women with previous GDM (175). It is generally believed that interventions to improve lifestyle and treatment with metformin, would have the same positive effect on diabetes prevention in women after

GDM, as it has been previously shown in the general population (3). However, considering the secular trend with increasing weight and weight gain in younger women, it is suspected that weight reduction in this age group, is difficult to achieve. Women with GDM have reduced effect of lifestyle intervention treatment on weight reduction, compared to the general population. Also, when metformin has been used, the women with GDM seems to benefit from metformin treatment, with a nearly 50% reduction in risk for T2D, compared to lifestyle intervention. Women with previous GDM have an especially high benefit of Metformin (176-178).

Finally, lactation has a well-established protective effect against the development of T2D, also after a GDM pregnancy (179-181). There is also evidence of the protective effect of breastfeeding on the risk of developing cardiovascular disease(182) and this positive effect seems to be regardless of BMI (183). Therefore, all women with GDM should be encouraged to breast feed their infant.

Key Message of Introduction

Gestational diabetes is a condition with hyperglycaemia during pregnancy affecting a large number of pregnancies worldwide. GDM is a condition with increasing frequency around the world as overweight and obesity become more common in young women of childbearing age. As general screening of pregnant women becomes more and more implemented, the number of women diagnosed with GDM also continues to rise. GDM affects the pregnancy and increases the risk of adverse pregnancy outcome. A woman with GDM has a higher risk of developing T2D, obesity and cardiovascular disease in the future. The risk of T2D and obesity is also elevated in the child.

Since GDM has implications on both pregnancy outcome and the future health of the woman and child, it is of importance to diagnose these women. Lifestyle-interventions and medical treatment, when needed, can improve pregnancy outcome. The same interventions can probably improve the future health of the woman and future research will reveal if this will postpone of even prevent onset of type 2 diabetes or cardiovascular disease.

Aims

The aim of this thesis is to evaluate risk factors during pregnancy for adverse pregnancy outcome and evaluate risk factors during pregnancy for developing T2D and other diseases after pregnancy.

- ➤ To evaluate if women, who later in life were diagnosed with diabetes, had hyperglycaemia associated complications during their previous pregnancies and deliveries.

- ➤ To analyse the impact of maternal BMI at the start of pregnancy and gestational weight gain during pregnancy on the risk of developing T2D and other metabolically related diseases later in life.

- ➤ To study the effect of having a predisposition for diabetes (defined as onset of diabetes later in life) and overweight, alone or in combination, on pregnancy outcome

- ➤ To evaluate glucose control and pregnancy outcome in GDM pregnancies in regard to treatment modality in two different time periods.

Material and Methods

Study population

Paper I-III

MISS cohort

We included women from the MISS (Melanoma in southern Sweden)-cohort. A cohort of 29 488 women, in the ages 25-65 years, representing every eighth woman (12.5%) in the Population Register, in the southern region of Sweden was established in 1990 to study risk factors for malignant melanoma. The MISS-cohort have been followed since then. At the time of cohort establishment, the women answered a questionnaire regarding social status, previous illnesses, medication, weight and height. In a follow-up-study of the same cohort 10 years later, in which 23 524 women participated, a more extensive questionnaire was used, with additional questions regarding diseases, medication and lifestyle. The women were then between 45 and 85 years old.

The Swedish Prescribed Drug Register

From the register from we received data regarding prescribed anti-diabetic medications among the women in the MISS-cohort. Women with a prescription for anti-diabetic medication were considered to have diabetes, irrespectively of their self-reported answer in the MISS-cohort.

Swedish Medical Birth Register

Swedish Medical Birth Register (SMBR) started in 1973 and approximately 100 000 births per year in Sweden have been registered since then and the dropout rate is only 0.5–3%. The register contains data concerning maternal characteristics during pregnancy, delivery and postnatal data regarding the infant. Between 1973 and 2005 we identified 30 559 pregnancies in the Swedish Medical Birth Registry (SMBR) related to the women participating in the MISS cohort. (Figure 1)
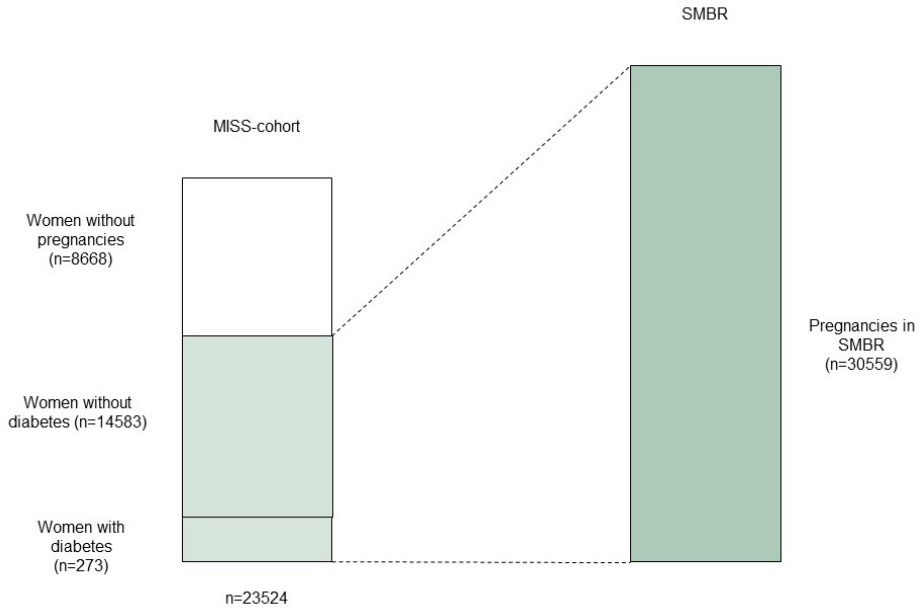
Figure 1.
Women from the MISS-cohort with pregnancies in SMBR

Paper I

We excluded all women without any registered pregnancies during the study period 1973–2005. The remaining women were divided into different groups according to if they had diabetes or not. One group consisted of women with type 1 diabetes. 45 women and 81 pregnancies. The other group consisted of women with diabetes at follow up or diabetes at a previous pregnancy (assumed to be gestational diabetes). This group consisted of 228 women with 455 pregnancies. The third group consisted of women who never developed diabetes and did not have diabetes registered during any pregnancy. This group was referred to as the control group and consisted of 14 583 women and 30 023 pregnancies. After excluding women with insufficient data from either SMBR or the MISS-cohort to calculate BMI during pregnancy there was 4615 women left in this group (Figure 2).
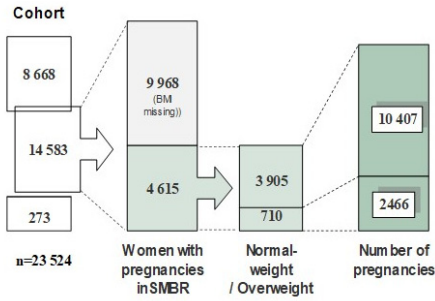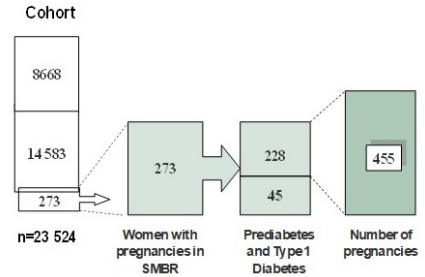
Figure 2.
Schematic view of women, with and without diabetes, and their pregnancies included in Paper I. In the cohort 8668 women did not have any registered pregnancies in SMBR.

Paper II

To analyse occurrence of disease after pregnancy we used self-reported data of MISS-cohort follow up from the questionnaire in the year 2000. We therefore excluded all pregnancies after 1991. Only 13 608 women had a first registered pregnancy in 1973-1991. We also excluded women with insufficient data from either SMBR or the MISS-cohort to calculate BMI during pregnancy (Figure 3).

Figure 3 Schematic view of subjects included in Paper II.

Paper III

For this study we included pregnancies with a known initial maternal BMI and data regarding diabetes later in life. In total there was 30559 pregnancies in 14856 women from the MISS-cohort. There was data on prepregnancy BMI for their first registered pregnancy in 4687 women. These women had 13037 registered pregnancies that were included in the analysis. The pregnancies were additionally grouped according to if the woman had a predisposition for diabetes and initial maternal BMI (Figure 4).
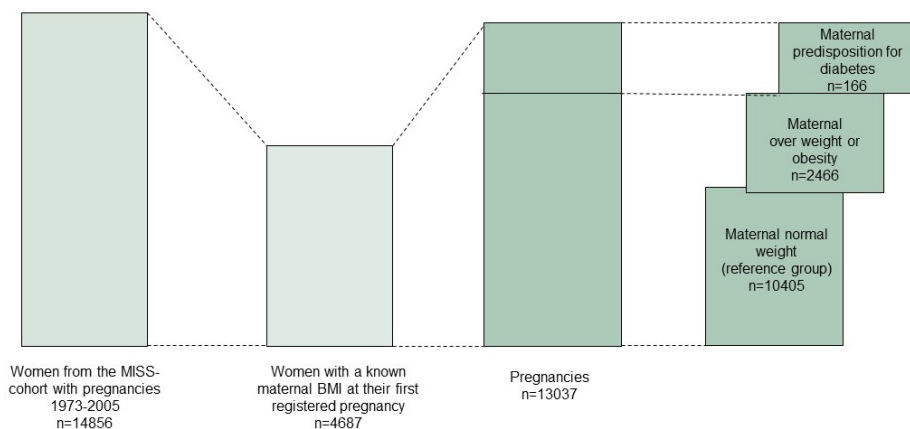
Figure 4.
Schematic view of pregnancies included in Paper III. Pregnancies of women with a known BMI during their first registered pregnancy is included. These pregnancies are divided into three groups according to BMI and predisposition to diabetes.
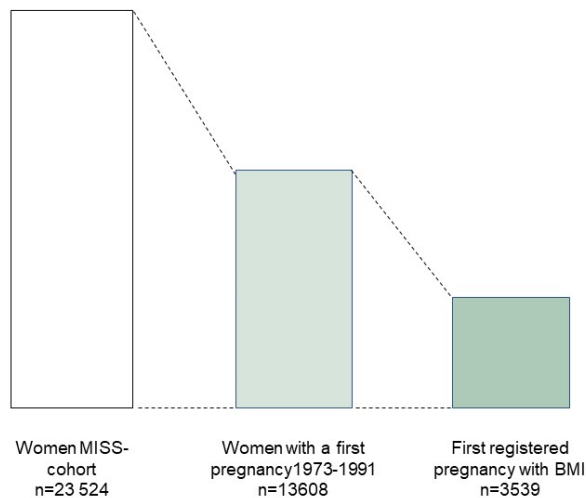
Paper IV

For this study a novel database was established. This database included women with gestational diabetes, treated at the Specialized Maternity Care Unit in Lund 2012-2013 and 2016-2017.

OBSTETRIX

This is a register with data regarding the prenatal status of the women, as well as post-natal data regarding the infant. It also included data regarding the delivery.

DIASEND

This is a telemedicine solution for transfer of blood glucose values. The woman can connect her blood glucose-meter or CGM system to the system using a cloud-function or by connecting the meter via a chord to her computer. Previously a connection of the glucose meter to a mobile modem, were required. The diabetologist can observe and

analyse the values from a different site. Basic statistics as mean glucose values and SD can be obtained for different days or weeks, or even for the entire duration of the pregnancy.

All pregnant women diagnosed with GDM and with follow up during pregnancy at the Specialized Maternity Care Unit in Lund and with data on pregnancy outcome and delivery in the OBSTERIX during the years 2012-2013 and 2016-2017 were included.

Twin pregnancies were excluded. We also excluded pregnancies with Continuous Glucose Monitoring (CGM) registration of blood glucose. Pregnancies in women with previous Gastric Bypass Surgery were excluded (Figure 5).
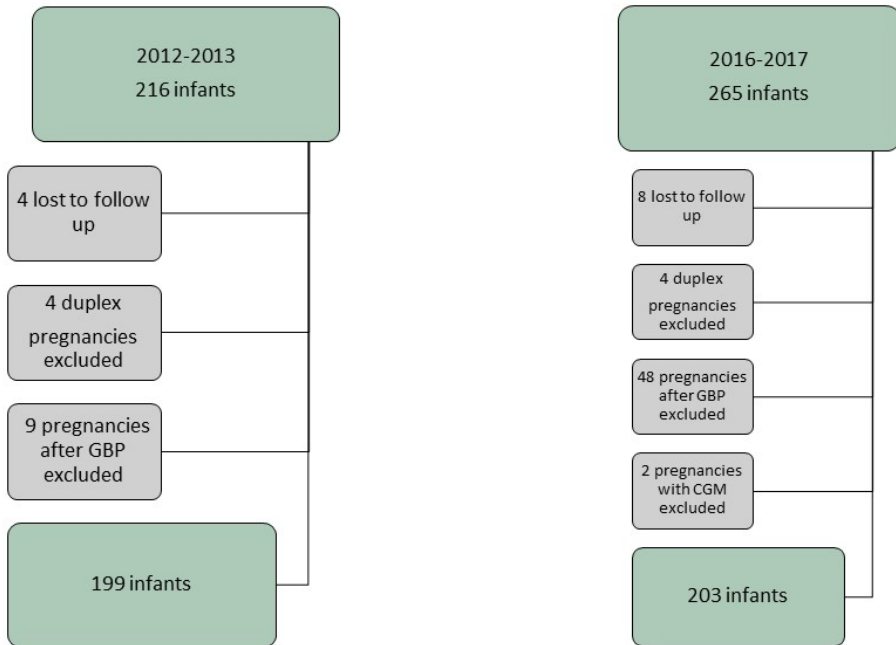
Figure 5.
Schematic view of Study Population Paper IV

Methods

BMI

Paper I-III

In paper I-III, BMI was calculated from data regarding the maternal weight at admission to the prenatal care unit, at approximately 10-12th week of gestation. Data regarding length was retrieved from SMBR. If data regarding length was missing in the register of that pregnancy, data regarding length from another pregnancy of that woman or from the MISS-cohort, was used when available.

Paper IV

In Paper IV, BMI was calculated from data regarding weight and length at admission to the prenatal care unit as registered in OBSTETRIX, at approximately 10-12th week of gestation.

Apgar scores

Paper I, III-IV

Apgar scores are measured by medical personnel at 1, 5 and 10 minutes post-delivery. It is an indication of the wellbeing of the new-born infant. It rates skin colour, heart rate, respiration, irritability and muscle tone. The maximum score is 10. A low Apgar score indicates that medical intervention might be needed. In this study Apgar scores were used as an indication of complications after delivery. A low Apgar score was defined as an Apgar score of ≤7. The data regarding Apgar scores were collected from SMBR (Paper I and III) or from Prenatal Care medical journal in OBSTETRIX (Paper IV).

Macrosomia

The definition of macrosomia is a birth weight ≥ 4500g (Paper I) or a birth weight ≥ 4000g (Paper III-IV). Internationally there are different opinions regarding the definition. Those who advocate 4500g as the lower limit, refer to studies were having a cut off of 4500g demonstrated a better prediction of a high risk for severe adverse events during pregnancy and delivery(119, 120).

LGA

Paper I, III

The data regarding LGA is derived from the Swedish Medical birth register.

Paper IV

LGA was defined according to a sex-specific reference curve from a Swedish population (121).

Definition high median blood glucose

Paper IV

We defined a high median blood glucose as ≥6 mmol/L. A high frequency of glucose excursions was defined as a frequency of ≥6.6% of SMBG ≥8 mmol/l. These definitions were based on the median values in this cohort.

OGTT

Paper IV.

All pregnant women, attending prenatal care unit in our region were offered a generalscreening with 75g OGTT at 28 weeks of gestation. Women with risk factors, such as previous GDM, a family history of diabetes, obesity, previous macrosomic birth were screened at 12 weeks of gestation and, if negative results, additionally screened at 28 weeks of gestation. A cut off level of capillary blood-glucose ≥10.0 mmol/L were applied for diagnosing GDM.

Statistical Analysis

Paper I

Statistical analyses were performed using the SPSS version 17.0 statistical software for PC, (SPSS Inc, Chicago, Illinois). Mean and standard deviations are reported for continuous variables (weight, weight gain, BMI and birth weight of infant, parity). Median and quartiles are reported for non-parametric variables such as gestational age. Frequencies in percent are reported for categorical variables such as smoking, macrosomia, caesarean section, instrumental delivery and normal Apgar at 10 minutes.

For comparison between the groups Mann Whitney U-test was used for non parametric variables (gestational week, Apgar score) and Student T-test was used to compare

parametric variables (maternal age, weight, BMI, GWG). For comparison of frequencies (smoking, caesarean section, LGA) Chi 2 test was performed. Chi 2 test was replaced by Fisher´s exact test if any observation in any cell was below five. For calculation of correlation between weight and weight gain, Pearson´s correlation (bivariate) was used. A binary logistic regression in different models were used to analyse multivariate risk factors for low Apgar score, caesarean section and macrosomia. p-values <0.05 were considered significant.

Paper II

Statistical analysis was performed using the SPSS version 22 statistical software for PC (SPSS inc, Chicago, Illinois). Mean and SD are reported for normally distributes data such as age, maternal weight and GWG. Medians and range are reported for BMI groups. Frequencies in percent are reported for categorical variables such as diabetes, obesity and cardiac disease. Student´s T-test was used to compare age, maternal weight and GWG. For comparison between the different BMI groups an ANOVA test was used. To measure associations between obesity and GWG and future outcomes, odds rations (ORs) were calculated using Chi2 test. Binary logistic regression analysis was used to evaluate different risk factors and the future risk for disease. P-values <0.05 were considered significant.

Paper III

Statistical analyses were performed using the SPSS version 17.0 and 22 statistical software for PC, (SPSS Inc, Chicago, Illinois). Median and range are reported for non-parametric variables such as BMI, birth weight, gestational length, GWG and maternal age. Frequencies in percent are reported for categorical variables such as smoking, caesarean section, low Apgar score and instrumental delivery.

For comparison between the groups Mann Whitney U-test (BMI, gestational weight gain, gestational length, maternal age, birth weight,) were used. For comparison of frequencies (smoking, caesarean section, LGA, low Apgar score) Chi 2 test was performed. Chi 2 test was replaced by Fisher´s exact test if any observation in any cell was below five. Correlations were tested with Pearson´s and Spearman´s correlation test depending om normal- and non-normal distribution. Logistic regression analyses were done to estimate the impact of different factors on the risk for caesarean section and macrosomia. BMI in the multiple regression analysis was presented in 5kg/m^2 intervals. p-values of <0.05 was considered significant.

Paper IV

Statistical analysis was performed using SPSS® Statistics Version 24. Median and Range are reported for all non-parametric values. Mann-Whitney U-test was used when comparing non-parametric data such as, maternal weight and BMI, gestational length, birthweight and insulin-dose and placental weight, and median blood glucose values.

Chi2 analysis was made to analyse differences in frequencies of LGA and macrosomia, caesarean section, smoking, and non-Scandinavian ethnicity and heredity. A logistic regression analysis was made with different variables to evaluate OR for different risk factors for LGA and macrosomia. In the regression analysis BMI is reported in 5 kg/m^2-intervals. P-values <0.05 were considered significant.

Ethical Approval

All papers

All studies were conducted in accordance with the Helsinki Declaration. The studies were approved by the Regional Ethical Board at Lund University, Box 133, S- 221 00 Lund, Sweden.

2007/244, 2009/307, 2014/78, 2016/5, 2016/333

Results

Paper I

The women with type 1 diabetes had fewer pregnancies during the study period compared to the control population. Overall, women with diabetes had a higher BMI at the beginning of pregnancy and a higher frequency of caesarean section.

Table 5
Description of different groups of pregnant women

	Typ 1 diabetes (A)	GDM or later type 2 diabetes (B)	No diabetes (C)	p-value (A and C)	p-value (B and C)
Number of women	45	228	14 583	NT	NT
Number of infants	81	455	30 023	NT	NT
Age at first pregnancy	26.9	26.7	26.9	ns	ns
Parity	1.8±0.8	2.0±1.1	2.1±1.0	0.04	ns
Smoking (%)	7.4	13.2	12.1	ns	ns
Maternal weight at beginning of pregnancy (kg)	67.2±13.0	69.2±13.9	63.2±10.4	0.01	<0.001
Maternal BMI (kg/m2)	24.2±4.5	25.2±5.1	22.7±3.4	0.003	<0.001
Maternal mean weight gain (kg)	14.1±6.1	13.3±5.4	14.1±4.7	ns	0.03
Gestational lenght (weeks)	39.1	39.9	40.1	<0.001	0.001
Macrosomia (%)	24.7	28	18.1	ns	<0.001
Frequency planned Caesarean section (%)	7.4	4.8	2.7	0.009	0.005
Frequency Caesarean section (%)	38.3	15.2	10.0	<0.001	<0.001
Frequency instrumental delievery (%)	2.5	2.2	1.3	ns	ns

GDM=Gestational Diabetes Mellitus, BMI=Body Mass Index, NT=not tested

Women with GDM or later type 2 diabetes had a lower weight gain than the control group. The weight gain was inversely correlated to the pre-pregnancy weight in this group of women (r=-0.34; p<0.001). For the other groups there was no correlation between maternal weight and GWG (Figure 6).
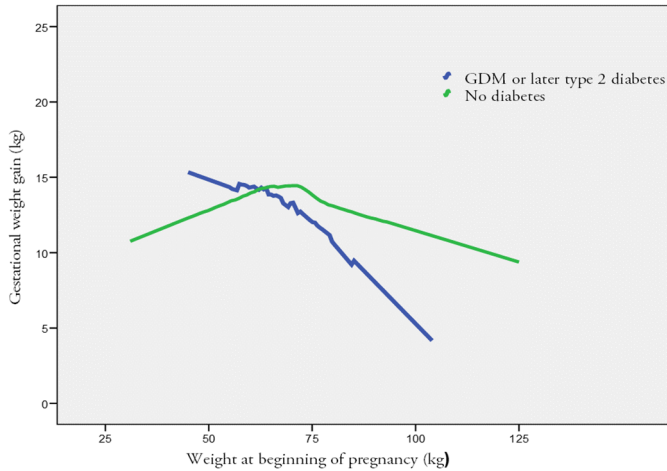
Figure 6.
Pregestational weight and gestational weight gain.

Despite a shorter gestational length and lower maternal GWG, the infants in the GDM/prediabetes group had a higher birth weight compared to controls (3602±680g vs. 3507±579g; p=0.001). This is also apparent in the higher frequency of LGA and macrosomia in this group, compared to controls (Figure 7).
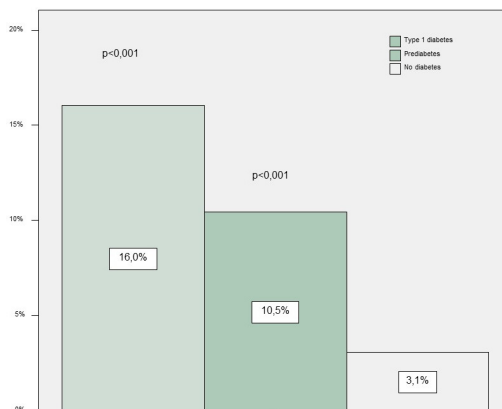
Figure 7.
The frequency of LGA in different groups.

40

The infants of women with GDM or later type 2 diabetes, had significantly lower Apgar scores at 1, 5 and 10 minutes compared to control group (p<0.001, p=002 and p<0.001, respectively). In a multivariate logistic regression analysis, the OR for a sustained low Apgar score at 10 minutes was only significant for a low birth weight and a short gestational length (Figure 8) (Table 6).
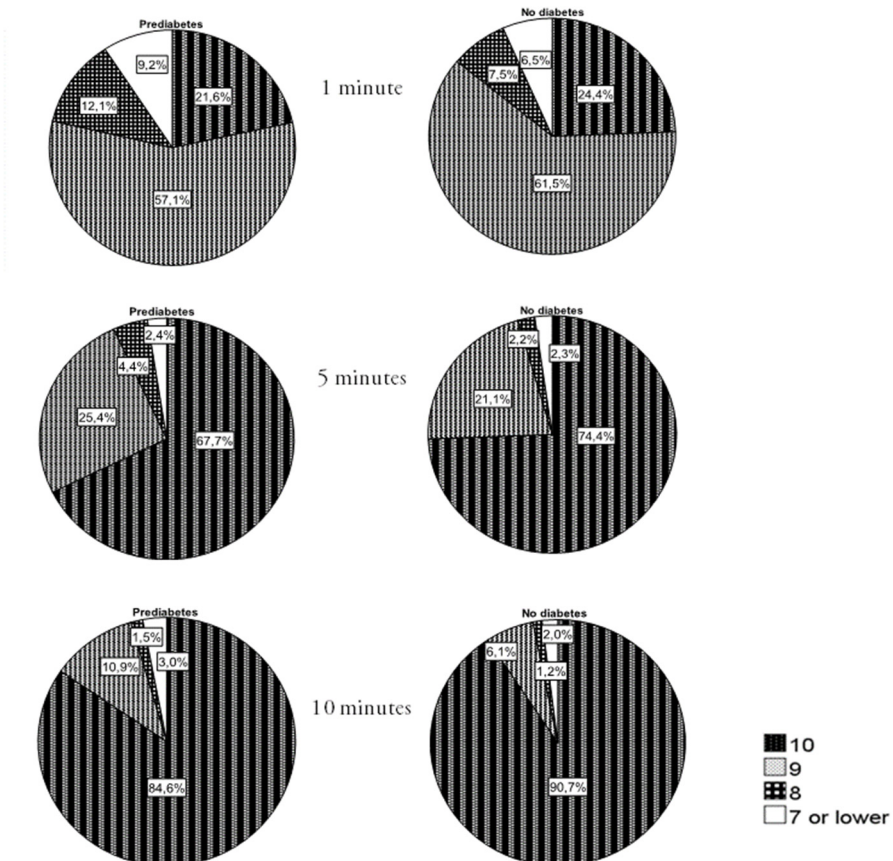
Figure 8.
Apgar scores at 1, 5 and 10 minuter in the different groups

Table 6.
Odds Ratio (OR) for different adverse outcomes of pregnancy, such as Caesarean section, Low Apgar score and Macrosomia.

	Variable	OR	95% CI	p-value
	Low Apgar score 1 minute			
n=12255	Prediabetes	1.70	1.17-2.48	0.006
	Birth weight (hg)	0.98	0.97-0.99	0.001
	Gestational length (weeks)	0.93	0.90-0.97	<0.001
	Prepregnancy BMI	1.04	1.03-1.06	<0.001
	Smoking	1.02	0.90-1.15	Ns
	Low Apgar score 10 minutes			
n=10069	Prediabetes	1.70	0.61-4.74	ns
	Prepregnancy BMI	1.02	0.98-1.07	ns
	Birth weight (hg)	0.97	0.93-1.00	0.05
	Gestational length (weeks)	0.83	0.76-0.91	<0.001
	Smoking	0.84	0.57-1.23	ns

Variable		OR	95% CI	p-value
		Caesarean section		
		Model I		
n=9633	Prediabetes	1.02	0.30-3.54	ns
	Maternal age (years)	1.12	1.08-1.16	<0.001
	Prepregnancy BMI	1.16	1.10-1.22	<0.001
	Weight gain (kg)	1.01	0.97-1.05	ns
	Birth weight (hg)	0.97	0.93-1.00	ns
	Gestational length (weeks)	0.88	0.79-0.99	0.03
		Model II		
n=30368	Prediabetes	1.48	0.94-2.34	ns
	Maternal age (years)	1.20	1.18-1.21	<0.001
	Gestational length (weeks)	0.81	0.77-0.84	<0.001
	Birth weight (hg)	0.99	0.97-1.00	ns
		Model III		
n=13000	Prediabetes	1.81	1.01-3.24	0.048
	Maternal age (years)	1.20	1.18-1.22	<0.001
	Birth weight (hg)	0.98	0.96-1.00	0.054
	Gestational length (weeks)	0.79	0.75-0.83	<0.001
	Prepregnancy BMI	1.02	1.01-1.03	0.001
		Macrosomia		
		Model I		
n=9444	Prediabetes	2.10	1.32-3.35	0.002
	Gestational length (weeks)	1.78	1.70-1.87	<0.001
	Weight gain (kg)	1.09	1.08-1.11	<0.001
	Prepregnancy weight (kg)	1.05	1.05-1.06	<0.001
	Mother's age (years)	1.03	1.02-1.04	<0.001
	Smoking	0.43	0.37-0.51	<0.001

BMI=Body Mass Index, OR=Odds Ratio, CI=Confidence Interval, NS=Non significant

To summarize, the women who later in life developed diabetes, had hyperglycaemia related adverse outcomes, with higher frequency of LGA infants, shorter gestational length and a higher frequency of caesarean section. A low gestational weight gain is beneficial for overweight women and women with GDM, however the mean weight gain among the women in this study was still above IOM recommendations.

Paper II

In this study the effect of high prenatal BMI and a high GWG on the woman´s future risk for disease was explored.

Only the woman´s first registered pregnancy was analysed. Characteristics of these women by BMI in early pregnancy is presented in Table 7. The women with obesity were slightly older than women of normal weight. The women who were obese had a lower weight gain than women of normal weight. The women who were obese had the lowest weight gain and the mean weight gain for this group was just within the IOM recommendations. In the group of women who were overweight, the weight gain was well above the recommended limit.

Table 7.
Characteristics of women by BMI in early pregnancy

	BMI <20	BMI 20-25	BMI 25-30	BMI ≥30	P-value
Mean age at first registered pregnancy (Yrs±SD)	26.7±4.3	27.1±4.4	26.7±4.8	28.8±6.1	0.002
Prepregnancy weight (Kg)	52.4±4.5	61.3±5.5	74.7±5.7	87.1±6.5	<0.001
Median BMI at start of pregnancy (Kg/m²)	19.1	21.8	26.5	31.6	<0.001
Mean maternal weight gain (Kg)	13.8±4.	14.8±4.6	14.7±5.2	8.9±4.8	<0.001
Median BMI at followup 10-17 yrs after pregnancy (kg/m²)	21.3±17.4	*23.8±3.1*	29.1±4.5	32.5±6.9	<0.001

At follow up, 10-17 years after their first registered pregnancy, 216 (1.6%) of the women had been diagnosed with diabetes. In the highest BMI class (BMI≥30kg/m2), 12.3 % of the women had developed diabetes. With a higher BMI at the start of pregnancy, the frequency of both overweight and obesity at follow up increased. Women who were overweight (BMI ≥25-30 kg/m2) at the time of pregnancy had a high proportion of obesity or overweight, 44% and 85%, respectively, 10-17 years after pregnancy. This is demonstrated in Figure 9.
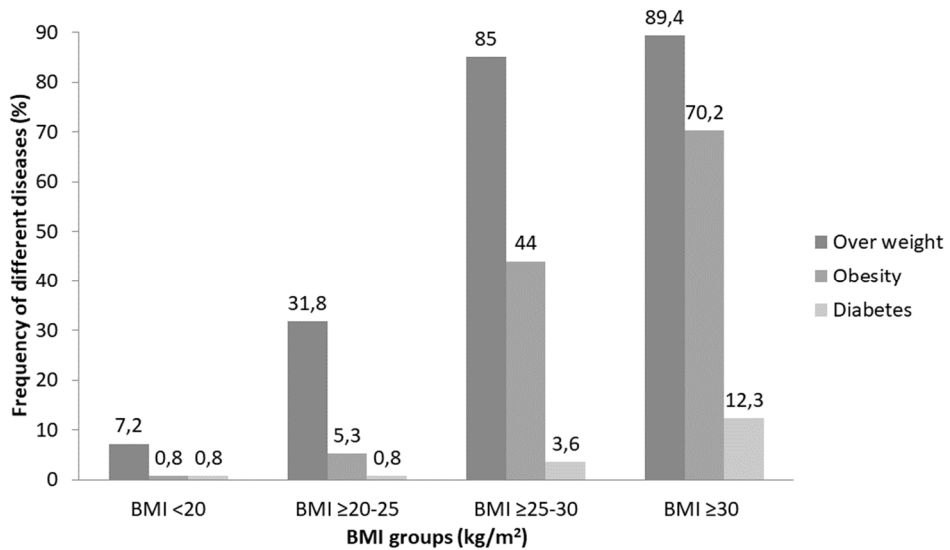
Figure 9.
Frequency of different diseases 10-17 years after pregnancy by BMI group.

There was overall a frequency of 3.3% of cardiac disease, 7.1% endocrine diseases, 0.4% stroke and 2.8% psychiatric disease 10-17 years after pregnancy. There was a positive association between a high BMI and the risk of developing obesity, diabetes and cardiac disease. The OR for different diseases is reported in table 8. There was more than a six-fold increase in the risk of developing diabetes if the woman was overweight at the beginning of her first pregnancy. There was more than 2-fold increase in the risk of cardiac disease.

Table 8
High BMI (≥25kg/m2) and the risk of different disease 10-17 years after pregnancy.

	OR	95% CI	p-value
Obesity	21.9	16.3-29.5	<0.001
Diabetes	6.4	3.5-11.6	<0.001
Cardiac	2.7	1.5-4.9	0.001
Endocrine disease	2.3	1.5-3.4	<0.001
Psychiatric disease	1.6	0.9-2.8	NS

A high gestational weight gain did not have any impact on the future risk of diabetes or cardiac disease in this study, as demonstrated in Table 9. However, a high GWG decreased the risk of psychiatric disease.

Table 9.
High gestational weight gain (≥15kg) and the risk of different diseases 10-17 years after pregnancy.

	OR	95% CI	p-value
Diabetes	0.6	0.4-1.1	NS
Cardiac disease	0.7	0.4-1.3	NS
Stroke	2.9	0.7-12.0	NS
Endocrine disease	0.9	0.7-1.3	NS
Over weight	2.0	1.7-2.3	<0.001
Obesity	2.2	1.7-2.8	<0.001
Psychiatric disease	0.6	0.4-0.9	0.03

In a regression analysis model with risk factors for future disease, only maternal BMI was a significant risk factor for developing diabetes later in life, while a high GWG was significant for the development of overweight and obesity (Table 10).

Table 10.
Maternal BMI and gestational weight gain as risk factors for diabetes, overweight and obesity in a multivariate analysis.

	OR	95% CI	p-value
Risk for diabetes			
n=3537			
Early gestational BMI (kg/m^2)	1.1	1.0-1.1	0.043
GWG (kg)	1.0	0.9-1.0	NS
Maternal age (years)	1.0	1.0-1.1	NS
Risk for overweight			
n=2749			
Early gestational BMI (kg/m^2)	1.8	1.71-1.89	<0.001
GWG (kg)	1.1	1.06-1.11	<0.001
Maternal age (years)	1.0	0.96-1.01	NS
Risk for obesity			
n=2749			
Early gestational BMI (kg/m^2)	1.8	1.68-1.89	<0.001
GWG (kg)	1.14	1.11-1.18	<0.001
Maternal age (years)	0.95	0.91-0.94	0.005

Paper III

The aim of this study was to compare pregnancy outcome in women with a predisposition for T2D to pregnancy outcome in women who did not develop diabetes, with or without overweight and obesity.

For this purpose, we divided the pregnancies into four different groups. The first group consisted of pregnancies in women with pregestational obesity or overweight but without diabetes at any time. This group (GROUP 1) is referred to as "overweight" pregnancies (n=2466). The women with "transitory" diabetes reported in SMBR (assumed to be GDM) during any of her registered pregnancies, including pregnancies of women with diabetes reported at follow up (but not during pregnancy) was included in the next group (n=166). We then divided these pregnancies of women with predisposition to diabetes into two subgroups according to maternal BMI, (GROUP 2 - BMI ≥ 25 kg/m^2 (n=75) or GROUP 3 - BMI < 25 kg/m^2(n=91)). GROUP 4 consisted of pregnancies of women with normal weight (BMI<25kg/m2) who did not have diabetes at any time and this group was used as a reference population (n=10405). Table 11 reports pregnancy characteristics for the different groups.

Table 11.
Characteristics of pregnancies in the different supgroups.

	GROUP 1 Overweight	GROUP 2 Predisp to diabetes over weight	GROUP 3 Predisp to diabetes normal weight	GROUP 4 Controls	p-value Over weight vs. Controls	P-value predisp to diabetes over weight vs. Over weight	P-value predisp to diabetes normal weight vs Controls
N	2466	75	91	10405			
Frequency LGA %	7.1	23.3	11.6	2.9	<0.001	<0.001	<0.001
Macrosomia %	28.5	34.7	28.6	17.6	<0.001	0.473	0.012
Frequency caesarean section %	14.9	24.0	14.3	10.1	<0.001	0.031	0.2
Low Apgar 1 min %	8.4	14.9	6.6	6.2	<0.001	0.05	0.9
Low Apgar 5 minutes %	2.1	1.4	2.2	1.5	0.4	0.6	0.6
Low Apgar 10 minutes %	0.9	1.7	1.4	0.6	0.9	0.6	0.4
Birth weight g	3689 (570-5680)	3760 (870-5800)	3595 (1950-5250)	3530 (540-5820)	<0.001	0.165	0.042
Gestational length weeks	40.1 (25-44)	39.6 (26-42)	39.7 (34-42)	40 (24-44)	<0.001	0.12	0.08
Median Maternal BMI kg/m^2	27.1 (25.0-45.4)	28.3 (25.1-44.7)	21.5 (16.9-24.9)	21.5 (13.2-25.0)	<0.001	<0.001	0.45
Median GWG kg	13.0 (-7-30)	11.0 (0-24)	14.5 (5-27)	14.0 (-2-38)	<0.001	0.03	0.297
Median age of mother all pregnancies yrs	32 (17-46)	32 (19-42)	29 (19-41)	30 (17-49)	<0.001	0.827	0.552
Smoking %	22.0 520/2369	26.1 18/69	29.1 25/86	22.0 2170/9865	0.96	0.41	0.12

The pregnancies differed in some respects. Overall, women with a high prepregnancy BMI had the lowest GWG. Women who were obese and had a predisposition for diabetes gained even less than women who were only obese. However, women with a predisposition for diabetes, also had the shortest gestational length.

The weight gain was inversely correlated to the pre-pregnancy weight among both overweight pregnancies and among the overweight pregnancies with a predisposition to diabetes (r=-0.23; p<0.001 and r=-0.30; p=0.04, respectively), while there was a positive correlation in the control group (r=0.16; p<0.001).

Pregnancies in women with a predisposition to diabetes had a higher frequency of macrosomia. If the woman at the same time was overweight at the start of pregnancy, there was a synergistic effect on the frequency of LGA. Pregnancies in women with predisposition to diabetes had a more than three times higher frequency of LGA compared to pregnancies in women without predisposition to diabetes. Pregnancies with both a predisposition to diabetes and overweight had an almost eight times higher frequency of LGA, compared to control group. Predisposition for diabetes was an equal risk factor as a high BMI, for the risk of macrosomia (Table 12).

Table 12.
Multivariate regressionanalysis for the risk of macrosomia

	Variable	OR	95% CI	p-value
n=12466	BMI interval*	1.5	1.45-1.65	<0.001
	Predisposition for diabetes	1.5	1.07-2.15	0.020
	Nulliparity	0.65	0.59-0.72	<0.001
	Maternal age	1.0	0.995-1.015	0.31

*BMI interval by 5kg/m^2

We found that women with a predisposition for diabetes had a higher frequency of caesarean section. However, in a logistic regression analysis a higher BMI-class, a first pregnancy and a higher maternal age were the dominating risk factors for caesarean section. A predisposition for diabetes did not significantly increase the risk of caesarean section (Table 13)

Table 13.
Multivariate regression analysis for the risk of caesarean section

	Variable	OR	CI 95%	p-value
n=12509	BMI interval*	1.2	1.2-1.4	<0.001
	Predisposition to diabetes	1.5	1.0-2.3	0.083
	First Pregnancy	1.6	1.4-1.8	<0.001
	Maternal age	1.1	1.06-1.08	<0.001

*BMI interval by 5kg/m^2

In a subgroup of data only the woman´s first registered pregnancy was included, and the number of cases is therefore reduced. Similar to previous analysis with all pregnancies included, the birth weight was significantly higher and there was a significantly higher frequency of LGA in the group with a predisposition for diabetes, compared to control group. When analysing the first registered pregnancy, the frequency of macrosomia in pregnancies with a predisposition for diabetes was numerical higher but did not reach statistical significance.

Paper IV

In this study the aim was to evaluate pregnancy outcome of GDM pregnancies, in regard to treatment modality and glucose control in two different time periods.

The median glucose values in the last trimester was significantly lower and the frequency of high blood glucose values was lower in Period 2. However, the OGTT-value was also significantly lower during 2016-2017 compared to 2012-2013.

In the basal characteristics there were some expected differences. Regarding heredity and ethnicity there was a higher frequency of women with a first degree relative with diabetes and there was also a higher frequency of women of Non-Scandinavian Ethnicity in Period 2. Among the women with Scandinavian ethnicity the frequency of a first degree relative with diabetes increased from 34% to 47% between the different time periods (p=0.07). Among the women with non-Scandinavian ethnicity there was a significant increase of heredity for diabetes from 36% to 58% (p=0.007) between the different time periods.

The frequency of metformin use was significantly higher in Period 2 and the frequency of insulin use and the median insulin dose (IE) at the end of pregnancy was significantly lower in Period 2. The number of women with metformin treatment was 30 and among these there were 15 women who needed add on insulin treatment. The majority of women with metformin (27 of 30) had a BMI ≥25 kg/m^2 (Table 14). Maternal BMI and GWG, were the dominating risk factor for macrosomia and LGA (Table 15).

Table 14.
Patient characteristics and pregnancy outcome in two different time periods.

	2012-2013	2016-2017	p-value
First degree relative with diabetes (%)	69/195 (35.4%)	102/194 (52.6%)	**p=0.001**
Non Scandinavian Ethnicity (%)	66/195 (33.8%)	92/198 (46.5%)	**p=0.011**
Collage education (%)	78/186 (41.9%)	74/183 (40.4)	ns
Smoking (%)	15/194 (7.7%)	5/192 (2.6%)	**p=0.023**
Macrosomia (%)	30/199 (15.1%)	33/203 (16.3%)	ns
LGA (%)	11/151 (7.3%)	16/196 (8.2%)	ns
Cesarean section (%)	50/180 (27.8%)	55/196 (28.1%)	ns
Insulin treatment (%)	89/199 (44.7%)	66/203 (32.5%)	**p=0.012**
Metformin treatment (%)	0/199 (0%)	30/203 (14.8%)	**p<0.001**
Maternal age Mean (years)	32.5±5.4	32.8±5.0	ns
Initial maternal weight mean (kg)	74.3±18.2	71.6±15.9	ns
Maternal length mean (cm)	164.2±7.3	163.5±6.2	ns
BMI Median (kg/m²)	26.3 (17.7-47-5)	26.3 (17.2-44.6)	ns
Maternal weight gain mean (kg)	10.0±6.3	10.6±5.8	ns
OGTT value Median mmol/L	10.6 (8.0-24.3)	10.5 (9.9-22)	**p=0.010**
Maximum Insulin dose Median (IE)	28.0 (4-184)	16.0 (4-114)	**p=0.001**
SMBG Median (n/day)	6.1 (0.3-7.3)	6.1 (1.1-8.3)	ns
Total number SMBG mean	344.3±123.5	336.3±130.4	ns
Blood glucose Median (mmol/L)	6.2 (5.3-9.0)	5.8 (4.6-8.4)	**p<0.001**
Percent SMBG values ≥8 (%) Range	9.6 (0.6-66.1)	4.6% (0-51.1)	**p<0.001**
Median Gestational Length (days)	275 (219-290)	274 (199-289)	ns
Infant birthweight Median (g)	3510 (1672-4760)	3521 (998-4700)	ns
Placental weight Median (g)	634 (320-1080)	625 (270-1080)	ns

LGA= Large for Gestational Age, BMI= Body Mass Index, OGTT= Oral Glucose Tolerance Test, SMBG=Self monitoring blood glucose.

Table 15
Riskfactors for LGA and Macrosomia

Binary regression analysis to detect significant risk for Macrosomia			
N=402	OR	CI 95%	p-value
High frequency Blood glucose ≥8 mmol/l	1.3	0.6-3.0	p=0.6
Median blood glucose	1.2	0.6-2.3	p=0.6
Maternal BMI	1.07	1.0-1.14	p=0.06
Maternal GWG	1.1	1.07-1.20	**p<0.001**
Smoking	0.2	0.025-1.9	p=0.163
Binary logistic regression analysis to detect significant risk for LGA			
High frequency Blood glucose >8 mmol/L	1.7	0.5-5.9	p=0.4
Median blood glucose	1.6	0.7-3.5	p=0.23
Maternal BMI	1.13	1.03-1.2	**p=0.007**
Maternal GWG	1.12	1.03-1.2	**p=0.005**
Smoking	0.46	0.05-4.4	p=0.5

Discussion

The aim of this thesis was to investigate risk factors during pregnancy and different pregnancy outcomes that could be indicative for future disease, such as diabetes and cardiovascular disease. We also wanted to investigate how a predisposition to diabetes, if untreated, would impact pregnancy outcome.

In the first studies it has been demonstrated that many women with diabetes had hyperglycaemia related complications during their preceding pregnancies. One could speculate that GDM has historically been an underdiagnosed condition. Since the women in Paper I-III were not routinely assessed for gestational diabetes, the natural course of the disease for more than a decade after pregnancy, could be assessed. Also, in most cases in this study there is no intervention during pregnancy that could bias the results. The risk of developing type 2 diabetes after a GDM pregnancy is high. Abnormal glucose tolerance is found in up to 60-70% (37, 184) after approximately a decade. It is therefore reasonable to assume that the women who had developed diabetes in this study, had hyperglycaemia or "prediabetes" during preceding pregnancies, and might have been diagnosed with GDM if they had been screened. The highest risk of future diabetes and cardiovascular disease was found in the group with a high BMI at the start of pregnancy. Gestational weight gain did not have any impact on future diabetes or cardiovascular disease. If any intervention during or after pregnancy would have reduced the women´s risk of diabetes can only be speculative. We also demonstrated that a predisposition for diabetes have negative impact on pregnancy outcome and when combined with overweight or obesity it synergistically increases the frequency of LGA infants, caesarean section and low Apgar scores in the infant.

Complications during pregnancy in women who develop diabetes.

In Paper I the women with a proposed stage of "prediabetes" had more complications during their preceding pregnancies. It was especially notable that they had a higher prepregnancy BMI, that correlated with the higher birth weight of the infants and this is in agreement with other studies that show that a high prepregnancy BMI causes a high infant birth weight (97, 100, 105, 106). A high frequency of LGA, supports the postulation that these women with a predisposition for diabetes, had hyperglycaemia during their pregnancies, but the high frequency of LGA could also be attributed the higher BMI in the women.

A lower weight gain is previously shown to reduce the risk of LGA infants in a population without diabetes (97). However, in this study it was these women with the lowest weight gain that had the highest risk of LGA and macrosomia, despite a shorter gestational length. Since LGA is a well-known complication to hyperglycaemia during pregnancy, one could speculate that the low weight gain among these women did not fully compensate the negative effect of "pre-diabetes" in pregnancy.

Although the reasons for caesarean section could not fully be analysed in this paper, there was a higher frequency of caesarean section in the "pre-diabetes" group. A significantly shorter gestational length in the group with a predisposition to diabetes is indicative of complications in late pregnancy and perhaps even an indication of induction of labour. The higher frequency of caesarean section could add to the surmise that there were complications in late pregnancy. Bearing in mind that the women had not been diagnosed with GDM or type 2 diabetes during pregnancy there is no reason to believe that caesarean section was due to active intervention due to known diabetes. However, the detection of a macrosomic infant could be a reason for (premature) induction of labour or caesarean section in this context. In the logistic regression analysis for caesarean section in general it was noted that maternal weight, prematurity and a small infant were the major risk factors for caesarean section and not a predisposition for diabetes. Since prematurity is associated with a risk of small infants and hyperglycaemia is associated with a risk of large infants, a logistic regression is probably not the best method for estimating the effect of hyperglycaemia.

The Apgar scores, as a measurement of the wellbeing of the infant, were lower in the group of women with GDM or later type 2 diabetes. This is additional indication that there were complications during delivery. In the logistic regression analysis, the prepregnancy BMI, GDM or later type 2 diabetes, a low birth weight and a short gestational length were all risk factors for a low Apgar score. However, only low birth weight and short gestational length were the dominating risk factors for a sustained low Apgar score.

BMI and GWG in the relation to the risk for future diabetes and other diseases

In Paper II we demonstrated a six-fold increase in the risk of developing diabetes and a two-fold risk in developing cardiovascular disease if the woman was overweight at the time of her first pregnancy. As one could have surmised, there was also a huge increase in the risk of obesity 10-17 years after pregnancy. Since the IOM recommendation for GWG for obese women is a very restricted weight gain, even a very small weight gain can be categorised as being excessive. Several studies have shown that a high GWG often leads to a high weight retention and the inability for the woman to regain her previous prepregnancy weight and increasing risk of obesity (113, 115). Additionally, multiple pregnancies increase the risk of developing type 2 diabetes (185) and weight retention and increasing overweight between pregnancies may partly explain this. The impact of a excessive gestational weight gain and its effect on future disease is debated

(112, 114, 137, 169, 186, 187). However, in paper II, GWG did not seem to have any impact on diabetes or cardiovascular disease later in life.

In obese and overweight women, pregnancies and deliveries are more often associated with hypertension, preeclampsia and gestational diabetes, and higher frequency of infants that are large for gestational age (188). It is also known that the GWG imposes different risk of adverse pregnancy outcome depending on the women´s initial BMI, hence the IOM recommendations for GWG in different BMI classes (189).

The increased risk of a high GWG on weight retention after pregnancy is well documented, but the risk on future disease in understudied. Since GWG often seems to be the culprit for weight retention and future obesity (115), a reduction of GWG would supposedly reduce the risks. Sadly, studies on lifestyle and diet interventions during pregnancy to minimize GWG have not shown a significant impact on preventing GDM(190). When one takes into account that the women who develop GDM have a high risk of diabetes even before pregnancy starts, it might not be surprising that the life style interventions and efforts done during the short period of a pregnancy might be insufficient to impact the risk factors that the woman have collected during many years prenatally. In addition, IFG or IGT might have been present even before pregnancy but to date, there is no test during pregnancy that can differentiate if this is the case.

In this thesis, however (as demonstrated in Paper II), it was the women with overweight and obesity, with the lowest mean weight gain, who had the highest risk for future disease. This is supported in a study by McClure et al where they could not demonstrate any impact of GWG on cardiometabolic risk factors, as blood pressure, lipids and glucose levels, eight years after pregnancy (191). It is possible that the weight gain during pregnancy is of minor importance in women with overweight (and possible pregestational metabolic disturbance) when considering their risk of future cardiovascular disease.

The conclusion is that a high BMI in young age is harmful for the woman's future health. GWG can have an effect on the future risk for overweight and obesity (192), but a metanalysis concludes that weight retention after pregnancy occurs irrespectively if the woman had a GWG within or above the IOM recommendations (193). Many studies concur that interventions regarding overweight and obesity would have the most effect if conducted before pregnancy (191). One can speculate that prenatal interventions would also have the greatest effect on the child´s and the father´s future health and be most beneficial for the whole population.

In this thesis, the future risk of disease in women with a high BMI before pregnancy is elevated. If OGTT during pregnancy is the best marker for cardiovascular risk in these young women, is still uncertain. To date there is no method or test available during pregnancy or postnatally to evaluate the woman´s risk for cardiovascular disease.

However, many studies have been made to assess biomarkers for future risk of disease (194-196).

The synergistic effect of BMI and a predisposition for diabetes on the risk for adverse pregnancy outcomes

The well-known risks of pregnancy in overweight women, are augmented if the women at the same time have GDM. The question has been raised whether GWG, being overweight before pregnancy and GDM are equal risk factors for LGA births and complications during delivery. A study of a Swedish cohort showed that both normal weight women with GDM and overweight women without GDM had similar risks of LGA-infants and caesarean section (197, 198). Both a high GWG and a high prepregnancy BMI increases the risk of delivering LGA infants (104, 199). In a previous study by Black et al, the risk for adverse pregnancy outcome in women who were overweight was even higher in women who at the same time had GDM (90). With this in mind, we have shown that overweight women with only a predisposition for developing diabetes have a higher risk of poor pregnancy outcome compared to women who are only overweight or obese. In conclusion, there is a synergistic effect of obesity and a predisposition for diabetes and the women with both risk factors have the poorest outcome.

Women with predisposition to diabetes had a more than three times higher frequency of LGA than women without predisposition to diabetes. If the woman had both a predisposition to diabetes and overweight there was an almost eight times higher frequency of LGA, compared to normal weight controls. Our findings are in line with a metanalysis where obese and overweight women had a higher risk of LGA infants, regardless of their GWG compared to normal weight controls. Additionally, in this study the risks increased with increasing weight gain (199).

In our study, the highest risk for caesarean section was seen in the group with overweight women and in women with a predisposition for diabetes. This group had the lowest GWG which contradicts previous studies where a high weight gain increases the risk of caesarean section (118, 200). In our study the GWG in the overweight women was low but still above IOM recommendations, which might explain why the beneficial effect of a low weight gain was not observed.

The impact of treatment modality and demographics on pregnancy outcome

There are many factors that impact pregnancy outcome. When measuring treatment success as improved mean blood glucose among the pregnant women, we are only analysing one aspect of a multifactorial treatment. The patient characteristics and ethnicity as well as treatment modality impact the pregnancy outcome. We did not measure the impact of our dietician´s advice or how often health care personnel

recommended physical activity, and this of course may also have an impact on the pregnancy outcome.

In Paper IV we observed that the mean blood glucose among the women with GDM had decreased over the years we studied. Therefore, a better outcome of pregnancy regarding macrosomia and LGA was expected. However, we were not able to demonstrate that.

There are contradicting reports regarding the impact of glucose excursions in gestational diabetes on adverse pregnancy outcomes, such as macrosomia and caesarean section. There are reports of both nonsignificant effect on caesarean section and reports on a better outcome when limited glucose excursions and a low SD of glucose measurements is achieved (128, 129).

It is clear, that there is a shift in treatment traditions in our clinic, with more metformin and less insulin treatment for GDM. If this will have an impact on the women´s (or the children´s) future health remains to be studied. The reason for the significantly lower glucose levels at the OGTT-screening in 2016-2017 compared to 2012-2013 is not easy to explain. The screening procedure had not changed between the two periods. Perhaps the women in the cohort of period 2 had a milder form of GDM, but this is only guess work and does not explain the results. If the women had a milder form of GDM a better outcome of pregnancies would be expected regardless of treatment, but this was not seen in this study.

Previously it has been shown that treatment modality may in some regard impact the delivery. Treatment with metformin may increase the risk of preterm delivery and treatment with insulin may increase the risk of LGA and postnatal hypoglycaemia but it does not seem to impact Apgar scores or mode of delivery (201, 202). We did not find any of these effects in our study, since it was underpowered to detect differences in pregnancy outcome in the women with GDM, who was already being well taken care of at our clinic.

In our changing world, migration will have an impact on the treatment of GDM. It is known that GDM in different ethnic groups have different impact on the risk for pregnancy complications as well as postnatal risk for diseases (203, 204). It is therefore wise to be aware of the demographic changes in the patient population when organizing health care for pregnant women. The treatment of GDM and the organisation of Maternity Care, might have to adapt to these demographic changes as well as new scientific evidence regarding treatment of GDM. There are still several different authorities with different opinions and recommendations regarding the best and most efficient diagnostic approach and treatment of GDM (52, 54, 55, 205). FIGO acknowledges that the organisation of care might not follow the same model worldwide, and in some instances, there is rational for settling for health care that is "good-enough" (156).

Despite the inability to show any difference in pregnancy outcome in Paper IV, our results may still be considered as treatment is successful with maintained excellent outcome for the women with gestational diabetes at our clinic.

There are some limitations to the studies included in this thesis. BMI measurements are made to assess if a person is of appropriate weight depending on the persons length. This is an important measurement in several of the studies, since it impacts the interpretation of the results if the woman was of normal weight or not. In Paper I-III, there is missing data regarding BMI. In many cases this is due to lack of data regarding height. We have tried to extract data regarding height from different datasets at our disposal, but there was still substantial lack of data. We did several assessments of women with known BMI and unknown BMI and concluded that the lack of data is random.

In the MISS-cohort there are several data that are based on self-reported data. Since the original study was done to investigate risk factors for melanoma the women´s self-reported answers are likely given in this context and not as answers to questions regarding their pregnancies and weight status. This might have influenced the answers given.

This study did not analyse blood glucose and there were no data regarding blood glucose or OGTT to diagnose GDM during pregnancy. From data in the SMBR it can be deducted that 12 women were considered to have gestational diabetes. This accounts for 0.04% of the total number of pregnancies. It can therefore be assumed that women with GDM or IGT during pregnancy had often been undetected at the time of the study, and a large proportion of these women developed diabetes later in life.

It is a retrospective study and the study does not investigate causality of different parameters or treatments on pregnancy outcome. However since the glycaemic status of the women was unknown to the caregivers there is also a chance to investigate the natural course of the "pre-diabetes" status, without any treatment bias of the results.

Since the start of this study (Paper I-III) and since the start of SMBR, the awareness of GDM have increased and screening for GDM has become more frequent. There has been continuing improvement of treatment of GDM. After the publication of the HAPO study there has been an effort all over the world to update the recommendations regarding screening and diagnostic criteria for GDM. With several treatment studies reporting on beneficial outcome of treatment of GDM and WHO changing the recommendations regarding diagnosing GDM, this condition has come more into focus. It is reasonable to believe that this have had an impact on the treatment of GDM and improved the outcome over the years. However, changes take time and the implementation of general screening for GDM is not yet fully embraced in Sweden. In addition, the follow up of women after GDM and treatment to avoid future disease, is sadly unobserved in Sweden. The National Board of Health and Welfare has given

recommendations for follow up after GDM, but these recommendations are very unspecific. Many women do not receive any follow up regarding diabetes risk or cardiovascular risk factors after a GDM pregnancy.

The study in paper IV was conducted at one clinic and the number of women is therefore small. Since the treatment of the population in 2012-2013 already was relatively successful and the frequency of complications was relatively low, it was difficult to detect differences in pregnancy outcome. The study design lack power to detect significant differences in the frequency of LGA and macrosomia, due to the relatively low number of women treated at our clinic during these time periods.

Another weakness of this study is lack of registered metformin dose and time of initiation of treatment. Since most women were diagnosed in the third trimester, it would be assumed that most women were treated with metformin during a maximum of 12 weeks. The choice of treatment was done at the diabetologist discretion, and the treatment was neither blinded nor randomized. Patient preference and clinicians´ individual assessments regarding patient´s compliance to treatment and expected treatment efficacy, undoubtedly affected the choice of treatment.

Previous studies have noted that there is a difference in pregnancy outcome in different ethnic groups. There is no data to distinguish the woman´s country of origin in this study, since we only divided the women in groups of Scandinavian and non-Scandinavian origin. There is also no data regarding the reason for doing a caesarean section in our study and was therefore not possible to analyse whether the indication for caesarean section was GDM-related or related to other complications.

To conclude, neglecting to diagnose GDM and neglecting to start treating risk factors have negative impact on pregnancy outcome. This thesis adds to the knowledge that general screening for GDM during pregnancy is beneficial for the pregnancy and probably for the woman´s future health. To reduce the risk of future disease it is beneficial for the woman to be of normal weight before pregnancy. If intervention during or after pregnancy can reduce the risk of diabetes or cardiovascular disease for these women will hopefully be thoroughly studied in the future.

Conclusions

➢ Women who develop diabetes later in life have a higher frequency of hyperglycaemia related adverse pregnancy outcome earlier in life.

➢ Women with a high BMI at the beginning of pregnancy have a high risk of developing obesity, as well as diabetes and cardiovascular disease later in life. A high gestational weight gain does not have any impact on the future risk of these diseases.

➢ Pregnancies in women with a predisposition for developing type 2 diabetes have an increased risk of macrosomia. If the woman is also overweight, this synergistically increases the frequency of LGA. If the woman has both risk factors there is an almost eight times higher frequency of LGA, compared to normal weight controls.

➢ Over the years the metabolic control among women with GDM in our clinic in Lund has improved with a maintained favourable pregnancy outcome, despite more frequent use of metformin and substantially less use of insulin treatment. The frequency of women with GDM of non-Scandinavian origin or with a first degree relative is increasing.

Future Research

In paper IV the demographic changes in Sweden was reflected by a higher proportion of women with non Scandinavian origin. It would be interesting to do future studies on the women from this cohort and include women with GDM at our clinic from 2015-2016. With a long follow up of a decade or more it would be possible to assess to what extent these women have developed diabetes mellitus or cardiovascular events and compare the risk for future cardiovascular disease in different ethnicities. It would be possible to investigate if the women have benefitted from our general screening and treatment of GDM during their preceding pregnancy in regard to earlier detection and treatment of diabetes and cardiovascular risk factors, as well as reduction of cardiovascular events, with the MISS-cohort as a comparative group. It would be interesting to compare the women´s individual lifestyles to women who did not have GDM during their pregnancy. Has the information given by the Maternal Health Care Unit and the diabetologist been able to improve the woman's lifestyle and future health even after pregnancy?

One group of women, who has not been addressed in this thesis but are equally treated in the same Maternal Health Care Unit in Lund, are the women with gastric bypass surgery before pregnancy, who are considered to have GDM during their pregnancy. These women have been obese before pregnancy but are at the time of pregnancy often of normal weight. Since obesity is a risk factor for diabetes and cardiovascular disease it would be interesting to explore the risk of diabetes and cardiovascular disease in these women and compare it to the risk of normal weight women with previous GDM. Do they have the same risk for future cardiovascular disease as women with GDM? Does treatment during pregnancy have any impact on pregnancy outcome or the future risk for disease? The group of women with gastric bypass surgery is increasing and their future risk after pregnancy merits further studies.

"Share your ideas. Don´t take for granted your education. Rejoice in what you learn, and spray it"

Tim Minchin

Populärvetenskaplig sammanfattning

I Sverige kompliceras 2-3% av alla graviditeter av graviditetsdiabetes. Olika graviditetshormoner leder till en minskad känslighet för det kroppsegna insulinet. Detta sker normalt under alla graviditeter, men om insulinproduktionen inte ökar i motsvarande grad, så stiger blodsockernivåerna. Graviditetsdiabetes diagnosticeras med hjälp av s.k. glukosbelastning och blodprovstagning. Kvinnan har vanligtvis inga symptom. Graviditetsdiabetes ökar risken för olika komplikationer som bl.a. kejsarsnitt och havandeskapsförgiftning. Graviditetsdiabetes ökar också risken för att få stora barn, vilket kan komplicera graviditet och förlossning. På senare år har man kunnat fastställa att behandling som normaliserar blodsockret under graviditeten minskar risken för graviditetskomplikationer. Graviditetsdiabetes behandlas med kost- och livsstils-förändringar och om läkemedelsbehandling krävs används insulin i första hand, men även olika per orala diabetesmediciner kan vara aktuella.

De flesta kvinnor får helt normala blodsocker direkt efter förlossningen. Det kvarstår dock en kraftigt ökad risk för att insjukna i typ 2 diabetes och hjärtkärl-sjukdom i framtiden. Risken för kvinnor som haft graviditetsdiabetes är 7 gånger högre än för kvinnor som inte haft graviditetsdiabetes. Upp till 70% av alla kvinnor med graviditetsdiabetes kommer att insjukna i typ 2 diabetes någon gång i livet. Man har också noterat att risken att drabbas av hjärtkärlsjukdom är dubbelt så stor även om kvinnan inte utvecklar typ 2 diabetes.

Eftersom förhöjda blodsocker innebär en ökad sjukdomsrisk för kvinnan både under och efter graviditet, rekommenderas en screening med glukosbelastning för att diagnosticera och behandla eventuell graviditetsdiabetes. Detta är dock ännu inte standard på alla mödravårdsenheter, i vare sig Sverige eller i världen. Det finns också rekommendationer kring uppföljning av riskfaktorer för hjärtkärlsjukdom och diabetes efter avslutad graviditet, men detta är inte implementerat i svensk sjukvård.

Denna avhandling består av fyra delarbeten.

I **Arbete I-III** har vi använt oss av en stor populationsbaserad databas med ca 30 000 kvinnor från södra sjukvårdsregionen, som deltagit i en studie om riskfaktorer för malignt melanom, Vi har från denna studie plockat ut de kvinnor som fött barn mellan 1973 och 2005 och hämtat data angående förlossningsutfall från Medicinska Födelseregistret. Graviditeter hos kvinnor som senare i livet drabbades av typ 2 diabetes studerades avseende graviditetskomplikationer och jämfördes med förlossningsutfallet

hos dem som aldrig utvecklade diabetes. Hos kvinnor med en predisposition för diabetes fann vi samma sorts komplikationer som man normalt ser vid graviditetsdiabetes. Kvinnorna som senare i livet insjuknade i typ 2 diabetes födde större barn och förlöstes oftare med kejsarsnitt jämfört med kvinnor som inte fick typ 2 diabetes.

Vi undersökte också faktorer under graviditet, som talade för en högre risk att insjukna i olika sjukdomar 10–17 år efter förlossningen. Kvinnor som var överviktiga under graviditeten hade mer än sex gånger ökad risk för diabetes efter graviditet och mer än 2 gånger ökad risk för hjärtkärlsjukdom 10–17 år efter graviditeten, jämfört med normalviktiga. Viktuppgång under graviditet påverkade inte risken för dessa sjukdomar senare i livet.

Förlossningsutfallet hos dem som senare i livet utvecklade diabetes typ 2 och som samtidigt var överviktiga under graviditeten jämfördes med förlossningsutfallet hos dem som senare utvecklade diabetes men var normalviktiga under graviditet. Att vara både överviktig och ha en predisposition för diabetes ökar synergistiskt riskerna för ett sämre förlossningsutfall med större barn och ökad risk för kejsarsnitt. I dessa studier såg vi genomgående att de kvinnor som hade högst BMI hade den lägsta viktuppgången under graviditet. Kvinnor med både övervikt och en predisposition för diabetes hade den lägsta viktuppgången, men hade en 8 gånger ökad risk att föda ett stort barn jämfört med normalviktiga kvinnor som inte utvecklade diabetes.

I **Arbete IV** jämfördes förlossningsutfall hos kvinnor med konstaterad graviditetsdiabetes som behandlades på Specialistmödravården i Lund 2012–2013 och 2016–2017. Under dessa två tidsperioder förändrades delvis behandlingsstrategier för gestationell diabetes och så även befolkningsdemografin i vårt upptagningsområde. Andelen kvinnor med ärftlighet för diabetes och andelen kvinnor med icke-skandinaviskt ursprung hade ökat mellan tidsperioderna. Vi såg att användandet av insulin hade minskat och metformin (tablettbehandling) förskrevs i större utsträckning. Medelblodsockernivåerna var bättre under den senare tidsperioden. Förlossningsutfallet var oförändrat mellan de två tidsperioderna.

Konklusionen är att kvinnorna i Arbete I-III sannolikt hade ett förstadium till diabetes eller regelrätt graviditetsdiabetes som man hade missat att diagnosticera och behandla. Både övervikt och förstadium till diabetes är likvärdiga riskfaktorer för ett sämre förlossningsutfall. Den största risken för diabetes och kardiovaskulär sjukdom i framtiden är övervikt i samband med graviditet. I Arbete IV kan man konkludera att demografin har förändrats på kort tid och att vi har lyckats förbättra blodsockret och bibehålla ett gott behandlingsresultat hos kvinnor med graviditetsdiabetes, trots minskad användning av insulin.

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