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Type 1 diabetes in Pregnancy – Perinatal outcome

with special reference to fetal macrosomia

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Stockholm 2012

Published by Karolinska Institutet.

ISBN 978-91-7457-691-7

Printed by
REPROPRINT AB
Stockholm 2012
www.reproprint.se
Gårdsvägen 4, 169 70 Solna

SUMMARY

The aim of this epidemiological study was to elucidate whether in recent years, obstetric and perinatal outcomes in pregnancies complicated by type 1 diabetes (T1DM) have improved or not. The objective was also to identify possible risk factors for adverse outcome for the mother, fetus and the newborn. All studies (I-IV) included in this thesis were based on national data from the Swedish Medical Birth Registry, during the time period 1991-2007.

In 5,089 type 1 diabetic pregnancies and 1.2 million controls we found significantly increased risks of all adverse outcomes in women with T1DM: adjusted odds ratios: severe preeclampsia: 4.47 (3.77-5.31), Caesarean delivery: 5.31 (4.97-5.69), stillbirth: 3.34 (2.46-4.55), perinatal mortality: 3.29 (2.50-4.33), major malformations: 2.50 (2.13-2.94) and large for gestational age: LGA (birth weight ≥ +2 SD): 11.45 (10.61-12.36) (study I).

The markedly elevated odds of an LGA outcome inspired us to characterize in more detail the distribution of birth size in a large national cohort of T1DM offspring (study II n=3,705) and to investigate if disproportionate body composition was associated with increased risk of perinatal complications (study III n=3,517). Percentiles for birth weight (BW), birth length (BL) and head circumference (HC) were formed based on data from non-diabetic pregnancies and standard deviation scores (SDS) were calculated for BW, BL and HC. The ponderal index (PI: BW in grams/(BL in cm) ^{3} was used as a proxy for body proportionality and fat mass and we defined disproportionate/overweight LGA as infants with a BW and PI ≥90^{th} percentile for gestational age and gender.

The distributions of BW, BL and HC were all unimodal but significantly shifted to the right of the normal reference. The distribution for BW was most markedly shifted to the right. 47% were LGA with a BW ≥90^{th} adjusted percentile. The mean ponderal index (PI) was significantly increased and 46% of LGA infants were disproportionate with a PI ≥90^{th} percentile and thus overweight at birth. A novel and unexpected finding was that fetal macrosomia was more pronounced in preterm and female infants (study II). Surprisingly, neonatal outcome was independent of body proportionality in appropriate for gestational age (AGA) and LGA infants. The risk of adverse outcome was significantly increased in LGA compared with AGA infants born at term (study III). There was a significant interaction between gestational age and body weight with prematurity overriding LGA as a risk factor for neonatal morbidity in moderately preterm infants.

In study IV, we examined the risk of adverse outcome in relation to pre-pregnancy body mass index in a national cohort of 3,457 T1DM pregnancies compared to 764,498 non-diabetic pregnancies. Maternal overweight/obesity increases the risk of adverse outcome in both women with and without T1DM. Within the T1DM cohort, obesity was associated with increased odds of major malformations adjusted OR: 1.77 (1.18-2.65) and preeclampsia adjusted OR: 1.74 (1.35-2.25). T1DM was a significant effect modifier of the association between BMI and major malformations, preeclampsia, LGA and neonatal overweight.

Conclusion: In spite of major improvements in the management of type 1 diabetic pregnancies over the years, the present findings clearly demonstrate that T1DM pregnancies still are associated with significantly increased risk of adverse outcomes. An important observation is the rising incidence of LGA infants, which partly can be attributed to a concomitant increase in maternal BMI. This development is worrying as LGA infants face an excess risk of both perinatal and future complications as compared to normal sized infants. The novel and unexpected finding of a gender difference in fetal macrosomia requires further investigations.

SAMMANFATTNING

Syftet med denna epidemiologiska analys var att jämföra obstetriskt och perinatalt utfall mellan graviditeter komplicerade av typ 1 diabetes (T1DM) och graviditeter utan T1DM. Syftet var också att identifiera potentiella riskfaktorer för maternella, fetala och neonatala komplikationer. Samtliga studier (I-IV) i denna avhandling är baserade på nationella data från Svenskt Medicinskt Födelseregister och omfattande åren 1991-2007.

I ett nationellt material omfattande 5089 T1DM graviditeter och 1.2 miljoner kontroller fann vi signifikant ökad risk hos kvinnor med T1DM för: (odds kvoter) svår preeklampsi:4,47 (3,77–5,31), kejsarsnitt: 5,31 (4,97–5,69), intrauterin fosterdöd: 3,34 (2,46–4,55), perinatal mortalitet: 3,29 (2,50–4,33), allvarlig missbildning: 2,50 (2,13–2,94) och LGA (large for gestational age: födelsevikt ≥ +2 SD över medelvärdet): 11,45 (10,61–12,36), (studie I).

Den kraftigt förhöjda risken för ett LGA utfall inspirerade oss att i närmare detalj karaktärisera distributionen av storlek vid födelsen i en stor, nationell T1DM cohort (studie II n= 3705) och att analysera om avvikande kroppsproportioner ökar barnets risk för komplikationer i nyföddhetsperioden (studie III n=3517). Percentiler för födelsevikt (FV), födelselängd (FL), huvudomfång (HO) samt ponderal index (PI=FV i gram/(FL i cm) ^{3} skapades baserat på data från graviditeter utan maternell T1DM. Standard deviation scores (SDS) beräknades för FV,FL och HO. Ponderal index användes som ett mått på kroppsproportionalitet och fettvävsmassa. Oproportionerlig LGA/neonatal övervikt definierades som FV och PI ≥90 percentilen för gestationsålder och kön.

Distributionen av FV,FL och HO var samtliga normala men signifikant högerförskjutna om referens populationen. Distributionen för FV var mest uttalat högerförskjuten om referensen. 47 % av barnen i diabetes cohorten var LGA med en FV ≥90 percentilen för gestationsålder och kön. Medelvärdet för PI var signifikant ökat i T1DM cohorten och 46 % av LGA barnen var oproportioneliga/överviktiga med PI ≥90 percentilen. Ett nytt och intressant fynd var att fetal makrosomi var mer uttalad hos flickor än hos pojkar, liksom hos för tidigt födda barn jämfört med fullgångna. Ett oväntat fynd var att risken för perinatala komplikationer inte skiljde sig åt mellan proportioneliga och oproportioneliga LGA barn. Däremot var risken för perinatala komplikationer signifikant ökad hos LGA jämfört med normalviktiga barn födda i fullgången tid. Gestationsålder var en signifikant effektmodifierare av associationen mellan kroppsvikt och perinatala komplikationer.

I studie IV undersökte vi risken för negativt graviditetsutfall i relation till moderns pre-gravida body mass index (BMI) i en nationell cohort om 3457 T1DM graviditeter och jämfört med 764,498 graviditeter till mammor utan diabetes. Maternell övervikt/obesitas ökar risken för negativt graviditetsutfall både hos kvinnor med och utan T1DM. Hos kvinnor med T1DM, var obesitas associerat med en signifikant ökad risk för allvarlig missbildning OR: 1.77 (1.18–2.65) och preeklampsi OR: 1.74 (1.35–2.25) jämfört med en normalviktig kvinna med T1DM. T1DM var en signifikant effektmodifierare av associationen mellan BMI och allvarlig missbildning, preeklampsi, LGA och neonatal övervikt.

Konklusion: Trots stora framsteg i det medicinska omhändertagandet av gravida kvinnor med T1DM, visar resultaten av dessa studier att graviditet vid T1DM fortfarande är förenat med klart ökad risk komplikationer. En viktig observation är den ökande incidensen av LGA barn, vilket delvis kan tillskrivas en samtidig ökning av maternellt BMI. Denna utveckling är oroande då dessa barn har en ökad risk för både perinatala komplikationer och framtida sjuklighet. Det oväntade fyndet av en könsskillnad i LGA förekomst kräver närmare analys.

LIST OF CONTENTS

LIST OF ABBREVIATIONS

T1DM	Type 1 diabetes
HbA1C	Haemoglobin A1C
CSII	Continuous subcutaneous insulin infusion
MDI	Multiple daily injections
ICD	International classification of diseases
LGA	Large for gestational age
SGA	Small for gestational age
HT	Hypertension
PE	Preeclampsia
PIH	Pregnancy induced hypertension
CHD	Chronic hypertensive disorders
CS	Caesarean section
BMI	Body mass index
IUFD	Intrauterine fetal death
PMR	Perinatal death
OR	Odds ratio
Adj. OR	Adjusted Odds ratio

LIST OF PAPERS

This thesis includes the following papers:

I. **Persson M**, Norman M, Hanson U. Obstetric and Perinatal Outcomes in Type 1 Diabetic Pregnancies. Diabetes Care, 2009; 32:2005-2009

II. **Persson M**, Pasupathy D, Hanson U, Norman M. Birth Size Distribution in 3,705 Infants Born to Mothers with Type 1 Diabetes. Diabetes Care, 2011; 34:1145-1149

III. **Persson M**, Pasupathy D, Hanson U, Norman M. Disproportionate body composition and perinatal outcome in large for gestational age infants to mothers with type 1 diabetes. BJOG, 2012, published online 3 Feb 2012, ahead of print

IV. **Persson M**, Pasupathy D, Hanson U, Westgren M, Norman M. Pre-pregnancy body mass index and the risk of adverse outcome in type 1 diabetic pregnancies- a population-based cohort study. BMJ Open, 2012:2: i 000601

BACKGROUND

Type 1 diabetic pregnancies (T1DM) are associated with increased risk of obstetric and perinatal complications, including preeclampsia, perinatal mortality and major malformations [1-11]. T1DM offspring are also at increased risk of perinatal hypoxia, preterm delivery, fetal macrosomia, birth trauma, respiratory disorders, postnatal hypoglycaemia, polycytaemia, hyperbilirubinaemia as well as neonatal and infant death [2, 11-19] , see table 1. Over the last decades, following the introduction of tight glycaemic control before and during pregnancy, outcomes of T1DM pregnancies have improved significantly. The rate of perinatal mortality has decreased from 30% in the 1950´s to 1-4% in recent years [20]. The introduction of self monitoring of blood glucose and measurement of Hba1c in the 1980´s has contributed significantly to this favourable development. Other important contributing factors are improvements in fetal monitoring, obstetric and neonatal care.

In 1989, representatives from government health departments and patient organizations met with diabetologists in St Vincent, Italy at a meeting held by WHO and the international diabetes federation in Europe. They agreed on a set of recommendations and plans for the prevention, identification and treatment of diabetes and its complications. The St Vincent declaration stated a goal to within a 5 year period "achieve a pregnancy outcome in the diabetic woman that approximates that of a non-diabetic woman" [21].

In spite of major advances in the clinical care, reported rates of adverse outcome in T1DM pregnancies from recent years remain significantly increased; with a four to five fold increased risk of preeclampsia, stillbirth and preterm delivery [3, 5, 15]. The incidence of fetal macrosomia remains high, in spite of apparently good metabolic control [22-24]. Thus, the goal set by the St Vincent declaration is still far from being met, at least not at a population level. There are however, centres of excellence that have reported favourable data on perinatal outcome in T1DM pregnancies [24]. It should be noted that the majority of reports on outcome of T1DM pregnancies are based on limited numbers of patients, ranging between 273 and 1,700, table 1. Furthermore, results from these studies do not necessarily reflect the outcome of the general T1DM population.

Population-based data on pregnancy outcome in T1DM are scarce. Given the relatively low incidence of some complications, for instance stillbirth and birth trauma, large sample size is needed for accurate risk estimation. Population based data are essential for robust estimates of complication rates, for assessing trends and the influence of management programs as well as for planning of health care and patient counselling. This thesis is a national study on more than 5,000 pregnancies complicated by T1DM. The primary aim was to present solid risk estimates of obstetric and perinatal complications in T1DM pregnancies and to investigate risk factors for adverse pregnancy outcome.

Before discussing these studies in more detail it is appropriate to give a brief historical background and an overview of maternal and perinatal complications associated with pregnancies complicated by type 1 diabetes.

Table 1. Pregnancy outcome in women with type 1 diabetes.

First Author	Hanson	Cnattingius	Väräsmääki	Jensen	Evers	Platt	Penney	Casson	McIntsosh	Research group	Murphy
Setting	Sweden	Sweden	Finland	Denmark	Holland	UK	UK	UK	UK	France	UK
Study design	Pop.-based	Nationwide	Nationwide	Pop.-based	Nationwide	Regional	Pop.-based	Pop.-based	Pop.-based	Pop.-based	Pop.based
Time period	1982-1985	1983-1986	1991-1995	1993-1999	1999-2000	1995-1999	1998-1999	1990-1994	2002-2003	2000-2001	2006-2009
Number of T1DM	491	914	954	990	323	547	273	355	1707	289	408
Outcomes											
Stillbirth	2.1	1.3	0.94	2.1*	-	3.01	1.85	2.5	2.58*	1.4	1.5
Perinatal mortality	3.1	-	1.5	3.1	2.8	4.3	2.78	3.6	3.17	6.6	2.4
Malformations	-	3.8	-	5.0	8.8	9.0	6	-			
Major malformations	-	-	-	-	4.2	-	-	9.4	4.8	4.5	4.2
Preeclampsia/PIH	20.6	-	-	18.1	12.7	-	-	-	-	18.7	7.8
Cesarean section	45.2	46	63.5	55.9	44.3	-	-	-	-	-	63.5
Preterm delivery	24.6	24	29.6	41.7	32.3	-	-	-	-	-	37.1
Birth weight Z score	-	-	-		-	1.30	-	1.38	-	-	
LGA > 90th percentile	-	-	-	62.5	45.1	-	-	-	-	-	52.9
LGA > + 2SD	20	17.7	34.7	-	-	-	-	-	-	-	35.7
SGA< 10th percentile	-		-	-	-	-	-	-	-	-	
SGA < - 2SD	1.0	2.1	1.5	-	-	-	-	-	-	-	
RDS of the newborn	1.6	-	-	17.1	5	-	-	-	-	10.6	
Jaundice	16.3	-	-	18.1	25			-	-	-	
Neonatal mortality	-	-	-	-	-	-	-	-	0.94	-	0.9
Infant mortality	-	0.9	-	-	-	1.6	-	1.99	-	-	

*Defined as fetal death >24 gestational weeks

TYPE 1 DIABETES AND PREGNANCY IN THE PAST

Before the discovery of insulin, very few women with diabetes succeeded to conceive and if they did so, pregnancy outcome was often poor. In the early 1900´s, maternal and perinatal mortality rates in diabetic pregnancies approached 50 and 70%, respectively [25].

The turning point came in 1922 when Banting and Best first succeeded to extract insulin from a dog and to treat a patient with T1DM. The first report of a diabetic pregnancy successfully managed with injections of insulin, came from London in 1924. Both mother and child survived. However, in spite of the introduction of insulin, complication rates in type 1 diabetic pregnancies remained high. The perinatal mortality rate in the 1940´s was still around 40% in pregnancies complicated by diabetes [26].

The first attempt to classify diabetes in pregnancy was introduced by Priscilla White in 1949. This classification system, including 7 different classes, was based on both duration of diabetes and the presence of complications (White class A: gestational diabetes, White class B: onset after 20 years of age, White class C: onset before 20 years of age, White class D: duration > 20 years and benign retinopathy, White class E: nephropathy, White class R: proliferative retinopathy, White class G: cardiac involvement). This classification system was accepted worldwide and was used for many decades for categorization of pregnant women with diabetes. The uniform classification system enabled meaningful comparative evaluations of perinatal outcome between different studies. The White´s classification was also helpful in the clinical work, making it possible to already at the first antenatal visit classify the patient as of high or low risk.

The Pedersen hypothesis

In 1952, Dr Jorgen Pedersen in Copenhagen introduced the concept that maternal hyperglycaemia leads to fetal hyperglycaemia and hyperinsulinaemia with potential harmful effects on the fetus [27]. This hypothesis, known as the Pedersen hypothesis, has been of great clinical importance and has helped clinicians and patients to understand the great importance of blood glucose regulation in pregnancy.

In 1959, Gellis et al stated that one of the most important prognostic factors for the fetus was maternal glucose control [28]. Even though many authors agreed on the importance of reaching a “reasonable” glucose level, there was no consensus regarding which level.

The importance of striving towards *normoglycaemia* during pregnancy was demonstrated in a thesis by Moller from Sweden in 1970. She compared pregnancy outcome between diabetic women receiving traditional pregnancy care (n=27) and women who were subject to “intensive care” (n=47), based on three key principles; keeping maternal blood glucose levels as close to normal as possible, early detection and treatment of pregnancy complications and avoidance of preterm delivery. The rate of adverse outcome was significantly lower in the intensively treated group compared with the group who received traditional care [29]. Unfortunately, this important study received little attention at the time as it was not published in any international medical journals.

The impact of maternal glycaemic control for the outcome of diabetic pregnancies was also demonstrated in a retrospective study by Karlsson and Kjellmer in 1972 [30]. The rates of perinatal mortality, major malformations and neonatal morbidities were all significantly lower in infants to mothers with a mean daily glucose level of < 5.5 mmol/ litre during the last

weeks of pregnancy compared with mothers with a mean glucose level above 5.5 mmol/ litre during the same time period. At that time, techniques for monitoring of maternal glucose levels were limited. Blood glucose concentrations could only be measured in hospital and therefore pregnant diabetic women were admitted for inpatient care at least once in the first and second trimester and from around 32 weeks of gestation until delivery [30].

An important cornerstone in the history of diabetes was the introduction of self-monitoring of blood glucose and measurement of Hba1c in the early 1980´s. In a clinical trial from 1984, women with T1DM were randomized to either hospital care (n=46) or to self-monitoring of blood glucose at home (n=54) during the 32: nd to 36th week of gestation. There were no significant differences in mean glucose level or pregnancy outcome between the two groups [31]. The result motivated a change in the management of diabetic pregnancies towards out-patient care and self monitoring of blood glucose. The importance of a good team work around the patient for a favourable pregnancy outcome was early pointed out [32, 33] and has since remained an important feature in the clinical care of women with T1DM.

EPIDEMIOLOGY, ETHIOLOGY AND DEFINITION OF TYPE 1 DIABETES

Sweden has, next to Finland the highest incidence of type 1 diabetes in the world with a yearly incidence of 42 cases per 100,000 [34]. Besides the Scandinavian countries, high incidences of T1DM are also reported from Sardinia, the UK, Holland, Canada and the US. The incidence of type 1 diabetes varies in different populations between <1 to 50/100,100 per year with a yearly increase of about 3 % in most countries [35]. The incidence of T1DM in Sweden peaks at 12 years of age in girls and at 14 years of age in boys, with the highest incidence during the winter months. In a recent analysis from Sweden it was demonstrated that the incidence of type 1 diabetes is increasing with a shift towards younger age at onset. This finding has been suggested to reflect a static or decreasing incidence in older age groups and indicate changes in exposure of environmental factors in early life [34]. As a consequence, the prevalence of T1DM in pregnancy will increase over time. Presently, 0.4% of all pregnancies in Sweden are complicated by T1DM.

Type 1 diabetes (T1DM) is considered an autoimmune disease with beta cell destruction mediated by both T cells and autoantibodies [36]. Type 1 diabetes is characterized by absolute insulin dependency and very low to non-measurable levels of insulin and C peptide in the circulation. A fasting plasma glucose value above 7 mmol/ litre and or a random plasma glucose value exceeding 11mmol/ litre are consistent with the diagnosis according to the WHO criteria [37]. Autoantibodies against beta cell antigens and insulin can be detected. The strongest determinant of susceptibility to T1DM is the association with HLA antigens, in particular HLA-DQ2/HLA-DQ8 and HLA-DR3/HLA-DR4. However, the aetiology of T1DM is complex with environmental factors interacting with genetic determinants. These environmental factors can initiate and / or accelerate beta cell destruction. It is hypothesized that environmental insults may take place already in utero. Data from epidemiological studies on the general population have shown significant associations between high maternal age in pregnancy, preeclampsia, maternal viral infections in pregnancy (in particular enteroviruses), delivery by Caesarean section and the subsequent development of diabetes in the offspring [38, 39]. Other potential initiating factors could be high birth weight, rapid postnatal weight gain, nutritional factors and viral infections in infancy [40-44]. Experimental studies indicate that active beta cells i.e. insulin secreting cells are more vulnerable to autoimmune attacks than resting beta cells. Factors associated with increased demand on insulin production and secretion such as rapid growth or infections may potentiate the beta cell destruction.

HORMONAL AND METABOLIC CHANGES IN PREGNANCY

Normal pregnancy

Metabolic changes in pregnancy occur to enable a continuous supply of nutrients to the growing fetus [45]. In early pregnancy, increased insulin sensitivity facilitates maternal anabolism and fat accretion. Parallel with the growing feto-placental unit, maternal insulin sensitivity decreases with 50-70%. Insulin resistance in pregnancy is mediated by cortisol and placental hormones (i.e. placental growth hormone, human placental lactogen: HpL, progesterone, prolactin) and is most likely due to defect post insulin receptor signalling. Tumour necrosis factor has also been implied in mediating insulin resistance in pregnancy [45]. Insulin resistance is present in both maternal liver and peripheral tissues [46], facilitating nutrient transfer from the mother to the fetus [47].

Random capillary blood glucose tests range from 2.93-6.28 mmol/ litre in non-diabetic pregnancies [48]. The average fasting capillary glucose in non-obese, non diabetic women has been reported to be approximately 4.0± 0.3 mmol/ litre in the third trimester [49]. In normal pregnancies, the fasting glucose values decrease as the pregnancy proceeds. Overnight fast is associated with a mean blood glucose decrease of 0.5 mmol/ litre in pregnant women as compared with the non-pregnant state. The decrease in plasma glucose concentrations is mainly a reflection of increased insulin sensitivity in early pregnancy and later on due to increased maternal plasma volume and increasing glucose consumption of the growing placental-fetal unit. Concomitantly, the postprandial glucose concentrations increase as a result of decreased maternal insulin sensitivity. Overnight fast in pregnancy, as opposed to outside pregnancy, is also associated with significantly decreased levels of amino acids and increased concentrations of free fatty acids and keton bodies, a state known as “accelerated starvation in pregnancy” [50]. With prolonged starvation, the mother rapidly develops significant ketonemia. This metabolic adjustment is very similar to that seen in infants and small children who have a large brain to body ratio. This metabolic adjustment during starvation in pregnancy is of great biological significance as it guarantees the fetus´ supply of keton bodies of maternal origin that can replace glucose as energy substrate in the brain and be used for synthetic purposes.

Another interesting feature of the metabolic adjustment in pregnancy is the marked increase in maternal leptin levels [51]. Leptin is an important regulator of satiety and energy expenditure, acting via receptors in the hypothalamus. Leptin is mainly secreted by adipose tissue but is also synthesized in the gastric fundus, muscle, bone, placenta and several fetal tissues. By the 12^{th} week of gestation, maternal leptin concentrations are approximately 30% higher than outside pregnancy, with the placenta as the primary source. The primary role for leptin in pregnancy is not clear but it has been suggested that leptin enhances maternal and placental lipolysis, beneficial for the growing fetus.

Type 1 diabetic pregnancy

In pregnancies complicated by maternal T1DM, the same metabolic changes occur as in the non-diabetic woman [46, 47]. The increased insulin sensitivity in early pregnancy coincides with the period of pregnancy nausea in many patients, which may increase the risk of

hypoglycaemia. However, in a recent review it was concluded that pregnancy nausea was not a significant risk factor for hypoglycaemia in women with T1DM [52].

Previous history of severe hypoglycaemia and impaired unawareness are independent risk factors for maternal hypoglycaemia in pregnancy [53]. Counter regulatory response to hypoglycaemia is further reduced in pregnancy. Other risk factors are long duration of diabetes, low Hba1c levels in early pregnancy and fluctuating plasma glucose levels [52]. Maternal hypoglycaemia is a common problem and the reported incidence range from 10% to 45% [53, 54]. However, the distribution of hypoglycaemia is skewed with 10% of women accounting for 60% of the severe hypoglycaemic events [52]. This complication may be significantly reduced (4.4%) by intense monitoring of glucose control and patient education allowing for individual levels of glucose control [24]. Carbohydrate counting and use of closed loop systems may also be helpful in order to reduce the risk of hypoglycaemia [52]. Women with T1DM are more prone to develop ketonemia in starvation than outside pregnancy. This pattern of metabolic response is more pronounced as pregnancy proceeds as a consequence of the increasing glucose demand of the conceptus.

In diabetic pregnancies, placental and fetal leptin production is significantly increased compared to non-diabetic pregnancies and is accompanied by a state of placental inflammation with elevated levels of interleukin1, 6 and TNF alpha [55]. The possible fetal impact of the increased placental levels of cytokines is not clear.

FETAL GROWTH REGULATION

Normal pregnancy

Normal fetal growth is the result of a complex interplay between placental, maternal and fetal metabolism [56]. The preliminary drive of fetal growth is genetic and initially characterized by very rapid cell division. Although the first part of pregnancy is characterized by massive mitogenesis, 95% fetal weight is gained during the second half of gestation [57, 58]. At 20 weeks of gestation, almost 50% of glucose and oxygen is consumed by the placenta. Thereafter, the fetus outgrows the placenta and during the second half of pregnancy the mean fetal daily weight gain is 15 grams. Pregnancy induced maternal insulin resistance reduces maternal uptake of glucose, increases lipolysis and amino acid turnover which in turn leads to enhanced transfer of nutrients to the fetus. The main energy substrate for the growing fetus is glucose, followed by lactate, amino- and fatty acids [47]. Glucose passes the placenta by an energy independent process “facilitated diffusion”, driven by concentration gradients over the membranes. Fetal glucose concentrations are normally between 3-5 mmol/ litre and approximately 0.5 mmol/ litre lower than in the mother [59]. Placental transfer of amino- and fatty acids is dependent on active transport mechanisms. The trans-placental transport of lipids is limited. Receptors for lipoproteins, carrying triglycerides, are present in the placenta and enables essential fatty acids to be transferred to the fetus. Fatty acids in maternal plasma may also be taken up directly in the placenta by specific fatty acid binding proteins [47].

Insulin and the insulin like growth factors

Insulin plays a central role in the regulation of fetal growth. Already slightly increased maternal glucose levels (in the upper normal range) are associated with increased incidence of elevated concentrations of C peptide (split product from insulin) in cord blood and birth weight > 90^{th} percentile [60]. Conversely, low levels of fetal insulin are associated with growth restriction [61]. Insulin stimulates cell uptake of substrates, release of the insulin like

growth factor IGF 1 and has mitogenic effects on human cells [62]. The insulin-like growth factors, IGF1 and IGF 2 are also important promoters of fetal growth and concentrations in cord blood correlate with birth weight [63-65]. The IGF`s are mitogenic peptides with effect on cell differentiation and insulin sensitivity [66, 67]. IGF concentrations are modulated by nutritional status, insulin and by other hormones (placental GH, thyroid hormone, glucocorticoids) and by levels of carrier proteins, the IGFBP´s. IGF1 enhances fetal tissue uptake and utilization of substrates and may also affect placental nutrient transfer [68]. IGF2 on the other hand, appears to enhance fetal growth mainly via placental size [69], but has also been demonstrated to alter glucose and amino acid transfer in cultured human trophoblasts [70]. IGF2 gene expression is more abundant than IGF 1 gene expression in mid and late pregnancy [69]. The IGF 1 receptor binds IGF1 with high affinity and with weaker affinity to insulin and IGF2. The IGF2 receptor binds IGF1weakly, but not insulin. The IGF´s do not pass the placenta. They are synthesized in virtually all fetal tissues and are measurable in fetal serum from 12 weeks of gestation. The IGF´s are also produced by placental tissues. The IGF´s are bound to carrier proteins, IGFBP´s, in the circulation. PAAP-A and ADAM 12 are proteolytic enzymes from the placenta that modify the IGF action by releasing it from the IGFBP. PAAP-A may be detected in maternal serum already at 4 weeks of gestation. Several studies have shown a strong correlation between low maternal levels of PAAP-A in early pregnancy and fetal growth restriction and other adverse outcomes [71-73]. High maternal levels of PAAP-A and ADAM 12 have been associated with high birth weight [74, 75]. This association is most likely mediated via placental factors, as PAAP-A and ADAM 12 are not believed to pass the placenta.

Other factors of importance for fetal growth

Other growth factors acting in utero are epidermal growth factor (EGF), TGF alpha and fibroblast growth factor (FGF-2). Leptin has a potential role in fetal growth regulation. Leptin induces mitogenesis in cultures of human trophoblasts [76] and stimulates angiogenesis in human endothelial cell cultures [55]. Leptin also stimulates placental hCG production, enhances placental uptake of amino acids [77] and production of extra cellular matrix proteins in the placenta. It has been hypothesized that leptin affects fetal growth via the placenta [78] and/ or by stimulating maternal lipolysis. Cord blood leptin concentrations are strongly associated with neonatal fat mass [79] and birth weight [80].

The preliminary drive of fetal growth is genetic. Maternal birth weight and adult weight and height have greater influence on fetal size than paternal anthropometrics [81]. Fetal growth is balanced against the size of the uterus, known as maternal constraint. It has been demonstrated a temporal change in placental gene expression with advancing gestational age, which may explain the accelerated fetal growth in the second and third trimester. The expression of paternal growth promoter genes increases with time as maternal growth suppressor gene expression decreases [82], a phenomenon known as genomic imprinting. Interestingly, increased expression of growth suppressive imprinted genes was found in placentas of growth restricted fetuses. Maternal birth weight, age, prepregnancy weight and pregnancy weight gain, height, parity, smoking and birth weight of previous children are well known factors of importance for size at birth [83-85]. A prerequisite for normal fetal growth is a well functioning placenta. There is a close correlation between fetal and placental weights. Placental abnormalities such as preeclampsia, leading to decreased nutrient and oxygen transfer to the fetus, are common causes of asymmetric fetal growth restriction [86]. Environmental factors of the intra uterine milieu appears to affect fetal fat mass more than the fat free mass [87] and there is a strong correlation between maternal pre pregnancy insulin sensitivity and fetal fat mass [88].

Type 1 diabetic pregnancy

A characteristic finding in the T1DM pregnancy is fetal growth acceleration. This is associated with increased fetal concentrations of growth factors i.e. insulin, the insulin-like growth factors IGF1 and 2 and increased availability of glucose, free fatty acids, triglycerides and amino acids [89, 90]. Studies on human placentas have shown increased expression of glucose - (GLUT1) [91, 92] and amino acid transporters in placentas of T1DM women with tight glycaemic control [93] compared to placentas of non-diabetic pregnancies. Increased activity of placental lipoprotein lipase has also been described in human T1DM placentas [94]. Fetal levels of insulin and leptin are significantly increased in T1DM pregnancies, and are independently associated with offspring birth weight [95]. Evidence from animal models indicate that hyperinsulinaemia and hyperleptinaemia in utero increases the risk of metabolic imbalance later in life with insulin and leptin resistance [96].

According to the Pedersen hypothesis, maternal hyperglycaemia in T1DM leads to fetal hyperglycaemia and hyperinsulinaemia. Experimental and clinical studies have shown that fetal hyperinsulinaemia is an important factor to explain fetal macrosomia [97] and levels of C peptide in cord blood correlate to birth weight in T1DM offspring [98]. There is a significant correlation between maternal glycaemia (mean and fasting values) and skin fold thickness in the newborn [99] as well as the average adipose tissue cell diameter [100]. Infants to mothers with diabetes have increased amounts of body fat [101-103] and enlarged adipose cells [100] even when the birth weight is normal [104, 105]. Studies on pregnant rhesus monkeys have demonstrated that infusion of insulin into the fetal compartment enhances fetal growth even when blood glucose levels are kept within the normal range [97]. Human fetal beta cells respond weakly to glucose infusion before 20-26 weeks of gestation and maternal glucose infusion in late pregnancy (non-diabetic mothers) does not induce sustained fetal hyperinsulinaemia [106]. A significant correlation between maternal plasma concentrations of branched amino acids and amnion C peptide levels has also been found in T1DM pregnancies [61]. The impact of amino acids on insulin secretion is further supported by the finding of a much prompter insulin response to infusion of branched amino acids than infusion of glucose in newborn infants [107]. Szabo and Szabo also demonstrated a positive correlation between maternal fasting levels of free fatty acids and birth weight and proposed that increased placental transfer of fatty acids contribute to fetal adiposity in diabetic pregnancies. High maternal levels of PAAP-A are associated with LGA neonates in pregnancies without maternal diabetes [74, 75]. The role of PAPP-A in fetal growth regulation in T1DM pregnancies is unclear. Results from the only published study on PAPP-A and fetal size in T1DM pregnancies, indicate normal levels of PAPP-A in women delivering an LGA infant and decreased levels in pregnancies with an AGA infant [108].

Maternal glucose and fetal size

It is difficult to establish which indices of maternal glycaemic control (i.e. time of the day, pre and post prandial glucose values) that best correlates to infant birth weight. Maternal glycaemic values can only explain a minor proportion of the variance in birth weight [24, 109] and reported rates of fetal macrosomia remain high despite apparently tight maternal glycaemic control [23, 110]. Some studies report the strongest correlation between fasting glucose values and birth weight [24], others that postprandial glucose values better predicted birth weight [111, 112]. In a recently published study of approximately 25,000 pregnant women without diabetes, there was a strong continuous association between maternal fasting, 1 and 2 h post OGTT (oral glucose tolerance test) at 24-32 weeks of gestation and birth

weight above the 90th percentile [60]. No single glucose measure (fasting, 1 and 2 hour) was clearly superior in predicting birth weight > 90th percentile. Preconceptual Hba1c [113], first trimester Hba1c [114], Hba1c in the third trimester [8] and Hba1c at delivery [115] all correlate with infant birth weight. It has been demonstrated that glucose variability in pregnant women with type 1 diabetes is not satisfactorily reflected by results from home monitoring of glucose and Hba1c levels [116]. The authors suggest that "unexplained" cases of fetal macrosomia are due to episodic hyperglycaemia. Pulsatile glucose infusion in pregnant sheep is associated with higher fetal insulin levels than sustained maternal glucose infusion [117]. Results from animal studies indicate that hyperinsulinaemia in early pregnancy may result in "mal programming" of neuro-endocrine networks with lasting negative effects on the metabolism of the offspring. One could hypothesize that fetal hyperinsulinaemia established in early T1DM gestation affects fetal growth throughout pregnancy.

THE PLACENTA AND TYPE 1 DIABETES

The placenta in T1DM pregnancies has received much attention [118]. The primary question is whether placental changes occur as an adaptive response to the diabetic milieu with the ultimate result of protecting the fetus or if the placenta itself contributes to the high incidence of perinatal complications. The development of placental functions precedes fetal development and growth. Thus, alterations in the intra uterine milieu in early pregnancy may lead to placental changes with later impact on fetal development. Preconceptional hyperglycaemia is associated with poor placentation, probably increasing the risk of spontaneous abortions, preeclampsia and fetal growth restriction. The term placenta of women with T1DM tends to be heavier than in controls with increased content of triglycerides and phospholipids. In women with adequate metabolic control, macroscopic changes are seldom seen. However, increased expression and activity of lipoproteinlipas, glucose and amino acid transporters have been demonstrated in T1DM placentas from women with tight glucose control and may partly explain the high incidence of fetal macrosomia. There is some evidence from experimental studies that insulin may upregulate the activity of placental transporters [94] . Placental insulin sensitivity changes over time, with increasing amounts of insulin receptors on the fetal side (endothelium) as pregnancy proceeds. Thus, it is possible that fetal hyperinsulinaemia may alter placental nutrient transporters.

Oxidative stress in T1DM placentas (lipid peroxidation) most likely causes placental damage with consequences for the fetus. Oxidative stress is believed to play an important role in the pathogenesis of major malformations and preeclampsia. Another interesting feature of the T1DM placenta is the increased expression of leptin mRNA. The placenta is an important source of leptin in pregnancy. Only 5% of placental leptin is secreted into the fetal circulation; the rest reaches the maternal circulation. Leptin upregulates placental growth by stimulating amino acid uptake, production of extra cellular matrix proteins and mitogenesis [51]. Furthermore, leptin stimulates angiogenesis in cultured endothelial cells. However, it is not known if leptin has any metabolic effects in utero. How the placental leptin gene is regulated is not known. Given the increased levels of leptin in diabetes it is possible that insulin activates leptin gene transcription. Leptin production is associated with increased production of cytokines (IL 1, IL 6, TNF alpha) which may induce an inflammatory milieu, leading to even higher levels of cytokines. Inflammation in the placenta is associated with altered lipid transport over the placental membranes, possibly increasing the risk of adiposity in T1DM offspring [51]. Data from animal models indicate increased risk of adiposity after prenatal exposure to cytokines [119]. It has also been proposed that leptin in itself may

enhance fetal fat accretion by stimulating the development of microvasculature in adipose tissue. Desoye and colleagues have proposed that cases of "unexplained" fetal macrosomia may be due placental failure to store glycogen [118], leading to excess release of glucose from the placenta to the fetal compartment.

OBSTETRIC AND PERINATAL OUTCOMES OF TYPE 1 DIABETIC PREGNANCY

Perinatal complications

Maternal hyperglycaemia, during the time of organogenesis (until the 8th week of gestation), increases the risk of spontaneous abortions and malformations; i.e. diabetic embryopathy. The critical period of organogenesis occurs when the woman might still be unaware of her pregnancy. Once the organogenesis is completed, the fetal period begins and lasts until the end of pregnancy. Environmental insults during the fetal period may hamper fetal development and lead to fetopathy. The classical diabetes fetopathy is characterized by macrosomia, increased amounts of adipose tissue and glycogen and a cushingoid, swollen appearance. In addition, the liver, spleen and interventricular septum of the heart are enlarged [2]. The diabetic fetopathy is the result of fetal hyperinsulinaemia during the second half of pregnancy. Meticulous glycaemic control and avoiding maternal hypoglycaemia are important for normal fetal development. Risk factors for neonatal morbidity in T1DM offspring include maternal hyperglycaemia [5, 30, 120-125], increased amniotic fluid concentrations of C peptide [126] and erythropoietin [127] and preterm delivery [128, 129].

All outcomes included in this thesis are specified in table below, page no 27.

Spontaneous abortion

Reported rates of spontaneous abortions in non-diabetic pregnancies vary between 10 and 25% [130]. Maternal hyperglycaemia in early pregnancy increases the risk of spontaneous abortions in type 1 diabetic pregnancies [131-134] and reported frequencies range from 7.7 to 26.2% [130]. The risk increases with the degree of maternal hyperglycaemia [135]. It has been suggested that control of post prandial hyperglycaemia is important to reduce the prevalence of fetal loss [136]. Jovanovic et al found an increased risk of spontaneous abortions also in the lower extremes of maternal glyceamia (i.e. hypoglycaemia) in T1DM pregnancies [137]. This association was not seen in the DIEP study. Advanced maternal age and non-white race have been identified as independent risk factors for spontaneous abortions in both women with and without T1DM [135]. Poor placentation, early malformations and maternal infections are other potential contributing factors to the increased risk of spontaneous abortions in T1DM pregnancies.

Stillbirth

Stillbirth is often defined as intra uterine fetal death after 22 completed weeks of gestation. However, during the study period stillbirth was defined in Sweden as intra uterine death after 28 weeks of gestation. The risk of stillbirth is two to five times elevated in T1DM pregnancies compared with non-diabetic pregnancies, with reported rates ranging from 0.94% to 3.1% [3, 5-9, 11, 138]. Almost half of the stillbirths in T1DM pregnancies occur before 30 weeks of pregnancy [139]. The risk of fetal demise increases from 30 weeks of gestation and the risk of stillbirth is greater than the risk of neonatal death at 36 weeks of gestation [20]. The majority of stillbirths after 35 weeks are considered "unexplained". In a series of 25

stillbirths to mothers with T1DM, 12 cases were categorized as “unexplained”. However, in 9 of these cases the maternal glycaemic control was not satisfactory [140]. Results from animal studies indicate an association between maternal hyperglycaemia and chronic fetal hypoxia. Induced hyperglycaemia and hyperinsulinaemia in fetal lambs, increases fetal oxygen consumption with a parallel decrease in arterial oxygen tension [141]. Hypoxia is the major stimulus for erythropoietin (EPO) synthesis in humans and as EPO does not pass the placenta and is not stored, fetal plasma EPO levels or amniotic levels can be used as a marker for fetal hypoxia [142]. In the human T1DM pregnancy, there is a strong correlation between concentrations of EPO in venous cord blood and antenatal glycaemic control [143]. In most cases of late stillbirth (after 35 weeks of gestation), iron stores are depleted in the fetal heart, brain and liver [144] indicating increased red blood cell production in response to hypoxia. Furthermore, there is a strong correlation between amniotic and fetal plasma EPO levels and umbilical artery PO2 and pH [145]. The correlation between fetal amniotic insulin and fetal plasma erythropoietin levels, independent of maternal hyperglycaemia, indicate that insulin per se may affect fetal oxygenation [143]. There is a U shaped relation between amniotic erythropoietin levels and fetal size in T1DM pregnancies [127], suggesting increased risk of fetal hypoxia in both ends of the birth weight distribution.

Important predisposing factors for fetal hypoxia are hyperglycaemia, maternal angiopathy (i.e. nephropathy, preeclampsia), maternal ketoacidosis and smoking [139, 146]. Maternal hyperglycaemia is also associated with increased risk of major malformations [132] and increased thickness of the interventricular septum of the heart [147, 148], both of which may result in intra uterine fetal death.

The single most important preventive measure to reduce the risk of stillbirth in T1DM pregnancies is to strive towards maternal normoglycaemia. There is no consensus on which technique for fetal surveillance of T1DM pregnancies that best indentifies fetuses at risk of stillbirth. Ultra sound assessment of fetal growth, non-stress test of fetal cardiac function, and measurement of umbilical and uterine arterial blood flow are commonly used [149]. In addition, Teramo has proposed that a much elevated amniotic erythropoietin concentration may serve as an indicator of a fetus in distress.

Perinatal mortality

Perinatal mortality is defined as the combined rate of stillbirth and mortality within the first week of life, the majority of which are intra uterine deaths [4, 5, 150]. The rate of perinatal mortality has decreased over time, as a result of improved socioeconomic situation and metabolic control as well as advances in obstetric and neonatal care. Perinatal mortality in T1DM pregnancies was around 30% in the 1950´s [20] and reported rates from recent years range between 1.5-6.6% [5-8, 11, 15, 151]. Still, these figures are equivalent to a 2-9 fold increased risk compared with the general obstetric population. The leading causes of perinatal death in T1DM pregnancies are major malformations, fetal hypoxia and preterm delivery [20].

Major malformations

The increased risk of major malformations in T1DM pregnancies is well established [130, 132, 152]. In a recent systematic review on malformations in women with diabetes, the overall risk was three to fourfold that of the background population [153]. In a cohort of 314 T1DM pregnancies, male gender was independently associated with congenital malformations

[154]. However, this observation was not confirmed in our cohort of more than 3,500 T1DM offspring nor in recent publication from the UK [155].

The most prevalent malformations in type 1 diabetic offspring are the same as in the background population: i.e. malformations affecting the cardiovascular / gastrointestinal / renal and central nervous system. The most common type of malformations is cardiac defects (transposition of the great arteries, coarctatio aorta, septal defects) [156] and neural tube defects [19]. The incidence of multiple malformations is also increased [157]. The risk of chromosome abnormalities is not increased.

The pathogenesis of malformations in diabetic pregnancies is not fully understood. Data from experimental studies has identified hyperglycaemia as the major teratogen in the diabetic pregnancy [158-160] and the risk of malformations increases with the degree of hyperglycaemia. It has been proposed that the harmful effect of hyperglycaemia is mediated by free oxygen radicals [161, 162]. In vivo studies on rodents have demonstrated a beneficial effect of dietary supplementation of scavengers (vitamin E, C) on the embryogenesis in a diabetic culture medium [163]. In humans without diabetes, periconceptual use of multivitamins reduces the risk for cardiac malformations [164]. It has been proposed that antioxidant therapy in T1DM pregnancies for the prevention of malformations should be further investigated [165].

Numerous studies have shown an association between elevated maternal Hba1c in early pregnancy and increased risk of embryopathy (fetal loss and malformations) [130, 132, 134, 155, 166, 167]. The risk of malformations increases with increasing Hba1c values [166] and the risk may be reduced by 50% for each 1% decrease in periconceptional Hba1c. However, the genetic susceptibility for malformations varies in animal studies [168]. One could speculate that maternal and fetal genetic factors could partly explain that 50% of pregnancies with first trimester Hba1c values exceeding + 8 SD from the mean (Hba1c >95 mmol/ litre or 10.1%), result in normal fetuses [132]. There is no threshold for Hba1c above which there is a clear increase in the risk of malformations. The risk of major malformations increases substantially when the Hba1c level is >8 the mean (Hb1c >95 mmol/ mol or 10.1%) [132, 166]. However, a significantly increased risk has also been recorded at Hba1c levels of + 2SD above the mean [134, 152, 167]. Based on averaging the results from several studies, it has been proposed that the preconceptional Hba1C level should ideally be kept below + 3.5SD from the mean [10]. Data from animal studies have shown an association between maternal *hypoglycaemia* and increased risk of malformations [169]. Such an association has not been found in humans. Results from experimental studies indicate that hyperglycaemia reduces the gene expressions of vascular endothelial growth factor and PAX-3 and it has been hypothesized that this might have pathophysiological impact on the risk of cardiovascular malformations and malformations in the central nervous system [2].

Besides hyperglycaemia, data from animal studies also indicate a possible teratogenic role of keton bodies and branched amino acids [161, 170]. In vitro studies on rodents show that altered metabolism of arachidonic acid and inositol is associated with increased risk of dysmorphogenesis [171]. Adding arachidonic acid, PGE2 or myoinositol to the culture medium has been demonstrated to block the embryonic dysmorhogenesis in rodent models [2]. However, high maternal Hba1c remains the strongest predictor of malformations. Discriminant analysis showed that after controlling for maternal Hba1c, no further predictive power was displayed by adding information on maternal age, duration of diabetes, measurable plasma C peptide in the mother or presence of microangiopathy [132].

Preconception care of women with type 1 diabetes may significantly reduce the risk of congenital malformations [172-177]**.** Preconception care should aim at a preconceptual Hba1c as close to normal as possible and folic acid supplementation is recommended. Obesity is a well known independent risk factor for malformations [178]. Women with diabetes planning to get pregnant should be encouraged to enter pregnancy with a BMI within the normal range. The importance of avoiding alcohol and nicotine (smoking/ snuff use) should also be emphasized. Ultrasound assessment of fetal anatomy and determination of alpha-fetoprotein as a marker of malformations in the central nervous system has made it possible to detect >70% of all malformations in T1DM women in early pregnancy [179].

Preterm delivery

Since 1990, dating of pregnancy is solely based on ultrasound examinations in Sweden [180]. Very preterm delivery was defined in our studies as birth before 32 completed weeks of gestation and preterm delivery as birth before 37 completed weeks of gestation. National data from Sweden from the 1980ies, reveal a rate of preterm delivery of 25%, which was four times that of the background population (6 %) [5]. Studies from recent years report an incidence of preterm delivery of 24-40% compared with 4-7% in the background population [3, 5, 8, 11, 15, 128] . Risk factors for preterm delivery in T1DM pregnancies are elevated maternal Hba1C in pregnancy [128, 181, 182], fetal macrosomia [182], overt and incipient nephropathy [128, 183] and preeclampsia [128, 151, 182, 184]. Preterm delivery contributes to the increased incidence of neonatal morbidity and mortality in the type 1 diabetic offspring [4, 129, 185]. Preconception care may decrease the risk of preterm delivery in T1DM pregnancies [186].

Fetal macrosomia

There are several current definitions of fetal macrosomia, making comparison between studies difficult. There are definitions based on absolute birth weight (i.e. >4 kg or >4.5 kg) and definitions adjusted for gestational age and gender (large for date LGA: birth weight >90th or the 97.7th percentile). It has been known since long that pregnancies complicated by maternal diabetes are associated with a high incidence of oversized infants. In spite of improved metabolic control in T1DM pregnancies, reported rates of fetal macrosomia remain high. This is a puzzling observation and the mechanism is not clear.

Low Apgar score and birth trauma

Signs of fetal distress and low Apgar scores are more common in T1DM offspring than in infants born to non-diabetic mothers. Abnormal fetal heart rate, increased scalp lactate and fetal acidosis are more frequently observed in T1DM pregnancies [146, 187, 188] and is most likely a reflection of fetal hypoxia [20]. Risk factors for perinatal hypoxia in T1DM pregnancies are maternal angiopathy (in particular nephropathy), maternal hyperglycaemia during delivery and preterm birth [146]. Infants to mothers with T1DM are also at increased risk of shoulder dystocia and birth trauma, including ruptured clavicle, humeral fractures and Erbs palsy [2, 13, 150]. The propensity for shoulder dystocia in T1DM offspring is suggested to be due to an decreased head to shoulder ratio. Shoulder dystocia is a risk factor for Erbs palsy. It has been proposed that the incidence of birth trauma in T1DM pregnancies can be normalized with liberal use of Caesarean section [189]**.**

Respiratory disorders

The incidence of acute respiratory disorders of the newborn is significantly higher in T1DM offspring compared to the background population [3, 5, 15, 151]. While transient tachypnea (TTN) usually is characterized by mild symptoms and a rather rapid resolution, respiratory distress syndrome (RDS) is often a more severe condition. TTN may be due to retained/ and or delayed absorption of lung fluid, whereas RDS is due to surfactant deficiency resulting in atelectasis. The risk of RDS increases with lower gestational age at birth [190].

The increased incidence of respiratory disorders in infants to mothers with T1DM is partly due to the increased rate Caesarean sections and preterm deliveries in women with T1DM [128, 191, 192]. However, maternal diabetes has been identified as an independent risk factor for respiratory distress syndrome [193]. It has been suggested that fetal hyperinsulinaemia delays maturation of the lung tissue, rending the infant more susceptible to respiratory distress syndrome [150].

Neonatal hypoglycaemia

Infants to mothers with T1DM are prone to develop postnatal hypoglycaemia and the risk correlates to levels of C peptide in cord blood [194]. According to the Pedersen hypothesis, maternal hyperglycaemia leads to fetal hyperglycaemia and hyperinsulinaemia. At delivery, when the umbilical cord is cut, the placental glucose transfer to the fetus ceases. This in combination with established fetal hyperinsulinaemia rends the neonate at increased risk of hypoglycaemia. Neonatal hypoglycaemia is commonly defined as glucose values below 2 SD or the 5th percentile of the mean for healthy newborns. In Sweden, neonatal hypoglycaemia is defined as plasma glucose of <2.6 mmol/ litre. Symptoms of hypoglycaemia are unspecific and include jitteriness, irritability, pallor or cyanosis, tachypnea, hypotonia, temperature instability and convulsions [124]. According to the Whipple´s triad a diagnosis of symptomatic hypoglycaemia includes 1) presence of clinical symptoms 2) a low blood/ plasma glucose concentration and 3) rapid disappearance of symptoms and normalization of blood/ plasma glucose following the administration of glucose/ other feeding. Glucose infusion is recommended if the plasma glucose <1.5 mmol/ litre, in infants with symptoms of neuroglycopenia and in infants with a plasma glucose of <2.6 mmol/ litre if born before 32 weeks of gestation or in combination with other morbidities [195]. The central nervous system is the greatest single glucose consumer in the body. The hepatic glucose production in newborns of 5-6 mg /kg /min is 2-3 times higher than in older children and adults, because of the proportionally larger brain to body ratio in infancy.

The high incidence of preterm births also adds to the increased risk of hypoglycaemia [128] in T1DM offspring. There is little evidence to support any harmful effects of transient neonatal hypoglycaemia. In a follow-up study of cognitive function in T1DM offspring, preterm delivery (<34 weeks) and parity >1 were identified as negative predictors of cognitive function but there was no association between neonatal hypoglycaemia and cognitive performance [196]. Symptomatic neonatal hypoglycaemia of short duration has been associated with increased incidence of abnormal MRI or ultrasound scans either in the neonatal period or at 2 months of age [197]. These lesions were predominately found in the peri-ventricular white matter and had a very high rate of spontaneous resolution. However, profound and longstanding neonatal hypoglycaemia (glucose around 1 mmol/ litre) increases the risk for cerebral dysfunction [198]. Keeping maternal glycaemic values as close to normal

as possible during labour and delivery and early feeding of the newborn decreases the risk of neonatal hypoglycaemia [124].

Hyperbilirubinaemia

Hyperbilirubinaemia is also more frequent in T1DM offspring compared to newborn infants of non-diabetic mothers. The mechanism is not fully elucidated. Increased blood cell production in response to fetal hypoxia [127] is most likely an important contributing factor [150]. Studies of pulmonary excretion of carbon monoxide in newborn infants to diabetic mothers suggest that delayed clearance of bilirubin is another factor to explain the increased risk of jaundice [199]. Glucoronic acid, synthesized from glucose, is required to transform bilirubin into its water soluble form. Early feeding of the newborn infant to T1DM mothers may therefore reduce the risk of hyperbilirubinaemia.

Long term outcome type 1 diabetic offspring

We have not investigated the long term outcome of T1DM offspring but a short summary of available data will be presented. The "fuel-mediated teratogenesis" theory postulates that maternal diabetes during fetal development may have long lasting impact on the offspring´s susceptibility to disease later in life [89]. Data from animal models have shown increased risk of overweight, impaired glucose intolerance and diabetes in offspring of diabetic rats [96]. This effect is transmitted to the next generation, as the offspring of the diabetic pregnancy develop gestational diabetes later in life. This transmission to the next generation is believed to be of non-Mendelian origin and rather reflect epigenetic events in utero. Fetuses of diabetic pregnant rats demonstrate alterations in hypothalamic areas of importance for appetite regulation [96] . The same alterations is found if insulin is infused into the hypothalamus of the developing fetal rat and is associated with central insulin and leptin resistance. It is hypothesized that fetal hyperglycaemia and hyperinsulinaemia may lead to "mal-programming" of hormonal networks thereby predisposing the offspring to future disease. Rhesus monkeys made hyperinsulinaemic in utero by insulin infusion to the fetal compartment develop glucose intolerance as pregnant adults [56].

Data from human studies have also shown increased risk of overweight/ obesity and pre-diabetes/ diabetes in offspring to mothers with diabetes. The effect of the intrauterine exposure is confounded by genetic factors, maternal BMI and postnatal environment including socioeconomic factors, nutrition and physical activity. However, results from studies on PIMA Indians and siblings born before and after the diagnosis of maternal diabetes, show significantly increased risk of diabetes and overweight in the offspring born after the mother´s diagnosis [200]. In a group of 15 non-diabetic adults born to mothers with T1DM, the risk of impaired glucose tolerance was significantly higher compared to 16 adults born to fathers with T1DM [201]. These findings indicate that intra uterine exposure to maternal diabetes is a risk factor in itself for future morbidity. This hypothesis is also supported by findings from carefully designed epidemiological studies on young adults exposed in utero to maternal gestational diabetes or T1DM, including both mothers with high and low predisposition for type 2 diabetes. After taking several important confounders into account (social status, ethnicity, maternal BMI, smoking, family history of diabetes, offspring BMI, physical activity etc), the risk of T2DM/impaired glucose tolerance was 4-times and 8-times increased, respectively in subjects born to mothers with T1DM and GDM [202]. Interestingly, this risk was independent of offspring birth weight and gestational age at delivery. The risk of overweight and metabolic syndrome is 2.3-2.6 times increased in young

adults born to mothers with T1DM, after adjusting for confounders including maternal BMI, birth weight and preterm delivery [203]. Lindsay et al also found significantly increased skin fold thickness and prevalence of overweight at 7 years of age in offspring of T1DM mothers, the risk still significantly increased after adjustment for maternal BMI [204]. Elevated levels of amniotic insulin in pregnancies complicated by pregestational or gestational diabetes, have been associated with increased risk of both overweight [205] and impaired glucose tolerance [206] in the adolescent offspring. The increased risk was independent of type of maternal diabetes and was not associated with macrosomia at birth. It has been proposed that exposure to maternal T1DM in utero conveys an additional risk for offspring overweight/ impaired glucose tolerance that is additional to the genetic burden of T1DM [206].
Impaired glucose tolerance (IGT), diagnosed at oral OGTT, was significantly more common at 2-5 years of age in infants born to mothers with T1DM as compared to controls. Furthermore, the risk of IGT was significantly greater in LGA compared with AGA T1DM offspring [207]. Others did not identify maternal diabetes as an independent risk factor offspring overweight [208] or increased risk of overweight/metabolic syndrome in offspring of T1DM mothers [209].

Significantly increased levels of cardiovascular risk factors have also been demonstrated in children (5-11 years) born to mothers with T1DM [210]. There was no difference between T1DM offspring and controls in fasting glucose, insulin levels or in BMI and blood pressure, but the children born to mothers with T1DM had significantly higher levels of LDL cholesterol and vascular markers of inflammation (i.e. adhesion molecules: PAI, VCAM-1, E-selectin). Furthermore, in the diabetes offspring cohort, there was a positive correlation between birth weight standard deviation score and PAI level and subjects born LGA had significantly higher fasting insulin levels and greater skin fold thickness compared to children born AGA [210].

In a Danish follow-up study of young adults to mothers with T1DM, the global cognitive score was significantly lower in T1DM offspring compared to controls. Risk factors for lower cognitive scores were preterm delivery and parity >1, whereas high social class and parental educational level were protective. There were no associations between cognitive score and maternal glycaemia or neonatal hypoglycaemia [196]. The overall cognitive function (IQ) did not differ from the background population at 6-12 years of age in 40 children born to mothers with T1DM [211].

Maternal complications

Pregnancy induced hypertension and preeclampsia

Pregnancy induced hypertension (PIH) is defined as a resting blood pressure of ≥140/90 in the latter half of pregnancy. Preeclampsia (PE) is defined as PIH and proteinuria (>0.3g/ 24h) after 20 weeks of gestation [1]. If hypertension (>140/90) is present before pregnancy, preeclampsia is considered if the blood pressure is increased by 15/30 and/ or if proteinuria is superimposed. PE and PIH are approximately two-four times as common in T1DM pregnancies compared to the general obstetric population [212]. Preeclampsia affects 10-20% of all pregnant women with T1DM [3, 5, 15] compared with 3-7% of the background population [213]. Symptoms of PE range from mild hypertension to severe disease with malignant hypertension, multi-organ failure, seizures and coagulopathy [214]. The only curative treatment is termination of pregnancy. PIH and PE are associated with increased the risk of fetal growth restriction, preterm delivery and perinatal mortality.

Diabetes angiopathy (in particular overt nephropathy) is associated with increased risk of preeclampsia [1, 181, 183, 212]. The risk is also increased in women with incipient nephropathy, [183, 184], an early sign of endothelial vascular dysfunction. 42% of T1DM women with microalbuminuria before pregnancy developed preeclampsia to be compared with 11% in an unselected group of T1DM women. In T1DM women without microalbuminuria the prevalence of preeclampsia (6%) was not significantly different from that of the control group [1]. Elevated Hba1c in early pregnancy increases the risk of preeclampsia but not pregnancy induced hypertension [215]. For each 1% increment in Hba1C at 7 weeks of gestation the odds ratio of preeclampsia is 1.6. Tightening the metabolic control in early pregnancy reduces the risk of preeclampsia [215]. Other factors associated with increased risk of preeclampsia in non-diabetic pregnancies are heredity for preeclampsia, previous pregnancies complicated by preeclampsia, dyslipidemia, obesity, prima parity and twin pregnancies [214].
The pathogenesis of preeclampsia is not fully understood. The spiral arteries in placentas from women with preeclampsia are characterized by insufficient cytotrophoblast invasion, leading to increased vascular resistance. Genetic and immunological factors are believed to be involved in the pathogenesis and proposed trigger factors are hyperinsulinaemia, hyperglycaemia, hyperlipidaemia and hyperleptinaemia. Reduced placental perfusion and ischemia is believed to result in the release of placental and fetal factors (reactive oxygen species, cytokines, cell membranes from syncytietrophoblasts fetal haemoglobin etc) leading to maternal endothelial dysfunction and systemic inflammation [213, 216]. Signs of vascular dysfunction measured as elevated levels of the adhesion molecules ICAM1/VCAM1 and reduced endothelial independent vasodilatation are present before preeclampsia develops in T1DM women. However, it was concluded that daily urine albumin excretion and blood pressure were the strongest predictors of preeclampsia [217]. Other early markers of preeclampsia in T1DM pregnancies are elevated plasma levels of atrial natriuretic peptide [218], blood concentrations of pro-renin [219] and increased urinary orosmucoid excretion [220]. Oxidative stress has been suggested to play a role in the pathogenesis. Recently, it was proposed that fetal haemoglobin is an important trigger of oxidative stress in preeclamptic placentas [213].

In a randomized clinical trial, antioxidant therapy reduced the risk of preeclampsia in non-diabetic pregnancies [221]. However, results from subsequent studies have not supported this finding [222, 223]. In a large randomized trial from UK, vitamin C and E supplementation increased the risk of fetal growth restriction in women with diabetes [223]. Strict metabolic control and antihypertensive treatment (methyldopa, calcium channel blockers, labetalol) also to women with microalbuminuria without hypertension are recommended to decrease the risk for preeclampsia [1, 149].

Mode of delivery

In most countries, the incidence of delivery by Caesarean section (elective and emergency) in T1DM pregnancies is significantly higher than in the general obstetric population [4, 224]. Reported rates range from 44 to 63.5% [3, 8, 11, 15]. Common indications for Caesarean section in T1DM are preeclampsia and other hypertensive disorders, fetal growth retardation or acceleration and fetal distress. In a cohort of 209 women with T1DM, pregnancy weight gain >15 kg and suspected fetal macrosomia were the strongest predictors of delivery by Caesarean section before onset of labour [224]. In fear of stillbirth in T1DM pregnancies, a common practice in many countries is to induce labour or to perform elective Caesarean

section at 38 weeks of gestation. If there are no pregnancy complications, women with T1DM in Sweden are encouraged to await spontaneous onset of labour. However, in lack of spontaneous onset, labour is induced at 40 weeks of gestation. Rates of instrumental deliveries (i.e. vacuum extraction, forceps) are also increased in T1DM pregnancies.

Outcome variables included in this thesis

Outcome	Variable	Identification	Definition
	Preeclampsia, severe	ICD code	Diastolic BP ≥ 110 after 20 weeks of gestation and/or proteinuria ≥ 5g/24h ICD 9: 642 F ICD 10: O 14.1/O 15
	Preeclampsia, moderate/mild	ICD code	BP ≥ 140/90 after 20 weeks of gestation and proteinuria ≥ 0.3g/24h ICD 9:642 E ICD 10: O 14.0
	Pregnancy-induced hypertension	ICD code	BP≥ 140/90 after 20 weeks of gestation ICD 9:642.D3 ICD 10: O 13
	Caesarean section (CS)	Predefined	Elective and emergency CS as composite outcome
	Instrumental delivery: *Vacuum extraction* *Forceps*	Predefined	Delivery by vacuum extraction or forceps
	Fetal distress after onset of labour	ICD code	ICD 9: 656.3 ICD 10: O 68.3/O 68.8
	Major malformation	Predefined	Fatal or life threatening malformations, or malformations leading to major cosmetic defect or handicap if not surgically corrected
	Stillbirth	Predefined	Intra uterine death after 28 weeks of gestation
	Perinatal mortality	Defined	Stillbirth + death within the first 7 days of life
	Neonatal mortality **Early** **Late, study I** **Late, study II**	Defined	 Death 0-7 days postpartum Death 7-28 days postpartum Death 0-28 days postpartum
	Infant mortality	Defined	Death 28-360 days postpartum
	Preterm delivery **Very preterm delivery**	Defined	< 37 weeks < 32 weeks
	Apgar score	Predefined	< 7 at 5 min < 4 at 5 min
	Birth trauma *Erbs palsy* *Clavicle fracture*	ICD code	 ICD 9: 767.6 ICD 10: P.14.0 ICD 9: 767.2 ICD 10: P13.4
	LGA	Predefined Defined	Birth weight ≥ +2SD above the mean for gestational age and gender Birth weight ≥ 90^{th} percentile for gestational age and gender
	SGA	Predefined Defined	Birth weight < +2 SD below the mean for gestational age and gender Birth weight <10^{th} percentile for gestational age and gender

	Ponderal index	Defined	Birth weight in grams/(length in cm) ^{3} Continuous variable Categorical variable > 90th percentile (yes/no)
	Neonatal hypoglycaemia **< 6h postnatal** **> 6h postnatal**	ICD code	Plasma glucose < 2.6mmol/l ICD 9: 775.0 ICD 10: P 704.A ICD 9: 775.0 ICD 10: P 704.B
	Hyperbilirubinaemia **Phototherapy** **Exchange transfusion**	ICD code	ICD 9: 99.83 ICD 10: V9392/DQ O15 ICD 9: 99.01 ICD 10: DR050
	Hypoxic **ischemic encephalopathy** **Severe/ Moderate**	ICD code	ICD 9: 768.7 ICD 10: P91.0C ICD 10: P 91.0B
	Neonatal seizures	ICD code	ICD 9: 779.0 ICD 10: P 90.9
	Respiratory distress syndrome	ICD code	ICD 9: 769 ICD 10: P 22.0
	Transient tachypnea	ICD code	ICD 9: 770.6 ICD 10: P 22.1
	Other respiratory disorders	ICD code	ICD 9: 786.06 ICD 10: all diagnoses starting with P22, P24, P25
	Standard deviation scores	Defined	Calculated for BW,BL,HC and PI

Predefined: predefined in the MBR. **ICD code**: defined according to ICD 9 and /or ICD 10 codes **Defined**: defined by our research group.

ANTENATAL CARE IN SWEDEN

In Sweden, healthcare is free of charge and with equal access for all citizens. Since 1937, all women in Sweden are offered free antenatal care. Almost all pregnant women in Sweden attend the antenatal clinic, with 9-13 visits in pregnancy. At the first antenatal visit, the mother is interviewed about her medical and obstetric history, medications and smoking/ alcohol habits. Data on prepregnancy weight and height are collected.
Ultrasound assessment of gestational age is routinely performed in Sweden since 1990 [180] and 98% of all pregnant women today have an ultrasound in the 16-18th gestational week with the primary aim to determine gestational age.

Pregnant women with T1DM in Sweden are regularly seen by specialized teams with endocrinologists, obstetricians and midwifes. The importance of prepregnancy care is emphasized, starting already at the paediatric clinic. Insulin and equipment for administration of insulin, home monitoring of blood glucose and test strips are free of charge. In Sweden, leading diabetologists have put much effort into providing health care personnel with guidelines on the management of diabetic pregnancies and to create information brochures for patients. National guidelines (by the National board of Health and Welfare) are available. These are evidence based recommendations on the screening for, prevention and treatment of diabetes and its complications and include recommendations regarding T1DM in pregnancy.

Management program for pregnancies complicated by T1DM in Sweden

Preconception care

Ideally, the care for women with T1DM planning a pregnancy, starts before conception. The beneficial effect of preconception care on pregnancy outcome has been demonstrated in several studies [15, 130, 172-174, 176, 177, 186, 225, 226]. In a recent meta-analysis of studies on preconception care in T1DM women, it was demonstrated that preconception counselling significantly reduces the risk of congenital malformations, perinatal mortality and preterm delivery [186]. Several studies have also reported significantly reduced risk of spontaneous abortions in women attending pre conception care [173, 226, 227]. In the Diabetes Control Complication Trial (DCCT), there was no significant difference in the risk of spontaneous abortions between women receiving intensive therapy (multiple daily injections or CSII) prior to conception and the conventional treatment group [228]. There were no significant differences between the two treatment groups for any of the other outcomes, including maternal hypertensive disorders and neonatal morbidity. The risk of major malformations was lower in the intensive treatment group; however the difference did not reach statistical significance (0.7 % vs. 5.9 %). The lack of a difference in outcome in the DCCT study is likely due to the highly selected study sample, with motivated patients in both groups.

On the other hand, preconception care seems to have less impact on neonatal outcome. In one study the NICU admission rate was halved in the preconception group [229], but did not differ significantly from non-attendees nor did the rates of fetal macrosomia, neonatal hypoglycaemia and respiratory distress syndrome [173, 230].

Murphy and colleagues demonstrated that women attending preconception care presented earlier at the antenatal clinic, had lower Hba1c levels at entry of pregnancy and were more likely to take folic acid supplementation compared to women who did not attend pre-

conception care. Furthermore, preconception care had an independent beneficial effect on pregnancy outcome, beyond glycaemic control and was a stronger predictor of pregnancy outcome than maternal obesity and social disadvantage [174]. Overall, every 1% reduction in Hba1c before conception may reduce the risk of adverse outcome by half [153]. Prepregnancy counselling should also include dietary advice, recommendations on physical activity and the importance of smoke cessation.

In Sweden preconception guidance is regularly given at the diabetes clinics. In addition, "pre-pre-pregnancy care" is offered all teenage T1DM patients already at the paediatric diabetes clinic.

Management during pregnancy and delivery - glucose monitoring

Blood glucose should be kept as close to the normal range as possible before and throughout pregnancy and delivery [149, 231]. The patient is advised to measure capillary glucose (self-testing) before and 1.5 hours after each meal, including afternoon snack and at bedtime. Sometime the glucose should also be tested in the middle of the night to adjust insulin doses. The patient should aim at fasting levels between 4-5 mmol/ litre, postprandial 5.5-6.5 mmol/ litre and at bedtime 6-7 mmol/ litre. The capillary blood glucose at night should ideally be kept between 4 and 6.5 mmol/ litre. The glucose results should be recorded together with doses of insulin, food intake and other events that might affect the glucose levels (infections, physical activity etc). There is no evident threshold of Hba1c above the normal range that is safe. In a prospective study from Denmark, the risk of perinatal mortality in T1DM pregnancies was increased even at a periconceptional Hba1c levels below 61mmol/ mol (6.9%). However, the risk of perinatal mortality did not differ significantly from the control group until Hba1c exceeded 61mmol/ mol [232] and the recommended preconception target of Hba1c is < 63 mmol/ mol (< 7%) [149]. Normally, Hba1C declines in pregnancy, with on average 0.5% -1% lower values in pregnant healthy women than outside pregnancy [233] and it is recommended that the target for T1DM women is reduced to < 52 mmol/ mol (< 6%) in pregnancy [149].

Hypoglycaemia

In early pregnancy, insulin sensitivity increases with elevated risk of maternal hypoglycaemia, (maximum around the 10^{th} week of gestation) [53]. Striving towards normoglycaemia must be balanced against the risk of hypoglycaemia. Aiming at lower mean glucose levels increases the risk of hypoglycaemic unawareness. Maternal hypoglycaemia is mainly a threat to the mother and an important risk factor for maternal death [234]. However, there is a potential risk of fetal brain damage in cases of severe and prolonged maternal hypoglycaemia [235]. Induced hypoglycaemia (insulin injection) in late T1DM pregnancy is associated with abnormal fetal heart registrations, which rapidly reversed when glucose concentration was brought back to normal [236]. Tight glycaemic control during pregnancy may also increase the risk of fetal growth restriction [237].

Insulin

Pregnancy is associated with increased insulin resistance and required insulin doses are normally increased from the 16th week of gestation and onwards [149]. The average increase ranges from 0.9 - 1.2 IU/ kg/ 24h, or approximately 40 extra units per day. At the end of pregnancy, insulin doses can often be reduced and after delivery the mother usually requires 1/3 of the dose used in pregnancy. Most pregnant women with type 1 diabetes are managed with multiple daily injections (MDI) with direct acting insulin analogues in combination with intermediate acting insulin analogues. Continuous subcutaneous insulin infusion (CSII-pump therapy) is another possibility [238]. CSII outside pregnancy has been associated with significantly lower Hba1c levels and reduced risk of hypoglycaemia compared to multiple daily injections [239]. Observational studies comparing CSII and MDI in pregnancy have demonstrated increased risk in the CSII group of maternal ketoacidosis and neonatal hypoglycaemia [240] as well as LGA infants and significantly higher mean blood glucose values in the third trimester [241].

In a meta-analysis of RCT studies comparing pregnancy outcome between women treated with multiple daily injections (MDI) and women on CSII, there were no significant differences in maternal or fetal outcomes [242]. However, it has been demonstrated that CSII is associated with decreased glucose variability in pregnancy, measured as mean average of glucose excursions [243]. So far, there is no evidence for CSII being superior to MDI for pregnancy outcome in T1DM and national guidelines state that pregnant women on MDI should not routinely be put on CSII.

Screening for complications and mode of delivery

Screening for the presence of thyroid dysfunction and diabetes angiopathy (retinopathy, incipient/ overt nephropathy, hypertension) is performed in early pregnancy and Hba1c levels are measured every 4 weeks [149]. Sonographic examination of fetal anatomy is performed around the 17-18th week of gestation and prenatal tests for malformations are considered (amniocentesis for alpha-fetoprotein etc). Fetal growth is estimated by repeated ultrasound measurements and fetal heart rate is regularly monitored from 32 weeks and onwards. In absence of complications (preeclampsia, fetal growth deviation etc) spontaneous onset of labour is awaited. Usually, induction of labour is performed at 40 weeks of gestation if spontaneous onset has not yet occurred. Close monitoring of maternal glucose levels during labour and delivery is important, aiming at a blood glucose concentration of 4-6 mmol/ litre. Maternal hyperglycaemia during delivery leads to fetal hyperglycaemia and increased oxygen consumption, with increased risk of lactacidosis and fetal distress. Maternal hyperglycaemia during labour and delivery is also associated with increased risk of neonatal hypoglycaemia [194].

THE SWEDISH MEDICAL BIRTH REGISTRY

This thesis is based on data from the Swedish Medical Birth Registry (MBR). The MBR is a national registry with prospectively collected information on demographics, medical history and outcomes on all mothers and infants discharged from Swedish Maternity Hospitals and Neonatal units. Standardized forms are used for data registration and these forms are transferred to the MBR. The registry started in 1973 and covers more than 98% of all pregnancies in Sweden. Registration in the database of all deliveries in Sweden is compulsory according to Swedish law. Until 2008, the MBR only contain data on stillbirths

occurring from the 28th week of gestation and onwards. After 2008, the registry also collects information on pregnancies ending in stillbirth from the 22: nd week of gestation. The MBR is subjected to repeated quality checks performed by the National Board of Health, most recently in 2002 and the conclusion of this validation was that the quality of data is high [244]. The MBR has also been evaluated by independent researchers in 1993 [245]. In addition, the registry is submitted to several quality checks every year, including data validation against information in other national registries such as the registry for congenital malformations. Observations from these quality studies have justified changes in the mode of operation to enhance the accuracy in registered data. In the latest extensive validation of the MBR undertaken by the National Board of Health, data from 1973 until 2002 was investigated for extreme/ missing values and validity. Registry data was checked against information in other national registries (registry for congenital malformations, registry for cause of death, inpatient registry etc) and 581 original records from 1998 were compared with data in the MBR. The validity of the following variables of interest for the present studies was considered high: maternal prepregnancy weight and height, birth weight and length, gender, gestational age and "hard" data such as live born yes/ no and major malformations yes/ no. The validity of maternal and infant diagnoses is a little less. In particular, data on very preterm and sick infants tend to be underreported to the registry. This is most likely due to the fact that these patients to a large extent are transferred between different clinics and often in need of care more than 1 month postnatal. Data on gestational age is considered of high quality and is in most cases based on data from ultrasound assessment of fetal size in the 16-18th week of gestation. If this data is not available, data on last menstrual period is used. Data on birth weight in the MBR in is registered in absolute numbers and as categorical variables i.e. small/ appropriate or large for gestational age. These categorizations are based on reference data from Marsal et al, reporting ultrasound estimated values of fetal weight and length from 89 uncomplicated singleton pregnancies delivered at term [246].

INTRODUCTION TO STUDY I-IV

Against the given background, it is evident that T1DM in pregnancy is associated with a number of unresolved questions.

In spite of major improvements in pregnancy outcome over the last decades, following the introduction of tight glycaemic control, the risks of obstetric and perinatal complications are still much elevated [3, 4, 9, 11, 151]. These complications include preeclampsia, pregnancy induced hypertension, instrumental delivery and Caesarean section, spontaneous abortion, major malformation, stillbirth, perinatal mortality, perinatal hypoxia, preterm delivery, fetal macrosomia, birth trauma, neonatal morbidity and mortality. The St Vincent declaration from 1989 - ŁŁe. to abolish the over risks associated with the T1DM pregnancy by the end of the last century - has not yet been met [6-8, 138]. To enable continued improvements in pregnancy outcome, for planning of health care and for patient counselling, repeated evaluations of complication rates are necessary. Large studies are required for accurate risk estimation given the relatively low incidence of T1DM in pregnancy and comparatively low rates of complications such as perinatal mortality and major malformations. The National Swedish Medical Birth Registry offers a unique possibility to investigate the outcome of all pregnancies in Sweden complicated by type 1 diabetes.

THE OVERALL AIM WITH THIS THESIS WAS

To perform a detailed analysis of pregnancy outcome in women with type 1 diabetes, with special reference to fetal macrosomia

THE SPECIFIC AIMS OF THIS THESIS WERE

To elucidate whether in recent years, obstetric and perinatal outcomes in pregnancies complicated by type 1 diabetes (T1DM) have improved or not

To characterize in detail infant size at birth, with special reference to body proportions, in a large cohort of type 1 diabetic offspring

To investigate if the risk of adverse perinatal outcome differs with body proportionality in infants to mothers with type 1 diabetes

To investigate if the risk of maternal, fetal and neonatal complications is dependent on maternal prepregnancy BMI in mothers with and without type 1 diabetes

GENERAL INTRODUCTORY REMARKS ON MATERIAL AND METHODS, STUDY I-IV

ETHICS APPROVALS

The studies were approved by the regional ethics committee in Uppsala on the 11/9 2005 and on the 22/7 2009, identification number 2005/216 and 2009/187, respectively.

SETTING

The four cohort studies of this thesis were conducted in Sweden and based on information from the Swedish Medical Birth Registry (MBR). The MBR provides unique opportunities for epidemiological studies, with its prospectively collected data and national coverage. Study I was based on data from the MBR during 1991-2003 and studies II-IV were based on data from the MBR during 1998-2007. In 1991-2003, there were in total 1,322576 deliveries in the registry. In 1998-2007, there were in total 947,096 infants delivered, including 4,208 infants to mothers with T1DM.

EXCLUSION CRITERIA STUDY COHORT

In all studies, only singleton pregnancies were included. In study I, 4% of all records in the whole dataset were excluded due to multiple pregnancies. Within the T1DM cohort in study II and III, 2.8% were excluded due to multiparity, 0.81% were excluded due to stillbirth and 4.2% due to major malformation.

EXTREME OR MISSING DATA

Maternal data

Records with extreme values on maternal age (< 13 years or > 54 years), weight (< 40 kg, or > 180 kg) or height (< 120 cm or > 200 cm) were excluded from the analysis. In the first cohort, 311,066 records were excluded due to either missing data on maternal weight and height or due to values outside the above mentioned limits. In total 441 records were excluded due to these data limits in the later cohort and 111,407 were missing for height and 71,192 were missing for weight.

In the second cohort, there were in total 13 records with unclear classification of diabetes: i.e. patients diagnosed with more than one type of diabetes. These records were not included in the analyses.

Infant data

In study II and III, only infants with full data on birth weight, length, gestational age and gender were included.

In total 155 records were missing for gender (no missing in the T1DM cohort) and 848 for gestational age, 8 of those were infants born to T1DM mothers.

3,402 records were missing for birth weight and 14,544 for birth length. Of those, 20 of the records missing for birth weight and 186 for length were infants born to T1DM mothers.

STATISTICAL METHODS

The Students t test was used for comparison of group means of normally distributed data. For comparison of continuous data between groups, where the assumption of normality was not tested for, we used Kruskall Wallis test (for nominal data with more than two groups) and Wilcoxons ranksum test (for nominal data with two groups). Comparison of binary or categorical data between groups was made using the χ^2 test and χ^2 test for trend. Standard deviation scores were calculated for infant anthropometric data, based on reference data from the general obstetric population in the dataset. Ponderal index was calculated as birth weight in grams/ (length in cm) ^{3} in study II and III.

Logistic regression analysis

Logistic regression analysis is used when the outcome/ dependent variable is dichotomous. The independent variables (covariates/confounders) may be continuous or categorical. The point estimates in logistic regression analysis are given as odds ratios; i.e. the ratio of the odds of the outcome under study in the exposed and unexposed group. The odds ratio is often presented with a 95% confidence interval (CI). If the CI contains 1, the odds ratio of the outcome is not significantly increased. The odds ratio may be approximated as a relative risk, given a low incidence of the outcome (< 10%). In this thesis, unconditional logistic regression analysis (un-matched data) was used in study I, III and IV.

Confounding, covariates and effect modification

Potential confounders were controlled for in the multivariate logistic regression analysis and by stratified analysis. Variables associated with the outcome were included as covariates if appropriate. Effect modification was demonstrated by stratified analysis and statistically tested for by including interaction terms in the regression models and by using the likelihood ratio test, study II, III and IV.

A p-value < 0.05 was considered significant. The analysis for study I was performed using SPSS 15. All statistical analyses for study II–IV were performed using STATA 10.1 SE.

Missing data

In study I, the regression analysis was confined to records with data on maternal BMI. In the multivariate regression analyses in study III and IV, missing indicator variables were introduced to handle missing data. In study III, missing indicator variables for maternal height and BMI were used and in study IV, missing indicator variables for maternal age and height were used.

MATERIAL AND METHODS STUDY I

This study was based on data from the Swedish Medical Birth Registry between 1991 and 2003. The aim of the study was to compare rates of pregnancy and perinatal complications between T1DM pregnancies and controls. Risk estimates were given as odds ratios. All women with a diagnosis of type 1 diabetes, based on ICD 9 and ICD 10 codes were included, and women without a diagnosis of diabetes served as controls. The study cohort comprised only singleton pregnancies, including 5,089 women with T1DM and 1,260207 women without T1DM. The ICD 9 system was introduced in 1991 and enabled differentiation of pregestational and gestational diabetes (GDM), but could not separate T1DM from type 2 diabetes (T2DM). In 1997, ICD 10 made separation of T1DM, T2DM and GDM possible. This means that we were not able to identify and exclude cases of T2DM from our cohort during the first half of the study period. The rate of T2DM in pregnancy in Sweden is low (< 0.05%) and we concluded that the overall contribution from any T2DM woman during the first 7 years of the study period was small and not significant. For comparison, during 1998 and 2007, there were in total 417 (0.04%) women with T2DM in the MBR. Outcomes were compared between hospitals in relation to number of T1DM pregnancies managed per year: i.e. < 10/10-19 or > 19. In addition, the study period was divided in two and outcomes were compared between period 1 (1991-1997) and 2 (1998-2003). Extreme data on maternal age (< 13 and ≥ 54 years), weight (< 40 and ≥ 180 kilos) and height (< 120 or ≥ 200 cm) were dealt with as missing data. No limits for birth weight or birth length were applied as the pre-defined variables SGA and LGA were used as neonatal outcomes. The multivariate regression analysis was confined to records with data on maternal BMI.

Maternal characteristics

Maternal characteristics included in this study were maternal age, parity, prepregnancy weight and height, body mass index (BMI), diagnosis of chronic hypertension yes/ no, smoking habits during the first trimester (0, < 10 cig/ day or ≥ 10cig/ day) and country of birth (Nordic or not Nordic). All these variables were collected from the MBR except from ethnicity. Country of birth was established by linking the MBR to the Civil Registration. BMI was calculated as prepregnancy weight in kg/length in m^2.

Outcome variables

Maternal complications during pregnancy and delivery and neonatal diagnoses were identified based on ICD codes, see Table 2, page no 27.

Hypertensive disorders of pregnancy

Pregnancy induced hypertension and preeclampsia (mild and severe) were recorded.

Mode of delivery and fetal distress

Delivery by Caesarean section (CS) was recorded. In the MBR, delivery by Caesarean section is recorded in two different variables; i.e. elective CS yes/ no and as the combined rate of elective and emergency CS. The validity of the latter variable is higher than that of the

former and consequently we have in all our studies chosen to present the combined rate. Instrumental delivery by forceps or vacuum extraction was also recorded in all vaginally delivered infants. Fetal distress was considered present if delivery by CS or vacuum extraction was performed as a result of suspected or manifest fetal hypoxia.

Stillbirth, perinatal and neonatal mortality

During the study period, stillbirth was in Sweden defined as intra uterine fetal death after 28 weeks of gestation. Rates of perinatal and neonatal mortality were also recorded.

Preterm delivery

Very preterm delivery was defined as delivery before 32 completed weeks of gestation and preterm delivery was defined as delivery before 37 completed weeks of gestation.

Low Apgar scores and birth trauma

Apgar scores < 7 at 5 minutes and < 4 at 5 minutes were recorded as well as Erbs palsy (brachial plexus injury) and shoulder dystocia in vaginally delivered infants.

Major malformations

Malformations were predefined in the MBR as major if fatal/ potentially life threatening or likely to lead to a major cosmetic defect/ handicap if not surgically corrected.

Size at birth

Infants were classified as small for gestational age (SGA) and large for gestational age (LGA) as birth weights ≥ 2SD above or below the mean for normal fetal growth according to Swedish reference data, respectively [246].

Respiratory distress syndrome and other respiratory disorders

All respiratory disorders were classified according to Hjalmarsons criteria [247]. We recorded cases of acute respiratory distress syndrome and the combined rate of other transient respiratory disorders of the newborn, including transient tachypnea, meconium aspiration, lung tissue bleedings, pneumothorax and emphysema.

Statistical methods

In the multivariate regression model the point estimates for outcomes were adjusted for potential confounders/ covariates: i.e. maternal ethnicity, maternal age, prepregnancy body mass index, parity, chronic hypertensive disorders and smoking habits.

MATERIAL AND METHODS STUDY II

The study cohort comprised 3,705 singleton infants (1,876 boys) born alive to mothers with T1DM in 1998-2007 and with gestational age 28-43 weeks. The reference population for fetal growth included 883,163 (452,809 boys) infants to mothers without T1DM. We

excluded records of stillbirths, multiple pregnancies, and major malformations, extreme values on birth weight/ length/ head circumference (≥ 6SD below or above the mean of the reference population) and records with missing data on birth weight/ length/ gestational age or gender.

Maternal characteristics

Maternal characteristics included were nationality (Nordic yes/no), age, parity, prepregnancy weight and height; BMI (calculated as weight in kg/length in m^2) and smoking during the first trimester (yes/ no).

Outcome variables

Infant size at birth (birth weight, length and head circumference) of type 1 diabetic offspring was described in relation to the reference population and expressed as standard deviation scores (SDS), large for gestational age (LGA, birth weight ≥ 90^{th} percentile for gestational age and gender), small for gestational age (SGA, birth weight < 10^{th} percentile for gestational age and gender) and as a ponderal index (PI, birth weight in grams/(length in cm) ^{3}. PI values were presented as a continuous and as a binary variable (equal to or above the 90^{th} percentile yes/ no). Size at birth was also analyzed separately in preterm and term infants as well as stratified by gender.

**Errata study 2) In the published paper it is stated that during the study period there were in total 947,064 deliveries, correct number is 947,096. The correct number of T2DM pregnancies included in the reference group is 417. The percentage of records excluded due to anthropometric data exceeding 6 SD, was 0.02%.*

Statistical methods

Standard deviation scores were calculated for birth weight, birth length and head circumference. Ponderal index was calculated as birth weight in grams/length in cm^3. Students T test, Wilcoxons rank sum test and chi^2 test were used for comparison of group means and proportions.

MATERIAL AND METHODS STUDY III

The study cohort comprised 3,517 singleton infants (1,776 boys) born alive to mothers with T1DM in 1998-2007. The reference population for fetal growth included 874,620 infants to mothers without a diagnosis of diabetes. We excluded records of stillbirths, multiple pregnancies, major malformations, infants born before 32 or after 43 completed weeks of gestation, extreme values on birth weight (< 200 or > 9998 gram) and length (<15 or > 65 cm) and records with missing data on birth weight/ length/ gestational age or gender. Infants born with a birth weight < 10^{th} percentile were excluded from the study cohort. In a first analysis, it was demonstrated that outcome was independent of infant body proportionality in AGA infants. In the subsequent analyses, all AGA T1DM offspring were pooled into one reference category.

Primary outcome

The primary outcome was composite morbidity consisting of any of the following diagnoses: Apgar score < 7 at 5 min, birth trauma (Erbs palsy and/ or fractured clavicle), acute respiratory disorders (respiratory distress syndrome or transient tachypnea),

hyperbilirubinaemia or hypoglycaemia requiring treatment. All diagnoses were identified based on ICD 9/10 code. Clavicle fractures and brachial plexus injury were recorded in vaginally delivered infants only. Hypoglycaemia was defined as plasma glucose < 2.6 mmol/ litre after 6 hours postnatal (ICD code P70.4 B). Hyperbilirubinaemia requiring phototherapy or exchange transfusion was recorded.

Secondary outcomes

Secondary outcomes included the before mentioned diagnoses analyzed separately and fetal distress after onset of labour (ICD10 O689), Apgar score < 7 at 1 min of postnatal age, neonatal seizures and hypoxic ischemic encephalopathy (moderate and severe as a composite variable), hypoglycaemia < 2.6 mmol/ litre before 6 h postnatal, preterm delivery (defined as birth before 37 completed gestational weeks) and neonatal and infant mortality. Neonatal mortality was subclassified into death within the first 7 days of life (early neonatal death) and death after 7 days but within the first 28 days of life (late neonatal death). Infant mortality was defined as death after the first 28 days of life but within the first year.

Statistical methods

Given the prevalence of morbidities in type 1 diabetic offspring [248], we estimated to detect a 30% difference in the prevalence of composite neonatal morbidity comparing proportionate and disproportionate LGA infants with 80% power (α=0.05). Unconditional logistic regression was used to explore associations between body proportions and neonatal complications with AGA type 1 diabetic offspring as the reference category. The odds ratios were stratified by gestational age and the final models for composite morbidity, respiratory disorders, hyperbilirubinaemia and hypoglycaemia included adjustment for mode of delivery and fetal distress. The regression model for birth trauma was restricted to vaginally delivered infants only and the odds ratios were adjusted for maternal height and BMI. In a sub-analysis, the odds ratios for birth trauma were also adjusted for differences in absolute birth weight. Missing indicator variables were used for maternal BMI and height. To elucidate any differences between proportionate and disproportionate LGA infants, the regression analyses were also performed with proportionate LGA infants as the reference category. In a sub-analysis, the adjusted models were also stratified by sex. We tested for interaction between sex and neonatal body size categories as well as between preterm birth and neonatal body size categories using the likely hood ratio test.

MATERIAL AND METHODS STUDY IV

The study cohort comprised 3,457 singleton infants (1,758 boys) born to mothers with T1DM in 1998-2007. The reference population for fetal growth included 764,498 singleton infants to mothers without a diagnosis of diabetes. Exposure in women with and without T1DM was defined as overweight (BMI $\geq$ 25-29.9 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2) and pregnancy outcomes were compared with that of normal weight women (BMI 18.5-24.9 kg/m^2). Women with BMI< 18.5 kg/m^2 (underweight) and records with missing data on BMI were excluded. As reference for fetal growth, percentiles of birth weight, length and ponderal index (birth weight in grams/length in cm) ^{3} were formed using data on infants to mothers without a diagnosis of diabetes, excluding records of stillborn infants, with major malformations or from multiple pregnancies.

Maternal and infant characteristics

Maternal characteristics included were nationality (Nordic yes/ no), age, parity, prepregnancy weight and height; BMI (calculated as weight in kg/ length in m²), chronic hypertension (yes/ no), smoking during the first trimester (yes/ no). Infant characteristics included sex, gestational age, birth weight and length.

Outcome variables

The primary outcome variable was large for date infants, defined as a birth weight equal to or above the 90th percentile for gestational age and gender.

Secondary outcome variables included major malformations, preeclampsia (severe and mild), perinatal mortality, delivery by Caesarean section and neonatal overweight (birth weight and ponderal index ≥ 90th percentile, for gestational age and gender).

Statistical methods

Unconditional logistic regression was used to explore associations between maternal BMI categories and adverse outcomes with normal weight (BMI 18.5-24.9 kg/m²) women as the reference category as follows: the odds ratios of adverse outcomes in relation to BMI category were estimated in women with type 1 diabetes with 1) normal weight women with type 1 diabetes as reference category and 2) with normal weight non-diabetic women as reference category and in non-diabetic women with normal weight non-diabetic women as reference category.

The final regression model included the following possible confounders/ covariates based on their association with the exposure and primary outcome: Nordic origin (yes/ no), maternal age, height, parity, smoking and chronic hypertension.

None of the variables acted as confounders on the association between exposure and the primary outcome. The final regression models for the secondary outcomes included covariates significantly associated with the outcomes in univariate analysis. Missing indicator variables were used for maternal age and height. The likelihood ratio test was used to explore potential interaction between BMI categories and T1DM for the risk of adverse outcomes.

RESULTS

STUDY I

This study demonstrates significantly increased risk of obstetric and perinatal complications in T1DM pregnancies compared with the general obstetric population.

Maternal characteristics

Women with T1DM were significantly more often of Nordic origin, had higher prepregnancy BMI and higher frequency of chronic hypertension. Smoking in early pregnancy showed a minor, but statistically significant difference between the groups, Table 1.

Maternal characteristics in type 1 diabetes and the general obstetric population in Sweden 1991-2003

	Type 1 diabetes	Controls
	N= 5,089	**N= 1,260,207**
Nordic origin (%)	92.6	86.8
Maternal age (years)	29.6 ± 5.1	29.0 ± 5.1
Primapara (%)	44.5	42.4
Height (cm)	166 ± 6.3	166 ± 6.2
Prepregnancy weight (kg)	71.4 ± 13.4	66.5 ± 12.1
Prepregnancy BMI (kg/m2)	25.9 ± 4.6	24.0 ± 4.1
Chronic hypertensive disease (%)	2.1	0.24
No smoking in pregnancy (%)	82,0	83,8
Smoking - < 10 cig/ day (%)	10.9	10,6
Smoking - ≥ 10 cig/ day (%)	7,1	5,6

Data are mean ± SD values or proportions in %. With the exception of maternal height, all differences between type 1 diabetics and controls are statistically significant with p-values < 0.001 (Students t-test or chi square test).

Obstetric outcomes

The incidences of hypertensive disorders in pregnancy, instrumental delivery and Caesarean section were all significantly increased in women with T1DM compared with the background population. In comparison with the background population, the risk of pregnancy induced hypertension was 1.5 times elevated in T1DM women [adj OR 1.53 (1.18-1.99)]. The odds of severe preeclampsia was 5 times elevated [crude OR: 5.58 (4.75-6.75). After adjustment for potential confounders, the OR for severe preeclampsia decreased but was still much elevated [adj OR 4.47 (3.77-5.31)]. The odds of instrumental delivery and delivery by Caesarean section were also significantly increased in T1DM pregnancies [adj OR Caesarean section: 5.31 (4.97-5.69)].

Pregnancy complications and mode of delivery in type 1 diabetic pregnancies (n= 5,089) and controls (n= 1,260,207)

Outcome variable	Proportions (%)		OR (95% CI) for group differences	
	Type 1 diabetes	Non-diabetes	Crude	Adjusted
PIH	1.6	0.87	1.93 (1.50 - 2.49)	1.53 (1.18 - 1.99)
Preeclampsia, mild	9.7	2.0	5.37 (4.81 - 6.00)	4.30 (3.83 - 4.83)
Preeclampsia, severe	4.3	0.8	5.58 (4.75 - 6.57)	4.47 (3.77 - 5.31)
Caesarean section	46	12	5.85 (5.49 - 6.25)	5.31 (4.97 - 5.69)
VE/ forceps	9.6	6.6	1.48 (1.33 - 1.66)	1.41 (1.25 - 1.58)

OR = odds ratio, CI = confidence interval, adjusted OR = OR adjusted for group differences in maternal age, body mass index, parity, chronic hypertensive disorder, smoking habits, and ethnicity. PIH = pregnancy induced hypertension, VE = vacuum extraction

Fetal and neonatal death

The incidences of stillbirth, perinatal and neonatal mortality were all significantly higher in T1DM pregnancies. The risk of stillbirth and perinatal mortality were 4 times elevated in the unadjusted model and 3 times elevated after adjustment for potential maternal confounders. The risk of neonatal death was 3 times higher in T1DM offspring as compared to the reference group, Table 2.

Other fetal and neonatal outcomes

In comparison with the background population, the incidences of all fetal complications and neonatal morbidities were significantly increased. The risk of major malformations was 2.5 times elevated: adj OR 2.50 (2.13-2.94). Noteworthy is the markedly increased incidence of large for date (LGA) infants in the diabetic cohort (31%) compared with the reference (3.6%). The OR for an LGA outcome was 11.36, even after adjustment for potential maternal confounders such as parity and BMI. On the other hand, the risk of an SGA outcome was decreased: adj OR 0.71(0.55-0.91), Table 3.

Fetal and neonatal complications in type 1 diabetic pregnancies and the general obstetric population

Outcome variable	Proportions – (% if not indicated otherwise)		OR (95% CI)- for group differences	
	Type 1 DM	Controls	Crude	Adjusted
Stillbirth	1.5	0.3	4.04 (3.02-5.40)	3.34 (2.46-4.55)
Fetal distress	14	6.2	2.45 (2.24-2.69)	2.34 (2.12-2.58)
Perinatal mortality, ‰	20	4.8	4.02 (3.11-5.20)	3.29 (2.50-4.33)
Neonatal mort., 0–7 d, ‰	5.1	1.8	2.91 (1.97-4.28)	3.05 (1.68-5.55)
Neonatal mort., 0-28 d, ‰	7.0	2.2	3.08 (2.02-4.70)	2.67 (1.72-4.16)
Birth < 37 weeks GA	21	5.1	5.27 (4.88-5.71)	4.86 (4.47-5.28)
Birth < 32 weeks GA	2.3	0.7	3.58 (2.89-4.44)	3.08 (2.45-3.87)
LGA	31	3.6	12.2 (11.4-13.1)	11.4 (10.6-12.4)
SGA	2.3	2.5	0.80 (0.63-1.02)	0.71 (0.55-0.91)
Major malformations	4.7	1.8	2.70 (2.37-3.08)	2.50 (2.13-2.94)
Apgar < 7 at 5 min	3.1	1.1	2.98 (2.54-3.50)	2.60 (2.14-3.17)
Apgar < 4 at 5 min	0.80	0.30	2.60 (1.79-3.78)	2.39 (1.64-3.51)
Erb`s palsy*	2.1	0.25	7.91 (5.77-10.8)	6.69 (4.81-9.31)
RDS	1.0	0.20	4.88 (3.51-6.81)	4.65 (2.20-9.84)
Respiratory disorders	9.5	2.6	4.02 (3.67-4.42)	3.42 (3.04-3.85)

OR = odds ratio, adjusted OR = OR adjusted for group differences in maternal age, body mass index, parity, chronic hypertensive disorder, smoking habits, and ethnicity. LGA = large for gestational age, SGA = small for gestational age, RDS = respiratory distress syndrome. *= vaginal deliveries only. GA= gestational age.

Results in relation to number of T1DM pregnancies cared for per year and hospital

In total 43% of all T1DM women were delivered in hospitals caring for < 10 T1DM pregnancies per year, 37.5% at hospitals caring for 10-19 T1DM pregnancies per year and 19.4% at large hospitals, caring for >19 T1DM pregnancies per year. A diagnosis of fetal distress and transient tachypnea was more common in larger hospitals, caring for >19 T1DM

pregnancies per year. Except from these two outcomes, there were no significant differences in outcome between hospitals of different size.

Results in relation to calendar year of birth

The incidence of LGA increased in the diabetic group from 27.6% in the first to 35.0% in the second time period of the study (P<0.001). The proportion of LGA infants increased significantly in the general obstetric population also, from 3.38% in the first to 3.77% in the last study period (P<0.001). Over time, the proportion of women with BMI > 30 kg/m² increased in both groups. In the first study period, 13.2% of type 1 diabetic women were obese compared with 18.4% during the second period (p<0.001). The corresponding figures for control women were 7.3% (period1) and 11.3% (period 2).

Missing data on maternal BMI and outcome

The reference population consisted of 1,260,207 women without type 1 diabetes. The multivariate regression analysis was confined to women with full data on BMI, n=954,292. In total 311,066 records were excluded due to missing or unlikely values on maternal weight and height. 3,728 of those were women with T1DM. 38% of the missing data on BMI was due to low registration rates of anthropometric data in 1991, with equal frequency in T1DM and non-diabetics. During the whole study period (1991-2003), BMI data was registered in 74.5% of T1DM women and in 74.4% of women without diabetes. In both the T1DM and reference cohort, the incidence of preeclampsia was slightly higher in women with data on BMI compared with those without BMI data. This difference did not reach statistical significance. The incidence of major malformations did not differ between women with and without data on BMI in either the T1DM cohort or reference group. An intriguing finding was that the incidence of stillbirth and perinatal mortality was significantly higher in women without data on BMI in both women with and without T1DM. The observed difference is most likely not due to a higher mean BMI in the group of women who were missing for this variable as we did not find any difference in the incidence of preeclampsia between the two groups and given the strong association between high BMI and preeclampsia. The increased incidence of stillbirth and perinatal death in women without data on BMI was similar in both T1DM and non-diabetic women. It is therefore unlikely that this finding would bias our results.

RESULTS STUDY II

This study demonstrates unimodal and significantly right-shifted distributions of birth weight, length and head circumference in T1DM offspring. Fetal macrosomia is more pronounced in female compared with male T1DM offspring and is greater in preterm than in term infants.

Maternal and infant characteristics

Women with T1DM were significantly more often of Nordic origin and had higher BMI than women in the reference group. In spite of a significantly lower mean gestational age at in the study group (37.7 *vs.* 39.4 weeks, respectively) the mean birth weight was significantly higher in infants born to mothers with T1DM: 3,775g (SD: 711) *vs.* reference group: 3,570 (SD: 547), respectively.

Maternal and infant characteristics (singleton pregnancies only).

	Type 1 diabetes	Reference population	P-value
	n = 3,705	**n = 883,163**	
Maternal characteristics			
Nordic origin	3,409 (92.0%)	736,327 (83.4%)	<0.001
Age, years	30.4 (5.0)	30.0 (5.1)	<0.001
Pre-pregnancy weight, kg	72.5 (13.6)	67.7 (12.8)	<0.001
Height, cm	166.6 (6.3)	166.4 (6.3)	0.242
BMI, kg/m^2	26.1 (4.7)	24.5 (4.4)	<0.001
Primipara	1,665 (44.9%)	389,430 (44.1%)	0.302
Smoking (first trimester)	373 (10.1%)	81,502 (9.2%)	0.078
Infant characteristics			
Gestational age, weeks	38 (2.0)	39 (1.7)	<0.001
Males	1,876 (50.6%)	452,809 (51.3%)	0.44
Birth weight, grams	3,775 (711)	3,570 (547)	<0.001
Birth weight, SDS	+1.27 (1.5)	+0.01 (1.0)	<0.001
Birth length, cm	50.5 (2.8)	50.5 (2.4)	0.88
Birth length, SDS	+0.70 (1.2)	+ 0.00 (1.0)	<0.001
Head circumference, cm	35.0 (1.8)	35.0 (1.7)	0.29
Head circumference, SDS	+0.57 (1.0)	+ 0.06 (1.0)	<0.001
LGA	1,753 (47.3%)	87,283 (9.9%)	<0.001
Ponderal index, g/cm^3	2.90 (0.3)	2.76 (0.4)	<0.001
Ponderal index $\geq 90^{th}$ centile	1,111 (30.0%)	91,173 (10.3%)	<0.001
Proportionate LGA	943 (25.5%)	56,634 (6.4%)	<0.001
Disproportionate LGA	810 (21.9%)	30,649 (3.5%)	<0.001

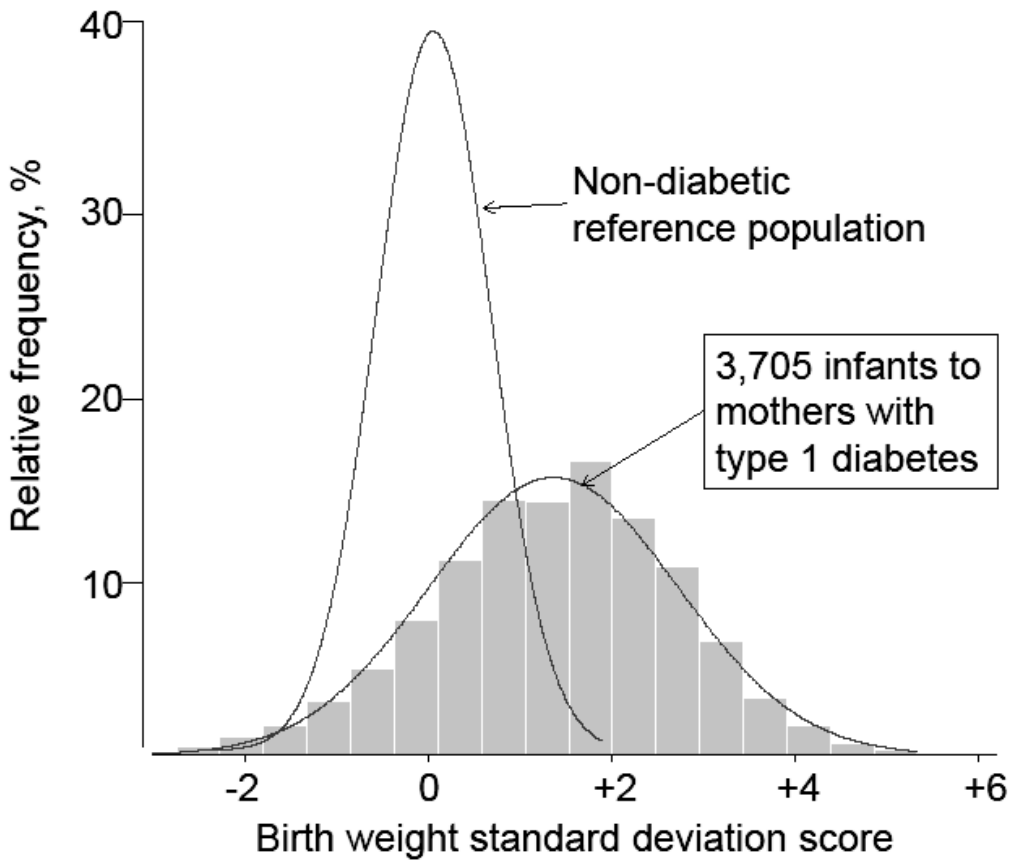
Data are mean (SD) or numbers (%). BMI = body mass index, SDS = standard deviation score, LGA = large for gestational age (birth weight ≥ 90th percentile), proportionate LGA = BW ≥90th percentile and ponderal index <90th percentile, disproportionate LGA = both BW and ponderal index ≥90th percentile.

Diabetes in pregnancy and size at birth

Infants to mothers with T1DM showed a bellshaped birth weight distribution. The distribution was wider and markedly shifted to the right of the normal reference, figure 1**.** All anthropometric measures were significantly shifted to the right in the study group, values are mean standard deviation scores (SDS) and (SD): birth weight: +1.27 (1.48), birth length: +0.70 (1.22) and head circumference: +0.57 (1.03). 47% of the infants in the study cohort were LGA (birth weight ≥ 90^{th} percentile) and 27% had a birth weight ≥+2SD above the mean.

The mean ponderal index was also significantly higher in T1DM offspring [mean: 2.90 (0.33) g/cm^3] compared with reference infants [mean 2.76 (0.35) g/cm^3]. One third of all infants in the study cohort had a PI ≥ 90^{th} percentile. The corresponding proportion in the reference group was 10%. 46% of LGA infants in the study group had a PI ≥ 90^{th} percentile, the corresponding figure in reference LGA infants was 35%.

Distribution of birth weight standard deviation scores in 3,705 type 1 diabetic offspring and in a non-diabetic reference population (n=883,163).

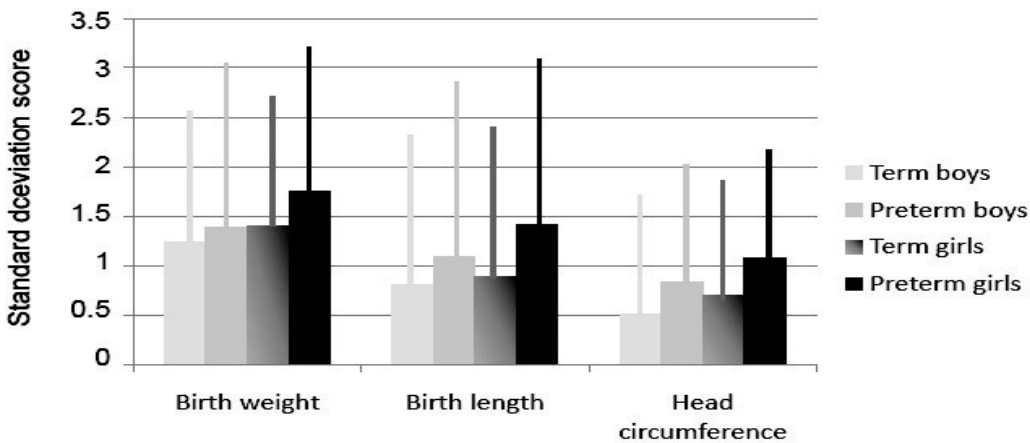


Birth size in relation to fetal gestational age

The growth deviation was more pronounced in preterm than in term T1DM offspring. The mean SDS for birth weight and length were significantly higher in preterm infants compared to infants born at term ($p < 0.05$). The proportion of LGA babies was also significantly larger in preterm infants (55.2%) compared with term infants (45.3%). The proportion of preterm infants with a PI $\geq 90^{th}$ percentile was also higher in preterm (36.5%) than in term infants (28.4%), $p < 0.001$, figure 2.

Standard deviation scores for birth weight, birth length and head circumference in type 1 diabetic offspring, stratified on sex and gestational age. Bars are means and horizontal lines indicate SD.

Figure 2



Birth size in relation to sex

Female T1DM offspring had significantly higher mean SDS for birth weight, length and head circumference compared with male infants to mothers with T1DM (p-value for all comparisons <0.01). Females in the study cohort were more often LGA (50% *vs.* 45%) and had a higher mean PI compared to male T1DM offspring (p-value < 0.01 for both comparisons), figure 2.

Birth size in relation to maternal BMI

Mothers of disproportionate LGA infants (both birth weight and PI $\geq 90^{th}$ percentile) born at term, had significantly higher BMI compared with mothers to proportionate LGA babies. This was true for both the study and reference group. In preterm infants no relation between maternal BMI and infant size was found.

Complementary analyses (data not shown in paper)

In opposite to the findings in the study cohort, males in the control group had significantly higher mean SDS for weight and length compared with females. The mean SDS for head circumference did not differ significantly between males and females. Males had higher mean absolute birth weight than females, however this difference was much larger than in the study cohort (control: males on average 129 grams heavier than females and the corresponding difference in study group was 29 grams). The incidence of LGA infants was similar between genders (p=0.54) in the control group and there was no difference between

males and females with respect to disproportionate birth size i.e. ponderal index ≥90th percentile. In accordance with the findings in the T1DM cohort, females to mothers in the control group also had significantly higher mean ponderal index than boys. However, the difference in mean PI between genders was slightly larger in the T1DM cohort compared with the difference observed in the control group. In total, 0.97% of women in the control group had a diagnosis of diabetes type 2 or gestational diabetes. 25% of the women in the control group with a diagnosis of diabetes gave birth to an LGA infant, 10% had a disproportionate LGA infant.

RESULTS STUDY III

This study demonstrates that the risk of perinatal complications is significantly increased in LGA compared with AGA T1DM offspring. The risk is independent of body proportionality in T1DM offspring. Gestational age is a significant effect modifier of the association between neonatal body size and adverse perinatal outcome.

Infant characteristics

The proportions of preterm births and girls were higher in LGA (44% preterm and 52% girls) compared to AGA (30% preterm and 47% girls) infants to type 1 diabetic mothers (p-value for both comparisons < 0.01). The mean birth weight in disproportionate LGA infants was approximately 200 grams higher compared with proportionate LGA infants. In comparison with AGA babies, LGA infants were more often delivered by Caesarean section and among these LGA infants the rate of Caesarean section was highest among infants with disproportionate body composition, Table 1. The mean difference in birth weight between term (n= 2,207) and preterm infants (n=1,310) was 763 grams (data not shown) and between boys and girls 43 grams (boys heavier). The mean difference in birth weight between AGA and LGA infants within the preterm group was 943 grams and the mean gestational age in this group was 36 weeks. The corresponding difference in birth weight between AGA and LGA infants in the term group was 840 grams with a mean gestational age at delivery was 39 weeks.

Mode of delivery and infant characteristics in 3,517 type 1 diabetes offspring. Data are numbers (%) or medians (interquartile range).

	AGA N=1,783	LGA N=1,734	
		proportionate N=943	disproportionate N=791
Infant characteristics			
Male	943 (53)	447 (47)	386 (49)
GA, wks	38 (37-39)	38 (37-39)	38 (37-39)
Preterm birth (GA=32-37wks)	542 (30)	407 (43)	361 (46)
Birth weight, g	3,500 (3,200-3,789)	4,210 (3,895-4,458)	4,390 (4,085-4,692)
Mode of delivery			
C. section	751(42)	480 (51)	513 (65)
Ventouse/forceps	234 (24)	104 (24)	37 (15)

AGA = appropriate for gestational age, LGA = large for gestational age, GA = gestational age

Neonatal mortality and morbidity, proportions

The overall rate of neonatal morbidity was comparatively low in the study cohort compared with results from previous studies and no infants died after the first month of life, Table 2.

The incidence of respiratory disorders was 4% (80% TTN) and was more frequent in preterm than in term infants. The incidences of low Apgar scores (<7 at 5 min) and hyperbilirubinaemia were also significantly higher in the preterm group (p-value < 0.01 for both comparisons). The risk of neonatal hypoglycaemia was independent of preterm delivery (11% in preterm and 9% in term infants, p-value > 0.05).

Apart from fetal distress and Apgar score < 5 at 7 min that was significantly more frequent in proportionate than disproportionate LGA infants, there were no significant differences in outcomes between the LGA groups.

The primary outcome, composite morbidity, was significantly more frequent in LGA as compared with AGA infants. The incidences of all secondary outcomes, except neonatal seizures and hypoglycaemia, were also significantly higher in LGA infants.

Neonatal outcome in appropriate (AGA) and large for gestational age (LGA) infants to type 1 diabetic mothers. LGA-infants are stratified according to body proportions (disproportion = ponderal index ≥ 90th percentile). Data are numbers (%).

	AGA N=1,783	LGA N=1,734		
		proportionate	disproportionate	P value
		N=943	N=791	P-LGA/D-LGA
Morbidity				
Composite morbidity	550 (31) ***	397 (42)	325 (41)	0.670
Fetal distress	295 (17) ***	132 (14)	70 (8.9)	0.001
Apgar score < 7 at 1min	169 (9.5) *	135 (14)	71 (8.9)	0.001
Apgar score < 7 at 5min	28 (1.6) *	27 (2.9)	19 (2.4)	0.552
HIE	2 (0.11)	2 (0.21)	0	x
Neonatal seizures	10 (0.56)	5 (0.53)	1 (0.13)	x
Birth trauma †	24 (2.5) ***	38 (8.7)	23 (9.0)	0.878
- **Erbs palsy †**	7 (0. 72) ***	18 (4.1)	12 (4.7)	0.710
- **Clavicle fracture †**	20 (2.1) ***	22 (5.0)	15 (5.9)	0.627
Acute respiratory disorder	50 (2.8) ***	48 (5.1)	44 (5.6)	0.662
- **TTN**	39 (2.2) ***	39 (4.1)	36 (4.6)	0.672
- **RDS**	12 (0.67)	9 (0.95)	8 (1.01)	0.905
Hyperbilirubinaemia	81 (4.5) ***	71 (7.5)	64 (8.1)	0.664
Hypoglycaemia 0-6 h	199 (11)	125 (13)	96 (12)	0.486
Hypoglycaemia > 6 h	163 (9.1)	97 (10.3)	89 (11.3)	0.518
Mortality				
Early neonatal death	1 (0.06)	1 (0.11)	3 (0.38)	x
Late neonatal death	3 (0.17)	0	1 (0.13)	x
Number of vaginal deliveries	971	438	255	<0.001

Abbreviations: Composite outcome: any of the following outcomes: Apgar < 7 at 5 min, birth trauma, acute respiratory disorders, hyperbilirubinaemia, hypoglycaemia >6h postnatal. HIE: hypoxic ischemic encephalopathy. Birth trauma = Erbs palsy and/or clavicle

fracture. TTN: transient tachypnea of the newborn, RDS: respiratory distress syndrome. † Only vaginally delivered infants. *p<0.05 and *** p<0.001 comparing AGA and LGA infants

Neonatal mortality and morbidity, odds ratios stratified by gestational age

Preterm infants There were no significant differences between proportionate and disproportionate LGA infants born preterm or between AGA and LGA babies.

Term infants Overall, there was no significant difference in the risk of adverse outcome between proportionate and disproportionate LGA infants born at term.

In term LGA infants, the crude odds ratio of composite morbidity was significantly increased compared with AGA, with little change in estimates after adding covariates to the regression model. Furthermore, the adjusted odds ratios for respiratory disorders and hyperbilirubinaemia were significantly increased in both LGA groups. The risk of birth trauma in vaginally delivered infants was 4 times increased in term LGA compared with AGA infants in the unadjusted model, Table 3. The odds ratios were no longer significantly increased in the final model, including adjustment for differences in absolute BW (data not shown in table).

Crude and adjusted odds ratios (OR; 95% CI) for neonatal complications in proportionate and disproportionate LGA type 1 diabetic offspring. AGA type 1 diabetic offspring is used as reference (OR=1) in all calculations, and outcomes are stratified according to gestational age.

	AGA	**LGA proportionate**	**LGA disproportionate**
	no=1,783	**no=943**	**no=791**
Composite morbidity			
No of cases=preterm/term	N=234/316	N=195/202	N=167/158
Crude OR Preterm	1.0	1.21 (0.94-1.57)	1.13 (0.87-1.48)
Crude OR Term	1.0	1.77 (1.43-2.20)	1.70 (1.35-2.15)
Adjusted OR Preterm	1.0	1.21 (0.94-1.57)	1.18 (0.90-1.54)
Adjusted OR Term	1.0	1.80 (1.45-2.24)	1.77 (1.39-2.26)
Birth trauma			
No of cases=preterm/term	N=6/18	N=10/28	N=7/16
Crude OR Preterm	1.0	2.29 (0.81-6.42)	2.57 (0.84-7.84)
Crude OR Term	1.0	4.71 (2.56-8.66)	4.87 (2.42-9.79)
Adjusted OR Preterm#	1.0	2.36 (0.82-6.73)	2.81 (0.89-8.83)
Adjusted OR Term#	1.0	4.72(2.54-8.78)	4.78 (2.36-9.71)
Respiratory disorders			
No of cases=preterm/term	N=37/13	N=33/15	N=28/16
Crude OR Preterm	1.0	1.20 (0.74-1.96)	1.15 (0.69-1.91)
Crude OR Term	1.0	2.72 (1.29-5.76)	3.65 (1.74-7.65)
Adjusted OR Preterm*	1.0	1.21 (0.74-1.98)	1.00 (0.60-1.68)
Adjusted OR Term*	1.0	2.38 (1.12-5.06)	2.77 (1.29-5.93)
Hyperbilirubinaemia			
No of cases= preterm/term	N=64/17	N=55/16	N=53/11
Crude OR Preterm	1.0	1.17 (0.79-1.72)	1.29 (0.87-1.90)
Crude OR Term	1.0	2.22 (1.11-4.42)	1.89 (0.88-4.07)
Adjusted OR Preterm*	1.0	1.16 (0.79-1.71)	1.36 (0.91-2.01)
Adjusted OR Term*	1.0	2.38 (1.19-4.76)	2.22 (1.01-4.88)
Hypoglycaemia			
No of cases=preterm/term	N=62/101	N=38/59	N=43/46
Crude OR Preterm	1.0	0.80 (0.52-1.22)	1.05 (0.69-1.58)

Crude OR Term	1.0	1.40 (1.00-1.96)	1.35 (0.94-1.95)
Adjusted OR Preterm*	1.0	0.81 (0.53-1.24)	1.15 (0.76-1.76)
Adjusted OR Term*	1.0	1.42 (1.01-2.00)	1.42 (0.97-2.08)

#Adjusted for maternal BMI and maternal height. *Adjusted for mode of delivery by Caesarean section and fetal distress (yes/no).Birth trauma: only vaginally delivered infants. Abbreviations: LGA: large for gestational age, RDS: respiratory distress syndrome, TTN: transient tachypnea of the newborn.

Interaction analysis gestational age and neonatal outcome

Gestational age was a significant effect modifier of the association between neonatal body size category and composite morbidity, acute respiratory disorders and hyperbilirubinaemia (p-value for all interaction tests <0.05), preterm birth being a stronger risk factor for perinatal complications than fetal macrosomia. On the other hand, there was no significant interaction between gestational age and neonatal body size category on the risk of hypoglycaemia and birth trauma. The stratified analysis indicated that there was a significant interaction between gestational age and body size category for the risk of birth trauma. However, the likelihood ratio test was not significant for this outcome, probably due to limited power.

Interaction analysis sex and neonatal outcome

The incidence of respiratory disorders were significantly higher in LGA males than in LGA females, p =0.036. However, there was no evidence of an effect modification by sex on the association between neonatal body size category and any of the outcomes.

Complementary analyses (data not shown in paper)

In contrast to the findings in the study cohort, there were significant differences in the risk of neonatal morbidities in disproportionate and proportionate LGA babies in non-diabetic pregnancies. Disproportionate LGA infants to non-diabetic mothers had significantly higher incidence of composite morbidity, Erbs palsy, low Apgar scores, respiratory disorders (respiratory distress syndrome and transient tachypnea), neonatal seizures and metabolic disorders (hypoglycaemia and hyperbilirubinaemia) (p-value for all comparisons < 0.001) compared with proportionate LGA infants. There was no significant difference between the two LGA groups regarding the incidence of fetal distress. As in the study cohort, disproportionate LGA infants were on average 200 grams heavier than proportionate LGA babies.

RESULTS STUDY IV

This study shows that high maternal pre pregnancy BMI is a very important risk factor for adverse pregnancy outcome in women with and without type 1 diabetes. High maternal BMI and type 1 diabetes are independent risk factors for maternal and perinatal complications. The risk of adverse outcome in women with concomitant type 1 diabetes and obesity exceeds that of either condition alone, indicating synergism between the two exposures. T1DM is a significant effect modifier of the association between BMI category and preeclampsia, major malformation, LGA and neonatal overweight.

Maternal and infant characteristics

35% of women with T1DM were overweight and 18% were obese, the corresponding figures in the reference population were 26% and 11%, respectively. The median BMI in women with T1DM was significantly higher (25.1 kg/m²) than for women in the reference group (23.6 kg/m²), p-value < 0.001. Women in the diabetes cohort were more often of Nordic origin, had higher prevalence of chronic hypertension and smoking during the first trimester (p-value for all comparisons < 0.01). Infants to mothers with T1DM had a significantly lower median gestational age at delivery (38 weeks, IQR: 37-39) than infants in the reference population (40 weeks, IQR: 39-41) and preterm birth was four times as common in T1DM offspring.

Maternal characteristics, type 1 diabetes and reference population

	Type 1 diabetes	**Non-diabetic population**	**P-value**
	N=3,457	N=764,498	
Maternal characteristics			
Nordic, n (%)	3,194 (92)	643,608 (84)	<0.001
Swedish origin	3,151 (91)	628,534 (82)	<0.001
Maternal age, years (median, IQR)	30 (27-34)	30 (27-33)	<0.001
Smoking first trimester, n (%)	384 (11)	72,766 (10)	0.001
Primipara, n (%)	1,559 (45)	337,199 (44)	0.242
BMI, kg/m² (median, IQR)	25,1 (23,0-28,4)	23,6 (21,6-26,4)	<0.001
Over weight (BMI ≥ 25-29.9), n (%)	1,195 (35%)	200,600 (26%)	<0.001
Obese (BMI ≥30), n (%)	618 (18%)	82,331 (11%)	<0.001
Height, cm (median,IQR)	167 (162-170)	167 (162-170)	0.250
Chronic hypertension, n (%)	92 (2.7)	2,472 (0.32)	<0.001
Infant characteristics			
Male, n (%)	1,758 (51%)	393,324 (51%)	0.485
Gestational age, weeks (md,IQR)	38 (37-39)	40 (39-41)	<0.001
Preterm delivery (n, %)	741 (21%)	35,878 (4.7%)	<0.001
Birth weight, g (md,IQR)	3,805 (3,350-4,265)	3,575 (3,240-3,915)	<0.001
Birth length, cm (md,IQR)	51 (49-52)	51 (49-52)	0.576
LGA, BW ≥90 percentile, n (%)	1,694 (49)	81,142 (11)	<0.001
AGA, BW 10-90 percentile, n (%)	1,661 (48%)	614,784 (80%)	<0.001
SGA, BW <10 percentile, n (%)	109 (3.2%)	76,214 (10)	<0.001

*Chi square test, Kruskall Wallis test, Chi square test for trends

Adverse outcome in relation to BMI category

Incidence

Overall, the incidence of all adverse outcomes was significantly higher in women with type 1 diabetes, irrespective of BMI category. The incidence of the primary outcome was highest in obese women, with and without type 1 diabetes; however the difference between BMI categories was not significant within the diabetes cohort. The incidence of all secondary outcomes was highest in obese women with and without type 1 diabetes, except for perinatal mortality in type 1 diabetic pregnancies with the highest recorded frequency in overweight women. Within the non-diabetic pregnancies, the incidence of all outcomes increased significantly with greater BMI category (chi square test for trends for all outcomes <0.001), Table 2.

Outcomes, type 1 diabetes and reference population stratified for BMI

	BMI 18.5-24.9	BMI 25-29.9	BMI≥30	P- value
LGA				
Type 1 diabetes	778 (47)	603 (50)	313 (51)	0.170
Non-diabetic	39,265 (8.2)	26,828 (13)	15,049 (18)	<0.001
Major malformations				
Type 1 diabetes	65 (4.0)	44 (3.7)	41 (6.6)	0.008
Non-diabetic	8,186 (1.7)	3,736 (1.9)	1,610 (2.0)	<0.001
Preeclampsia				
Type 1 diabetes	222 (14)	185 (15)	114 (18)	0.012
Non-diabetic	9,872 (2.1)	6,529 (3.3)	4,810 (5.8)	<0.001
Preterm delivery				
Type 1 diabetes	322 (20)	275 (23)	144 (23)	0.041
Non-diabetic	21,714 (4.5)	9,464 (4.7)	4,700 (5.7)	<0.001
Perinatal mortality				
Type 1 diabetes	14 (0.85)	15 (1.3)	6 (0.97)	0.566
Non-diabetic	1,554 (0.32)	948 (0.47)	593 (0.72)	<0.001
Cesarean section				
Type 1 diabetes	748 (46)	639 (53)	362 (59)	<0.001
Non-diabetic	64,131 (13)	34,081 (17)	18,166 (22)	<0.001
Neonatal overweight				
Type 1 diabetes	351 (21)	288 (24)	166 (27)	0.016
Non-diabetic	15,359 (3)	10,430 (5)	6,466 (8)	<0.001

*Chi square test, Kruskall Wallis test, Chi square test for trends

Logistic regression analysis

There was a similar pattern of increasing odds ratio (OR) for adverse outcome with greater BMI category in women with and without type 1 diabetes. Inclusion of maternal covariates in the regression models did not significantly change the estimates. Relative to a normal weight non-diabetic woman, the adjusted OR´s for LGA in overweight or obese women with type 1 diabetes were approximately 12, compared with [1.76 (1.73-1.79)] in overweight and [2.60 (2.55-2.66)] in obese non-diabetic women, Table 3.

Crude and Adjusted* Odds ratios (CI) for outcomes within the T1DM and non-diabetic population, respectively.

	Reference group				
	Non-diabetic	T1DM			Interaction#
	BMI 18.5-24.9	BMI 18.5-24.9	BMI 25-29.9	BMI≥30	P value
LGA, T1DM					
Crude	1.0	10.16 (9.10-11.36)	12.40 (11.22-13.70)	12.29 (10.50-14.40)	<0.001
Adjusted	1.0	10.72 (9.56-12.01)	13.55 (12.23-15.02)	13.26 (11.27-15. 59)	<0.001
LGA, reference					
Crude	1.0	-	1.74 (1.71-1.77)	2.52 (2.47-2.57)	<0.001
Adjusted	1.0	-	1.76 (1.73-1.79)	2.60 (2.55-2. 66)	<0.001
Major malformations,T1DM					
Crude	1.0	2.28 (1.71-3.04)	2.34 (1.81-3.02)	4.11 (2.99-5.65)	0.03
Adjusted	1.0	2.28 (1.71-3.04)	2.34 (1.81-3.03)	4.11 (2.99-5.65)	0.03
Major malformations, reference					
Crude	1.0	-	1.10 (1.06-1.14)	1.15 (1.09-1.22)	0.03
Adjusted	1.0	-	1.10 (1.06-1.14)	1.15 (1.09-1.22)	0.03
Preeclampsia, T1DM					
Crude	1.0	7.12 (6.02-8.42)	9.30 (8.11-10.67)	11.23 (9.15-13.77)	<0.001
Adjusted	1.0	7.17 (6.04-8.50)	9.91(8.61-11.40)	14.19 (11.50-17.50)	<0.001
Preeclampsia, reference					
Crude	1.0	-	1.61 (1.56-1.66)	2.96 (2.86-3.07)	<0.001
Adjusted	1.0	-	1.74 (1.69-1.80)	3.37 (3.25-3.49)	<0.001
Preterm delivery, T1DM					
Crude	1.0	4.86 (4.22-5.60)	6.23 (5.53-7.02)	6.39 (5.30-7.71)	0.16
Adjusted	1.0	4.72 (4.09-5.44)	5.98 (5.31-6.74)	5.97 (4.94-7.21)	0.15
Preterm delivery, reference					
Crude	1.0	-	1.05 (1.02-1.07)	1.28 (1.24-1.32)	0.16
Adjusted	1.0	-	1.04 (1.02-1.07)	1.26 (1.22-1.30)	0.15
PMR,T1DM					
Crude	1.0	2.55 (1.36-4.76)	3.93 (2.49-6.19)	3.14 (1.40-7.04)	0.29
Adjusted	1.0	2.46 (1.32-4.60)	3.72 (2.36-5.89)	2.86 (1.27-6.44)	0.31

PMR, reference					
Crude	1.0	-	1.47 (1.35-1.59)	2.24 (2.04-2.46)	0.29
Adjusted	1.0	-	1.46 (1.35-1.59)	2.22 (2.03-2.44)	0.31
Cesarean section,T1DM					
Crude	1.0	5.59 (5.00-6.25)	7.09 (6.42-7.83)	9.44 (8.04-11.08)	0.42
Adjusted	1.0	5.69 (5.09-6.37)	7.12 (6.44-7. 88)	9.35 (7.95-11.00)	0.36
Cesarean section, reference					
Crude	1.0	-	1.33 (1.31-1.35)	1.84 (1.81-1.88)	0.42
Adjusted	1.0	-	1.34 (1.32-1.36)	1.87 (1.83-1.90)	0.36
Neonatal overweight,T1DM					
Crude	1.0	8.46 (7.39-9.70)	9.93 (8.83-11.17)	11.71 (9.79-14.00)	<0.001
Adjusted	1.0	8.40 (7.32-9.64)	9.86 (8.76-11.11)	11.29 (9.42-13.53)	<0.001
Neonatal overweight, reference					
Crude	1.0	-	1.66 (1.62-1.71)	2.59 (2.51-2.67)	<0.001
Adjusted	1.0	-	1.65 (1.61-1.69)	2.55 (2.48-2.63)	<0.001

Both sets of analysis are performed with normal weight, non-diabetic women as reference *Adjusted for ethnicity, maternal age, height, parity, smoking first trimester, chronic hypertension #Interaction between BMI category and T1DM

Table 4 shows the OR for adverse outcome in women with type 1diabetes by BMI category with normal weight women with type 1 diabetes as the reference category. In obese women the adjusted OR of major malformations [1.77 (1.18-2.65)] and preeclampsia [1.74 (1.35-2.25)] were significantly increased compared with normal weight women. The OR of Caesarean section was significantly increased in both overweight and obese women, Table 4.

Crude and Adjusted* Odds ratios (CI), type 1 diabetes

	T1DM BMI 18.5-24.9	T1DM BMI 25-29.9	T1DM BMI≥30
LGA,T1DM			
Crude	1.0	1.13 (0.98-1.32)	1.14 (0.95-1.37)
Adjusted	1.0	1.18 (1.01-1.38)	1.21 (1.00-1.47)
Major malformations, T1DM			
Crude	1.0	0.93 (0.63-1.37)	1.73 (1.15-2.58)
Adjusted	1.0	0.92 (0.62-1.36)	1.77 (1.18-2.65)
Preeclampsia, T1DM			
Crude	1.0	1.17 (0.95-1.45)	1.45 (1.13-1.86)
Adjusted	1.0	1.21 (0.98-1.50)	1.74 (1.35-2.25)
Preterm delivery,T1DM			
Crude	1.0	1.23 (1.02-1.47)	1.25 (1.00-1.56)
Adjusted	1.0	1.22 (1.02-1.47)	1.25 (1.00-1.56)
PMR T1DM			
Crude	1.0	1.48 (0.71-3.08)	1.14 (0.44-2.98)
Adjusted	1.0	1.47 (0.70-3.03)	1.08 (0.41-2.83)
Cesarean section,T1DM			
Crude	1.0	1.38 (1.19-1.60)	1.69 (1.40-2.04)
Adjusted	1.0	1.37 (1.18-1.60)	1.67 (1.38-2.03)
Neonatal overweight, T1DM			
Crude	1.0	1.17 (0.98-1.40)	1.35 (1.09-1.67)
Adjusted	1.0	1.19 (0.99-1.42)	1.36 (1.09-1.69)

*Adjusted for ethnicity, maternal age, height, parity, smoking first trimester, chronic hypertension

Effect modification

T1DM was a significant effect modifier of the association between BMI category and the risk preeclampsia, major malformations, LGA and neonatal overweight.

Complementary analyses, missing data on BMI and outcome (data not shown in paper)

Data on pre-pregnancy BMI was missing in 15% of the T1DM cohort and in 14% of the non-diabetic cohort. The incidence of preeclampsia and major malformations did not differ between women with and without data on BMI in either T1DM women or in the reference group. An intriguing finding was that the incidence of stillbirth and perinatal mortality was higher in women without data on BMI compared to those with data on BMI and this was true in both the study and reference group. The incidence of perinatal mortality was 1% higher in T1DM women with missing data on BMI compared with women with data on BMI (2% *vs.* 1%). The difference was of similar magnitude in the reference group, where it due to large numbers also was statistically significant. The difference in incidence of stillbirth and perinatal mortality observed is most likely not due to a higher mean BMI in the group of women with missing data on BMI. The link between high BMI and preeclampsia is well established and we did not find a difference in the risk of preeclampsia comparing women with and without data on BMI.

COMMENTS STUDY I-IV

These studies show that pregnancy in T1DM is associated with markedly increased risks of obstetric and perinatal complications such as preeclampsia, stillbirth, major malformations perinatal mortality and morbidity. Maternal overweight/ obesity in T1DM increases the risk of adverse outcome further.

One of the most striking findings was the very high incidence of fetal macrosomia (31% had a birth weight $\geq$+2SD and 47% had a birth weight $\geq 90^{th}$ percentile). A more detailed characterization of size at birth demonstrated unimodal and significantly right-shifted distributions of birth weight, length and head circumference. The distribution for birth weight was more markedly shifted to the right of the reference than the distribution for birth length, indicating disproportionate fetal growth. Neonatal overweight or disproportionate body composition characterized by a ponderal index $\geq 90^{th}$ percentile was confirmed in almost half of the LGA T1DM offspring and in one third of the total T1DM cohort. A novel and very interesting finding was that fetal macrosomia was more pronounced in female T1DM offspring than in males and was greater in infants born preterm compared to term deliveries. The gender difference in size at birth runs in opposite directions compared to non-diabetic pregnancies and has not been reported before. Furthermore, an unexpected finding was that the risk of perinatal complications in T1DM offspring was independent of body proportionality.

These studies are by far the largest to present data on pregnancy outcome in T1DM women compared with the background population. The size of the study groups also enabled stratified risk analysis. In contrast to the majority of previous publications on pregnancy outcome in T1DM, we were able to provide population based data. The study design decreases the risk of selection bias and the study cohorts are homogenous with respect to ethnicity and medical management in pregnancy.

A potential limitation with the present studies is the lack of data on maternal metabolic control, duration of diabetes, pre-existing microangiopathy, socioeconomic status, physical activity and diet. Thus, the impact of these variables on the risk of adverse outcome could not be assessed. However, in contrast to in the general obstetric population social disadvantage was not demonstrated as an important risk factor for adverse pregnancy outcome in women with diabetes in a recent study from the UK [8, 174].

For study II and III, we are also aware of the potential limitation regarding accuracy in measurement of infant length. However, in Sweden, birth length is measured according to a standardized procedure using a measure board for length. We consider it unlikely that any potential systematic error of length measurement would differ between infants to mothers with and without type 1 diabetes; i.e. the possible misclassification of birth length is non-differential. It is noteworthy, that the number of infants excluded due to extreme birth length in the present studies was very low (0.01%). In study IV, body mass index was calculated from recalled data on prepregnancy weight and height. Women tend to underestimate their weight and it has been demonstrated that this bias increases directly with the degree of overweight [249]. A potential misclassification of women to lower BMI categories would lead to an underestimation of our findings of increased risks associated with high maternal BMI.

We demonstrate a rate of intrauterine fetal death of 1.5%, equivalent to a four times higher frequency compared to the general obstetric population. This is similar to Swedish national data from 1982-86 [4, 5] and with more recent data from the Nordic countries, France and the UK [3, 8, 9, 11, 151]. Higher rates of stillbirth have been reported in other studies from the UK [6, 7, 138]. The underlying mechanism for stillbirth in T1DM pregnancies is not fully understood. Maternal and fetal hyperglycaemia is associated with chronic fetal hypoxia, as indicated by correlations between amniotic erythropoietin levels and antenatal glycaemic control [139]**.** At the large perinatal centre in Helsinki, an amniocentesis is performed around the 37-38th week of gestation in all T1DM pregnancies, with the primary aim to determine levels of erythropoietin. If high levels of erythropoietin are noted, indicative of fetal hypoxia, delivery by Caesarean section is performed. The comparatively low rate of stillbirth (0.94%) and high rate of Caesarean section (63.5%) reported from Finland, are likely reflections of this management program [11]. There is a U shaped relation between amniotic erythropoietin levels and fetal size in T1DM pregnancies [127], suggesting increased risk of fetal hypoxia in both ends of the birth weight distribution. In the later of our two cohorts of T1DM pregnancies (1998-2007), the majority of stillbirths were LGA fetuses. There is no clear explanation for the varying rates of stillbirth reported. Differences in maternal metabolic control, prevalence of pre-existing angiopathy and other risk factors such as maternal overweight and social disadvantage are likely contributing factors. Unlike the majority of previously published studies on pregnancy outcome in T1DM, we were able to control for several important possible confounders, including ethnicity, smoking and maternal BMI. In non-diabetic pregnancies, important risk factors for stillbirth - besides diabetes - are non-white race, placental abnormalities, high maternal age, smoking, fetal growth restriction, previous stillbirths, high intake of coffee, maternal infections and high maternal haemoglobin in early pregnancy [250-253]. The contribution of these risk factors for the occurrence of stillbirth in T1DM pregnancies is less well explored.

The perinatal mortality rate of 2.0% in 1991-2003 was 1% lower than national data from the 1980ies [5]. In our second cohort from 1998-2007, the perinatal mortality rate had decreased further to 1.2%. Similarly, the stillbirth rate in T1DM pregnancies in 1991-2003 was 1.5% and in 1998-2007 0.81%. Improvements in preconception care and tighter metabolic control in pregnancy have most likely contributed to the decreasing incidence of both stillbirth and perinatal mortality in Sweden. Advances in prenatal diagnostics of malformations with an increasing incidence of induced abortions may also partly explain this finding. In the MBR, there is no data on the number of induced abortions or early fetal losses. Thus, this hypothesis could not be tested. Perinatal mortality rates for T1DM pregnancies reported from other European countries range from 1.5% [11] to 6.6% [151]. In the study reporting the highest rate of perinatal mortality (6.6%), more than 50% of study subjects had not attended

preconception care and were characterized by significantly higher first trimester Hba1c [151]. In a study comparing outcomes of women with T1DM and T2DM, the only significant risk factors for perinatal mortality and major malformations were lack of prepregnancy care and Hba1c at first antenatal visit [8]. Unlike most previous publications [3-6, 9, 11, 15, 138, 151], we also report data on neonatal mortality. The risk of neonatal death within 28 days of birth was approximately 3 times elevated in T1DM offspring. We did not analyze causes of death in the present study, but major malformations and preterm delivery are common causes of neonatal death in pregnancies complicated by T1DM [4].

High maternal BMI is a well known risk factor for stillbirth and perinatal mortality as well as for other adverse pregnancy outcomes in the general obstetric population [178, 254-260]. Study IV clearly demonstrate that maternal overweight/ obesity is a significant risk factor for adverse outcome also in women with T1DM. The odds of all most all outcomes increased with greater BMI category. The lack of a significantly increased risk of perinatal mortality with increasing BMI category within the diabetes cohort in our study indicates that diabetes is a stronger risk factor for perinatal mortality than maternal overweight/ obesity.

It is hypothesized that the increased risk of pregnancy complications in overweight and obese women is due to increased maternal fat mass. In the present study, prepregnancy BMI was used as a proxy for maternal fat mass because there is a strong correlation (r^2= 0.86) between prepregnancy BMI and maternal fat mass in women without diabetes [261]. Importantly, BMI does not provide information on the localization of fat mass. One hypothesized link between high maternal prepregnancy BMI and increased risk of adverse outcome is increased visceral fat mass. The visceral fat mass is associated with increased insulin resistance, inflammation and lipotoxicity with potential harmful effects on maternal vascular and placental function and fetal development [262]. The pathophysiological mechanism behind the increased risk of adverse pregnancy outcome in overweight/ obese mothers is not clear but is most likely complex. Genetic- and environmental factors such as poor socioeconomic status, poor maternal diet and physical inactivity are probable contributing factors. However, given the clear and similar pattern, in both women with and without type 1 diabetes, with increased risk of adverse outcome with higher maternal BMI implies that BMI per se is an important risk factor to address. It is reasonable to assume that preventive measures, aiming at normal prepregnancy BMI, may reduce the risk of complications in type 1 diabetic pregnancies.

In study IV, we demonstrate that maternal overweight/ obesity increases the risk of major malformations in both women with and without T1DM. Within the diabetes cohort, maternal obesity was associated with a 77 % higher risk of malformations compared to women of normal weight. This is in line with the finding of an interaction between maternal diabetes and obesity on the risk of malformations in a mixed population of women with different types of diabetes [263]. However, the increased risk of major malformations in relation to BMI in the present analysis should be interpreted with caution as maternal overweight and obesity rend ultrasound assessment of fetal anatomy difficult [264] and we do not have data on the number of induced abortions due to malformations. Thus, the increased risk of malformations noted in the obese group might in part be due to detection bias.

Overall, major malformations occurred 2-3 times more often in women with T1DM compared to women without diabetes. This occurrence is comparable with some [7, 8, 15, 151] but not with all reports – significantly higher rates of major malformations have been reported from the UK [6]. It is, however difficult to compare rates of malformations as incidences are fairly low, definitions applied vary as well as the follow up time. Accurate estimation of

malformation rates is dependent on a large sample size and stringent definition of the outcome. Including only major malformations decreases the risk of missed diagnoses in the postnatal period.

In accordance with previous studies [3, 15, 151] the incidence of preeclampsia was five times higher in the diabetes cohort. The pathophysiological mechanism behind preeclampsia is not clear but it is hypothesized that placental ischemia proceeds the release of maternal and placental factors harmful to maternal blood vessels [213]. Risk factors for preeclampsia in patients with T1DM are high Hba1c in early pregnancy, overt and incipient nephropathy, chronic hypertension and maternal obesity [183, 184, 212, 215]. In study IV, we demonstrate that the odds of preeclampsia for a woman with obesity and T1DM are 14 times that of a normal weight woman without diabetes. Within the T1DM cohort, obesity was associated with a significantly increased odds ratio of preeclampsia compared to a woman of normal weight [adj OR 1.74 (1.35-2.25)]. In line with previous studies, we also found increased risks of preeclampsia in our reference group of overweight and obese non-diabetic women [178, 257, 265]. Obesity is associated with decreased insulin sensitivity and already slightly elevated levels of fasting glucose, within the upper normal range, are associated with increased risk of preeclampsia in women without diabetes [60]. In Sweden, there is no uniform screening for gestational diabetes. It is possible that the increased risk of preeclampsia and major malformations in overweight and obese women in the reference group is partly due to undetected cases of impaired glucose tolerance or diabetes. Interestingly, maternal prepregnancy BMI has been demonstrated as a stronger predictor of major malformations than severity of gestational diabetes [266].

The incidence of preterm delivery of 21% was quite low compared to other studies of T1DM in pregnancy (reported range: 29.6 – 41.7%) [3, 8, 11, 15]. Nonetheless, the risk of preterm delivery was four times elevated, contributing to increased incidence of neonatal morbidity. Higher rates of preterm delivery reported from other countries are most likely due to a more frequent use of delivery inductions [3] i.e. the preterm deliveries are not necessarily spontaneous. The lower Caesarean section rate in our study could partly be explained by a more expectative policy, where spontaneous onset of delivery is encouraged. At many centres induction of labour is performed around the 38^{th} week of gestation because of fear for late intrauterine fetal death. Awaiting spontaneous onset of labour in T1DM pregnancies without known fetal or maternal complications was not associated with increased risk of complications [267].

One of the most striking findings in present studies was the markedly increased incidence of fetal macrosomia. In study I 31% of T1DM offspring were LGA defined as birth weight $\geq +2$ SD above the mean and in study II 47% had a birth weight $\geq 90^{th}$ percentile. The reason for the high incidence of LGA is not known. Possible contributing factors are the increasing prevalence of maternal overweight [268] and decreasing incidence of maternal microangiopathy [269]. High rates of fetal macrosomia have also been reported from several other countries [3, 8, 11, 15, 109, 138, 270]. In spite of this, the distribution of size at birth is poorly characterized in T1DM offspring. We are aware of two previous studies on the distribution of BWSDS in newborn infants to mothers with T1DM [109, 188]. The finding in the current study of a bell-shaped BWSDS distribution with a mean of +1.27 SD above the mean of a non-diabetic reference population is in line with previous findings. Similar values of mean BWSDS in T1DM offspring has been reported from the UK [6, 138]. The distribution of birth weights was more markedly shifted to the right than the corresponding distribution of birth lengths, indicating disproportionate fetal growth. This was also reflected by the significantly higher mean ponderal index in T1DM offspring compared to controls.

Hyperinsulinaemia in utero is likely reflected by a disproportionate increase in insulin sensitive tissue mass such as adipose-, liver- and muscle tissue but not bone mass that is believed to be relatively insulin insensitive. Newborn infants to mothers with diabetes may have several hundred grams in excess of adipose tissue [102]. High PI in type 1 diabetic offspring is likely a reflection of primarily increased fat mass [101, 103]. Several attempts have been made to find a mathematical transposition to relate body fat to body weight that consists of weight to height ratios. The ponderal index may serve as a proxy for adipose tissue mass in epidemiological studies for comparisons of groups [18].

According to the Pedersen hypothesis maternal hyperglycaemia leads to fetal hyperglycaemia and hyperinsulinaemia. However, maternal glucose values can only explain a minor proportion of the variance in birth weight [24, 109, 115]. Given the relatively large proportion of LGA infants with a ponderal index $\geq 90^{th}$ percentile also in the control group (35%), other factors besides maternal hyperglycaemia are important to explain the high incidence of disproportionate fetal growth. High maternal BMI in non-diabetic pregnant women is a significant risk factor for macrosomia and increased fat mass in the offspring, independent of maternal glucose levels [254]. In line with this, we found that the odds of an LGA outcome was 13 in obese T1DM women compared to non-diabetic women without diabetes and of normal weight. For comparison, the odds of an LGA infant in T1DM women of normal weight was 11 times that of a normal weight control without diabetes. However, within the T1DM cohort the odds ratio for LGA did not differ significantly with greater BMI category, also demonstrated in two recent publications [8, 270]. In accordance with the study by Ehrenberg our findings indicate that maternal overweight is an important risk factor for LGA, but maternal diabetes has an even greater impact [271]. On the contrary, the risk of delivering a disproportionate LGA infant (PI $\geq 90^{th}$ percentile) was significantly increased in obese women within the type 1 diabetic cohort. In the study by Fegahli the risk for a disproportionate LGA infant was independent of maternal overweight [270]. However, the study sample was of limited size and the lack of association might therefore be due to lack of power. The increasing prevalence of preeclampsia with greater BMI category might contribute to the non significant increase of LGA infants with increasing maternal BMI within the T1DM cohort.

An interesting finding in our studies was the significantly higher mean BWSDS in preterm and term girls compared to boys. Birth weight is higher in males than in females in uncomplicated pregnancies. In the present study, males in the study group had a mean absolute birth weight that was 29 grams higher than in females, compared with males in the control group being on average 129 grams heavier than females. This difference has since long been attributed to higher prenatal androgen exposure in males than in females. In a recent large epidemiological study based on data from the Canadian Birth Registry, it was demonstrated a steady temporal decrease in the male-female birth weight difference between 1981 and 2003. The authors speculated that the observed decreasing birth weight difference was due to an increased prenatal exposure to anti-androgen disrupters (i.e. manufactured chemicals) [272]. However, this hypothesis was refuted in a study by Miles et al [273] investigating the influence of two well defined single gene disorders, one leading to complete androgen insensitivity and the other to increased amounts of androgens (i.e. congenital adrenal hyperplasia). This study showed that difference in birth weight between genders was independent of androgen effects.

It is well recognized that females normally have proportionally greater amounts of adipose tissue than males [274] in spite of significantly lower body weight and this difference is evident already at birth [275-277]. Significantly greater skin fold measures have also been

demonstrated in girls born preterm compared with preterm boys [278]. Umbilical leptin levels reflect total fat mass in the newborn [79]. Newborn AGA girls to non-diabetic mothers have significantly higher leptin levels in cord blood compared to boys, even after adjusting for ponderal index [64]. In newborn infants to non-diabetic mothers, umbilical levels of C-peptide, insulin and pro-insulin are higher in females than in males [275] despite similar cord glucose values and significantly lower mean birth weight. Cord blood levels of C peptide are significantly increased in T1DM offspring but it is unclear if there is a gender difference. The incidence of pregnancy complications like GDM and obesity is increasing. Both complications occurring separately or in combination are associated with increased fetal size at birth and hyperinsulinaemia. Against this background, it is possible that the higher BWSDS in female T1DM offspring reflects an increased fat mass and a more pronounced hyperinsulinaemia as compared with boys and this may contribute to the decreasing birth weight difference between genders.

In non-diabetic pregnancies, it has been demonstrated that ultrasound dating of pregnancy is associated with an increased risk of underestimation of gestational age in females [180]. This means that girls born at term are more likely than boys to actually be delivered post term. Erroneously dated pregnancies with female fetuses could thus contribute to our finding of a higher incidence of LGA female T1DM offspring. However, the significantly increased mean ponderal index in girls indicates that the gender difference can be attributed to other factors than systematic error of pregnancy dating. Significantly higher mean ponderal index has also been reported in girls born to non-diabetic mothers [64] which was also confirmed in our data set. Furthermore, fetal growth in pregnancies complicated by T1DM is different from that of non-diabetic pregnancies and results from studies of fetal growth in non-diabetic pregnancies are not necessarily valid for fetuses to T1DM mothers. Investigation of potential gender differences in fetal growth in T1DM pregnancies could hopefully shed light on mechanisms involved.

In accordance with previous findings [3], we found a very high incidence of LGA babies among infants born preterm. The proportion of preterm infants with disproportionate body composition (ponderal index $\geq 90^{th}$ adjusted percentile) was significantly higher (36.5%) compared to babies born at term (28.4%). The most likely explanation for this finding is that in T1DM pregnancies in which fetal growth acceleration occur, delivery before 37 weeks of gestation is judged as medically indicated. Ultrasound examination of women with T1DM may detect fetuses at risk of macrosomia as early as in the 18^{th} week of gestation [279]. This is in accordance with the finding of significantly higher umbilical cord levels of C peptide in preterm compared with term T1DM offspring [194]. In addition, maternal hyperglycaemia in early pregnancy is a risk factor for spontaneous preterm delivery and the higher mean BWSDS in preterm compared with term infants could therefore be an effect of maternal hyperglycaemia in early pregnancy that is more pronounced than in women giving birth at term.

It is well recognized that LGA infants to T1DM mothers face increased risk of perinatal complications such as asphyxia [139], birth trauma [280], hyperbilirubinaemia [12, 14, 16] and hypoglycaemia [12, 14]. There is also evidence of increased risk of future morbidities [43, 207, 210]. Overall, the rates of neonatal morbidity in our cohorts (study I and III) were lower than in previous studies of T1DM offspring [3, 8, 15, 151]. It is a common belief that the risk of perinatal complications is higher in LGA infants with a disproportionate body composition (i.e. overweight with high ponderal index) compared to LGA infants with a balanced relation between weight and length (i.e. constitutionally large infants). This hypothesis is supported by the finding of a strong association between cord blood levels of C

peptide and birth weight [98] and maternal glucose and skin fold thickness [100] in T1DM offspring. Furthermore, the risk of neonatal morbidity in T1DM offspring is also related to the degree of fetal hyperinsulinaemia [185, 194]. Against this background, an unexpected finding was that, in both girls and boys, the rates of perinatal complications did not differ between proportionate and disproportionate AGA or LGA infants. As expected, the risk of perinatal complications was significantly higher in LGA as compared with AGA infants born at term. In preterm infants, the risk of complications did not differ between any of the three body size categories, preterm birth being a significant effect modifier of the association between neonatal body size category and the risk of neonatal morbidity. There was no evidence of any significant interaction between sex and neonatal body size category.

We found that the risks of hypoglycaemia and hyperbilirubinaemia were comparable between proportionate and disproportionate LGA infants. This is in accordance with findings by Leperqc [80], but in contrast with other reports [12, 14]. These diverging results could be attributed to differences in maternal glycaemic control during pregnancy and delivery, definitions of neonatal outcomes applied and monitoring of metabolic parameters in the newborn. In our clinical practice, there is no distinction made between proportionate or disproportionate LGA infants to T1DM mothers regarding early feeding and routines for monitoring of glucose and bilirubin.

The incidence of respiratory distress syndrome (RDS) was low in the later cohort (1998-2007) (0.8%) compared to other studies on T1DM offspring [3, 15]. This low rate is most likely due to exclusion of very preterm infants and the comparatively high mean gestational age (38 weeks) in our study cohort. In keeping with Bollepalli and colleagues, we did not find a significant difference in the risk of RDS between proportionate and disproportionate LGA.

To our knowledge, our study is the first to show a comparable risk of birth trauma in proportionate and disproportionate LGA T1DM offspring. As previously demonstrated, the risk of birth trauma was significantly higher in LGA compared with AGA babies. The risk estimates of birth trauma must be viewed in light of the higher Caesarean section rate in disproportionate LGA (65%) compared to proportionate LGA infants (51%). A higher Caesarean section rate in disproportionate LGA may have been clinically indicated in order to prevent birth trauma and it is possible that the rate of birth trauma would have been higher in disproportionate than in proportionate LGA infants, given a similar rate of vaginal delivery in the two groups. After adjusting for differences in absolute birth weight, the excess odds for birth trauma in LGA infants became statistically insignificant, suggesting that high absolute birth weight is the strongest risk factors for birth trauma.

The significantly decreased risk of fetal distress in disproportionate infants is most likely also a reflection of the higher rate of Caesareans sections (65%) in this group. Indeed, the incidence of fetal distress decreased in parallel with increasing incidence of Caesareans section over the neonatal body size categories (chi square test for trends, p-value <0.001). The highest rate of fetal distress and the lowest rate of Caesareans delivery were recorded in AGA infants. Delivery by Caesarean section is an independent risk factor for transient tachypnea of the newborn [191]. Thus, the significantly higher rate of Caesareans delivery in disproportionate LGA as compared with proportionate LGA infants may artificially lead to a higher rate of respiratory disorders in the former group. This would have been especially relevant to consider if the rate of respiratory disorders would have been significantly higher in disproportionate than proportionate LGA infants. The difference, however, was little and statistically insignificant. It could be argued that fetal distress and mode of delivery should not be included in the regression models as they could be seen as effects of the exposure and

thereby considered as mediators for some of the outcomes (i.e. hypoglycaemia, low Apgar score and respiratory disorders). However, we also present crude odds ratios for comparison.

Interestingly, in contrast to the findings in the study cohort, disproportionate LGA infants in the control group had significantly increased risk of neonatal morbidities compared with proportionate LGA infants. In Sweden, there is no uniform screening program for gestational diabetes. One might speculate that the increased incidence of neonatal morbidity in disproportionate LGA infants in the control group could be attributed to undetected cases of gestational diabetes.

In conclusion, these studies show that women with T1DM and their offspring still face significantly increased risks of adverse outcome. The risk of complications increases with maternal overweight and obesity. The incidence of fetal macrosomia is unexpectedly high and a large proportion of T1DM offspring is overweight at birth. Fetal macrosomia (i.e. high absolute birth weight) is an important risk factor for perinatal complications. Striving towards normal prepregnancy BMI and improved glycaemic control throughout pregnancy (i.e. using closed loop systems) can hopefully contribute to a more favourable outcome. Reliable methods for early detection of pregnancies with accelerated fetal growth are a prerequisite for preventive actions.

GENERAL DISCUSSION AND IMPLICATIONS

THE MAJOR FINDINGS OF THIS THESIS WERE THAT IN PREGNANT WOMEN WITH TYPE 1 DIABETES:

1) The odds of major malformations, preeclampsia, stillbirth, preterm delivery, perinatal mortality and Caesarean delivery were 2.5 to 5 times above the reference representing the general, non-diabetic obstetric population.

2) The odds of giving birth to a large for gestational age infant (birth weight equal to exceeding 2SD above the mean) were 11 times above the normal reference.

3) The distributions of birth weight, birth length and head circumference were all unimodal and significantly shifted to the right of the normal reference. Fetal macrosomia was more pronounced in girls than in boys as well as in preterm compared to term infants.

4) The incidence of disproportionately heavy LGA infants (birth weight and ponderal index $\geq 90^{th}$ adjusted percentile) was 1.3 times above normal.

5) The risk of neonatal morbidity was 1.7 to 5 times higher in LGA vs. AGA T1DM offspring.

6) Within the T1DM cohort, the increased risk of neonatal morbidity in LGA infants was independent of body proportionality.

7) The incidence of overweight and obesity among T1DM women was 1.4 and 1.7 times above normal, respectively.

8) Obesity was associated with marked increased odds for adverse outcome: 2.9 to 14 times above normal (preeclampsia x 14, LGA x 13, C. section x 9, preterm delivery x 6, major malformations x 4 and perinatal mortality x 2.9).

The results of this thesis thus clearly demonstrate that women with type 1 diabetes still face significantly increased risks of maternal and perinatal complications. In spite of major advances in the care of these patients and dramatically improved outcome over the last 50 years, the rates of perinatal mortality and major malformations remain significantly higher than in the general obstetric population. The goal set by the St Vincent declaration in 1989, to within a five year period abolish the over risks associated with T1DM in pregnancy, is still far from being met.

STRENGTHS AND LIMIATIONS

The primary strength of this thesis is the population based study design, including a very large number of T1DM pregnancies. The MBR offers a unique possibility to assess the risk of adverse outcomes in pregnancies complicated by maternal disease of comparatively low prevalence, such as T1DM. The majority of published studies on pregnancy outcome in T1DM have limited power for accurate risk estimation of rare complications such as major malformations and stillbirth. The sample sizes of the different studies in this thesis allowed for assessment of risks also in stratified analyses. Furthermore, many studies are based on data from centres of excellence and the results are not necessarily representative for whole populations of T1DM patients. Pregnancy care of women with T1DM in Sweden is uniform over the whole country and the study populations in this thesis are also homogenous with respect to ethnicity. We were able to provide national data on pregnancy outcome in women with T1DM and the results can most likely be generalized to countries with similar health care systems and socioeconomic situation. The data in the MBR was prospectively collected in standardized forms, decreasing the risk of biased registration of information. The MBR is the source of a large number of epidemiological studies in Sweden. The quality of data in the MBR is regularly validated by the National Board of Health and has also been evaluated by independent researchers. The conclusion of these validations is that data is of high quality. In study II-IV, the total number of records with apparent misclassification of the diabetes diagnosis was only 13. However, large registries like the MBR inevitably contain errors in recorded data and the coverage of different variables differs. Most importantly, systematic miscoding of data must be looked for, as this might bias the results.

Random and systematic errors

Random errors can be described as variability in the data. Risk estimates in epidemiological studies are presented as point estimates with a confidence interval, for instance as odds ratios. The confidence interval reflects the random error or the precision of the point estimate. In large studies, any influence of random error is small but it might cause problems given a small sample size. Systematic errors, on the other hand might impose problems even in large studies. The systematic errors may be categorized into three groups: selection and information bias and confounding. Information bias occurs when data on exposure and/ or outcome is misclassified. Selection bias implies that the study sample is not representative of the source population, giving rise to the study cohort, i.e. the association between exposure and disease differs between study participants and non-participants. Careful planning of study design reduces the risk of selection and information bias.

Selection bias with respect to T1DM pregnancies is most likely small in the studies of this thesis, given the population based study design. **In study I** we know that women with T2DM were included in the first half of the study period due to inability to separate T1DM from T2DM with the ICD 9 code system. T2DM is very uncommon in pregnancy in Sweden and the number of women with T2DM included was small (<0.05%) with limited impact on our findings. For comparison, during the study period between 1998 and 2007 the prevalence of T2DM in pregnancy was only 0.04%.

In study II we included only infants with full data on birth weight, length, gestational age and gender. One could speculate if infants with missing data were more likely to be growth restricted or macrosomic and/ or more likely to be born preterm. However, when including all records, without restricting the analyses to those with data on all variables, the mean

standard deviation scores for weight and length did not differ significantly from the results in the original analysis (mean SDS birth weight all gestational ages: +1.26, sd 1.50 *vs*. reported mean value +1.27, sd 1.49), nor did the mean gestational age of the study cohort.

We decided to exclude infants born before 28 completed weeks of gestation in study II. This might be criticized as preterm infants are more likely to be growth restricted and by excluding the most preterm infants the mean birth weight standard deviation score of the study cohort could have increased. However, it is known from previous studies that the distribution of standard deviations for anthropometric measures is U shaped in newborns, with the highest values in preterm infants [281]. This phenomenon is most likely due to a larger proportion of outliers in the lower gestational age group, partly explained by less accurate weight and length estimates in preterm infants. Another contributing factor could be that errors in pregnancy dating will have larger impact in lower gestational ages as fetal growth rate decreases near term. Given this we decided to exclude the most preterm infants from the analysis. However, when repeating the analysis with the very preterm infants included (n=27), the mean birth weight standard deviation score of the study cohort was slightly lower (+1.261, sd 1.50) but not significantly different from the reported mean (+1.268, sd 1.49).

We compared the size at birth of T1DM offspring with infants of the general obstetric population. Accordingly, the reference group included all singleton pregnancies to mothers without T1DM, excluding major malformations, stillbirths and records with extreme data on neonatal and maternal anthropometry [282] but without excluding mothers with possible disease. Besides maternal diabetes, most maternal diseases in pregnancy would, if anything, lead to decreased fetal growth. Thus, it could be argued that including mothers with potential disease in the reference group could lead to an overestimation of our findings [18]. However, when analyzing the data again after exclusion of maternal disease in the reference group (T2DM, gestational diabetes, SLE, ulcerous colitis, chronic hypertension, epilepsy, asthma, urinary tract infections in pregnancy) the mean BWSDS,BLSDS and number of LGA infants in the study cohort remained the same (approximated values :mean BWSDS: +1.27, BLSDS: +0.71, LGA: 47%).

If one argues for the exclusion of records with maternal disease from the reference group, it seems logical to exclude the same diagnoses also from the study cohort. When running the analyses again, this time excluding the same maternal diagnoses from both reference and study cohort , the mean BWSDS and BLSDS and proportion of LGA infants were all slightly higher (mean BWSDS: +1.32, BLSDS: +0.75, LGA: 49%).

Information bias may be differential or non-differential. Differential misclassification occurs if the classification of exposure is dependent on the outcome, or vice versa. When the misclassification of exposure or outcome is not dependent of each other it is referred to as non-differential misclassification. Non-differential misclassification of a dichotomous outcome tends to "dilute" the effect of the exposure on the outcome and implies an equal misclassification rate of exposure data in both cases and controls.

In our studies it is possible that registration of infant's birth weight and length may differ between infants born to mothers with and without diabetes, given the wide spread knowledge that infants to mothers with diabetes tend to be bigger. The infant´s weight is measured using an electronic scale with high precision and data on birth weight in the MBR has been shown to be of high accuracy. Measuring birth length is more complex with a higher risk of measuring errors and lower precision. However, it is unlikely that any potential systematic error of length measurement would differ between infants to mothers with and without T1DM, i.e. any misclassification of infant length in T1DM offspring is non-differential. The

risk of differential misclassification of adverse pregnancy outcomes in the T1DM group, i.e. detection bias, was small. All the outcomes included in this thesis are diagnoses that could not pass undiscovered, regardless of diabetes status and thus we consider the risk of detection bias as low.

A common type of information bias in epidemiological studies is follow-up bias, i.e. study subjects who drop out may differ from those who stay in the study until termination. This type of bias is very limited in register studies like the ones included in this thesis.

Confounders are associated with the exposure and the outcome without being on the casual pathway between exposure and disease. There are different methods of handling confounders. Randomization is the only means by which all confounders, even unknown confounders, are dealt with. Other ways of controlling confounders are matching cases and controls for the specific confounder, for instance age or to arrange study subjects into different strata with fixed values on the confounder. The analysis may also be restricted to subjects with a specified value on the confounder. Confounding is the only systematic error that can be controlled for after the phase of study design. In multiple regression analyses, the influence of several confounders may be handled at the same time. In this thesis, we were able to adjust for several important confounders. **In study I**, adjusting for potential maternal confounders altered the risk of adverse outcome substantially. It can be discussed however, which risk estimate that is most relevant for the patient and clinician. The crude estimate is a more accurate assessment of the risk for complications in the "real" patient, allowing for all present risk factors to influence the odds ratio. The adjusted estimate will provide a clearer picture of the risk of complications related to solely T1DM. **In study III and IV**, risk estimates did not change significantly after adjusting for potential confounders. As randomization is not possible in these types of studies, we cannot exclude residual confounding by unknown or erroneously classified confounders. In addition, as we were restricted to the data available in the registry, these studies did not allow controlling for some confounders of potential interest (glycaemic control, duration of diabetes, pre-existing microangiopathy, maternal diet, physical activity, socioeconomic situation).

It is not always obvious which variables to include in the multivariate regression model. In **study I,** we included several covariates in the multivariate logistic regression analysis i.e. maternal ethnicity (Nordic origin yes/ no), maternal age, BMI, parity, chronic hypertension and smoking in early pregnancy. The same model was applied to all outcomes. We thus adjusted for chronic hypertension also when investigating the odds of preeclampsia. Chronic hypertension is a risk factor for preeclampsia and could also be seen as an effect of the exposure (T1DM), acting as a mediator on the causal pathway towards the outcome and hence it can be argued that it should not be adjusted for. **In study III,** we included fetal distress and mode of delivery (delivery by Caesarean section yes/ no) in the multivariate model for the primary outcome (composite morbidity) and all the secondary outcomes except for birth trauma. It can be argued that these variables act as mediators for some of the outcomes (hypoglycaemia, low Apgar score and respiratory disorders) and therefore should not be included in the model. It is known from studies by Teramo et al that there is a U shaped relation between erythropoietin levels in cord blood and birth weight and levels of erythropoietin are closely correlated to cord blood acidosis. Given this association it is possible that fetal distress can be seen as an effect of the exposure in our study. Delivery by Caesarean section is also more frequently performed in pregnancies with large fetuses and may therefore be seen as an effect of the exposure. However, we decided to provide both estimates i.e. crude and adjusted odds ratios for comparison.

Effect modification

An effect modifier is defined as a variable with differential impact on the association between an exposure and a specific outcome. Effect modification may be explored by stratifying the analysis for the possible effect modifier and by creating interaction terms. We used both methods in our studies. **In study II**, we demonstrate that preterm delivery acts as an effect modifier, increasing the risk of fetal macrosomia in response to intrauterine exposure to T1DM. We also found that female T1DM offspring were more likely than their male counterparts to be large for date. **In study III** we demonstrate that preterm birth modifies the risk of neonatal complications associated with fetal macrosomia in T1DM offspring. We did not find evidence of effect modification of gender on the association between size at birth and neonatal outcome. **In study IV** we clearly demonstrate that T1DM status modifies the risk of major malformation, LGA, neonatal overweight and preeclampsia associated with high prepregnancy BMI. The impact of increasing maternal BMI on the risk of LGA, neonatal overweight and preeclampsia is greater in non-diabetic women as compared with T1DM women. This is most likely a reflection of T1DM being a much stronger risk factor than maternal BMI for these outcomes. Within the T1DM cohort, the risk for preeclampsia, major malformations, and delivery by Caesarean increased with greater BMI category. This implies that striving towards normal pre-pregnancy BMI is of importance in order to reduce the incidence of these complications.

IS IT POSSIBLE TO REACH NORMOGLYCAEMIA IN PATIENTS WITH T1DM?

The importance of striving towards normoglycaemia before and during pregnancy is well recognized and improving metabolic control reduces the risk of complications [15, 130, 172-174, 176, 177, 186, 225, 226]. However, reaching normoglycaemia in patients with T1DM is very difficult. The metabolic adaption to pregnancy rends this target even harder to attain. In non-diabetic subjects, approximately 70% of the insulin released from the pancreas is immediately transported to the liver via the portal circulation. The liver plays a fundamental role in glucose homeostasis, regulating the amount of glucose delivered into the circulation. Insulin depresses hepatic gluconeogenesis and glycogenolysis in the post prandial state. In patients with type 1 diabetes, insulin is administrated subcutaneously and supra-physiological doses are needed to suppress hepatic glucose output. This leads to high circulating levels of insulin in peripheral tissues with anti-lipolytic effects on adipose tissue. A much depressed mobilization of fatty acids from adipose tissue increases the risk of hypoglycaemia, fatty acids being a very important energy substrate for muscle tissue. Current insulin therapy makes it very difficult to obtain normoglycaemia, unless the patient has significant residual beta cell function. Very tight glycaemic control is associated with increased risk of hypoglycaemic episodes and unawareness of hypoglycaemia (reduced counter regulatory hormonal response to hypoglycaemia). Furthermore, the level of glycaemic control that may be attained differs between patients and it has been demonstrated that there is a moderate correlation (r=0.59) between pregnancy glucose values in subsequent pregnancies in the same woman [283]. Thus, individualized therapy is essential.

RELATION BETWEEN MEASURES OF MATERNAL HYPERGLYCAEMIA AND PERINATAL OUTCOME

Information on glycaemic profile

One contributing factor to the sustained high incidence of complications in T1DM pregnancies could be that the means by which glycaemic control is monitored is too crude. Continuous glucose monitoring in T1DM pregnancies revealed that the majority of women spend several hours per day outside the target range of glucose and these excursions were not reflected in capillary blood tests or HbA1c [116].

Fasting, post prandial glucose measures and glucose variability

It appears that different complications occur at different degrees of maternal hyperglycaemia. For instance, the risk of major malformations increases substantially when Hba1c levels exceed several standard deviations above the mean [132, 167] whereas the risk of LGA is increased even in pregnancies with apparent tight glycaemic control [24, 284]. Fetal and neonatal adiposity estimated by ultrasound is also increased in T1DM pregnancies with apparent impeccable glucose control [104] and studies by Whitelaw indicate that in order to obtain an infant with normal skin fold measures, maternal fasting and postprandial glucose levels should be kept below 5 mmol/ litre and 6 mmol/ litre, respectively [100]. Thus, the level of control required to abolish some complications might be lower than that of other outcomes.

It is also possible that some complications are closer associated with peak glucose values and other with high fasting glucose levels. Avoiding postprandial hyperglycaemia may be important to reduce the risk of preeclampsia, fetal loss, preterm delivery and LGA as well as neonatal adiposity [111, 112, 136, 285]. Rapid acting insulin is superior to human insulin in reducing post prandial hyperglycaemia and the overall glycaemic load [286]. In a large randomized trial (n=322), there was a tendency towards lower rates of fetal loss and preterm delivery in women treated with rapid acting insulin compared with women treated with human insulin. There was no significant difference in the incidence of LGA between groups, but the mean birth weight was lower in infants to mothers treated with rapid acting insulin [136]. The risk of complications might also be closer associated with glucose variability rather than fasting or post prandial values. Continuous glucose monitoring in T1DM pregnancy has been associated with decreased rates of LGA [287] and increased use of this technique in pregnancy may help to reduce the rate of complications.

Evaluating the patient´s reported glucose values is a complex task for the diabetes team. It has been demonstrated that patients have a tendency to report the home readings of glucose levels that fall into the target range and to leave out hyperglycaemic values [288].

Maternal and fetal metabolic milieu

It is well known that fetal hyperinsulinaemia increases the risk of perinatal complications in T1DM offspring. However, the degree of fetal hyperinsulinaemia may not necessarily be reflected by maternal glucose readings [289]. Early established fetal hyperinsulinaemia enhances glucose siphoning over the placenta, which may lead to maternal glucose levels close to the normal range. According the expanded version of the Pedersen hypothesis, not only glucose but also fatty acids and amino acids have potential impact on fetal development [290]. There are significant associations between maternal plasma levels of amino acids and

amniotic C peptide concentration in T1DM pregnancies [61]. Furthermore, Scahefer-Graaf et al have demonstrated a significant correlation between maternal and fetal cord blood free fatty acid levels and an association between fetal levels of fatty acids and offspring birth weight in women with gestational diabetes [291]. It is possible that levels of amino acids and free fatty acids may be altered even in cases of normoglycaemia. Thus, monitoring of glucose may not provide sufficient information to enable the right interventions. In addition, controlling the maternal metabolic milieu may not necessarily normalize the fetal metabolic milieu. All measures of metabolic control in the mother ignore the glucose consumption and metabolism of the placenta. Insulin sensitivity differs between individuals and the increased placental glucose transfer in case of fetal hyperinsulinaemia (glucose steal phenomenon) contribute to the poor correlation between maternal and fetal glucose-insulin homeostasis [289]. It has been proposed that elevated amniotic fluid insulin concentrations may be used as an indicator for fetal growth acceleration in diabetic pregnancies and as a basis for a more intensified insulin therapy [289]. The susceptibility for developing some complications such as malformations and fetal macrosomia may also vary with maternal and fetal genetic factors [168, 292, 293].

Allowing for individualized care of women with T1DM in pregnancy and increased use of new sophisticated techniques with closed loop systems will hopefully help to improve pregnancy outcome in T1DM women [294].

Fetal macrosomia

There is no clear explanation for the persistently high incidence of fetal macrosomia in T1DM pregnancies. The weak correlation between maternal glucose values and fetal size is intriguing and fetal macrosomia as well as placental changes are seen in spite of tight metabolic control [284, 295, 296]. However, the correlation between maternal glycaemia and skin fold thickness is stronger [100]. One possible contributing factor to the sustained high incidence of fetal macrosomia is the decreasing incidence of maternal microangiopathy, associated with fetal growth restriction. We have demonstrated that maternal overweight/obesity is a strong risk factor for LGA in non-diabetic pregnancies. Within the T1DM cohort, however, the risk increase for an LGA outcome associated with greater BMI category only reached border line significance. This is in line with the results from two recent studies on T1DM pregnancies [8, 270]. It has been demonstrated that maternal weight could only explain 2% of the variance in birth weight in T1DM pregnancies [109]. Accordingly, other risk factors besides maternal glucose levels and BMI must be considered. Fetal beta cells respond weakly to glucose stimulation before 26 weeks of gestation. It is possible that other factors besides glucose (branched amino acids, HpL and other placental factors) induce fetal hyperinsulinaemia in early pregnancy and that once established it will remain throughout pregnancy. Of interest in this context is also the state of subclinical inflammation found in placentas of women with T1DM. Placental leptin expression is much increased as well as cytokine production. Prenatal exposure to cytokines (Il 6, TNF-alpha) in mouse models is associated with a significantly increased fat mass in the offspring [119].

PAPP-A is involved in fetal growth regulation by activating IGF 1. A recent study by Kuc et al demonstrated that women with T1DM, delivering an LGA infant, had normal plasma levels of PAPP-A as opposed to the decreased levels in women delivering an infant of appropriate size [108]. Given the well established association between low levels of PAPP-A and poor pregnancy outcome [71, 73, 75], the authors speculated if T1DM mothers with normal PAPP-A levels and LGA infants actually had a tighter metabolic control in early pregnancy than mothers of AGA babies. In vitro studies on human trophoblasts have demonstrated that

hyperglycaemia reduces GLUT 1 expression [297]**.** Thus, it is likely that a tighter metabolic control in the periconceptual period favours successful placentation which in turn may lead to enhanced fetal growth. It has also been speculated that episodes of maternal *hypoglycaemia* may lead to enhanced secretion of placental growth hormone, in turn stimulating fetal IGF release and growth. An increasing understanding of the role of placental changes for the risk of fetal macrosomia and other adverse outcomes will hopefully enable new means of intervention.

FETAL MACROSOMIA AND GENDER DIFFERENCE

In study II, we found that fetal macrosomia was more pronounced in female compared to male T1DM offspring. In newborn infants to mothers without diabetes it has been demonstrated that females have significantly greater amount of body fat than males [278]. Also in newborn infants to mothers with gestational diabetes, females had a slightly higher percentage of adipose tissue mass than males [298]. The proportion of fat may be significantly increased even in cases of normal birth weight [105, 298]. It is thus possible that with a more detailed measure of body composition including estimation of fat mass, an even greater gender difference could have been detected in T1DM offspring. In spite of similar cord blood glucose levels, girls to non-diabetic mothers have significantly higher cord blood levels of pro-insulin, insulin and C peptide compared with boys [275]. The authors speculated that girls have an intrinsic insulin resistance. However, this is hard to establish without a more detailed analysis (i.e. clamp). It is possible that beta cells in female fetuses are more sensitive to glucose/ amino acid stimulation than in males, enhancing fat accretion in the female. It is difficult to assess fetal insulin sensitivity as fetal hyperinsulinaemia is compensated for by increased placental glucose transfer from the mother to the fetus. A possible explanation for the apparent insulin resistance in newborn girls could be an increased fat mass compared to males, the large fat mass in turn contributing to insulin resistance and increased insulin levels. It has also been proposed that there is a gender difference in genes involved in glucose regulation and that these genes are linked to the X chromosome [299].

It is possible that there is a gender difference in response to exposures in utero. In a recent study by Lingwood et al it was demonstrated that predictors of total fat mass differed significantly between genders in newborn infants to mothers with gestational diabetes [298]. Maternal fasting and postprandial glucose levels were the strongest predictors of male fat mass, but these variables had very little predictive value of female fat mass. On the other hand, maternal prepregnancy BMI was identified as the strongest predictor of female fat mass, however with weak effect on male fat mass. This intriguing finding suggests that information on fetal gender may be important in order to optimize the care of pregnant women with diabetes.

ANTENATAL DETECTION OF FETAL MACROSOMIA?

Ultrasound estimation of fetal macrosomia in diabetic pregnancies has low positive predictive power [300], regardless of which formula being used. In addition, the positive predictive power decreases with increasing fetal weight [301]. Serial ultrasound assessments may enhance the accuracy [301] but others have found clinical examination as predictive as sonographic estimation [302]. Abdominal circumference, reflecting growth of insulin sensitive tissue, may be useful in predicting fetal macrosomia in T1DM pregnancies [290].

So far, once the process of enhanced fetal growth in macrosomic fetuses to T1DM mothers is established, it has not been possible to reverse this development. Fetal macrosomia in T1DM pregnancies may be detected already at around the 18th week of gestation [279] but this is most likely too late for interventions. Given the low sensitivity of ultrasound based estimation of fetal weight, other markers for fetal macrosomia in T1DM pregnancies should be sought for. We are planning a study to elucidate if maternal plasma levels of PAPP-A in combination with indices of maternal glycaemic control can be used as a marker for fetal macrosomia in early T1DM pregnancy (gestational week 11-13).

MATERNAL RISK FACTORS FOR ADVERSE OUTCOME

It is also of great importance to address other risk factors, besides hyperglycaemia, for adverse outcome in T1DM pregnancies. The prevalence of overweight and obesity is increasing worldwide, with enormous impact on health and economy [303]. The prevalence of maternal overweight/ obesity in pregnancy is increasing over time and can to a large extent explain the increasing incidence of LGA infants in Sweden [268]. The detrimental effect of maternal overweight/obesity on pregnancy outcome is well established in the general obstetric population [178, 254-260, 265, 304] and our results add to this growing body of evidence by providing population based risk estimates associated with maternal overweight also in women with T1DM. The increased risk of severe complications seen in T1DM women with concomitant overweight/ obesity is of particular interest as the risk factor in this case is modifiable. The mechanism by which obesity increases the risk of adverse outcome is not fully understood. The visceral adipose tissue is of particular interest in this context. The visceral fat mass is associated with lipotoxicity, subclinical inflammation and signs of endothelial dysfunction [305]. Lean women accumulate on average 4 kilos of adipose tissue in pregnancy, mainly stored as subcutaneous fat in the lower body compartment [305]. Overweight and obese women tend to store the excess fat of pregnancy in the upper body compartment, largely consisting of the visceral fat depot. The visceral fat mass is more metabolic active than the subcutaneous fat mass and more responsive to lipolytic stimuli [306] and is the source of more than 60% of the total amount of non-esterified free fatty acids (NEFA). In addition to elevated levels of NEFA, the visceral fat mass is also associated increased production of cytokines (CRP, IL 6, TNF alpha) and increased storage of ectopic fat in the liver, pancreas and muscle. High levels of NEFA induce lipotoxicity and decreases insulin sensitivity. The effects of lipotoxicity also include increased oxidative stress, activation of intra cellular pathways for cytokine production, endothelial dysfunction, decreased trophoblast invasion and altered placental metabolism. Placentas from obese women contain higher levels of macrophages and cytokines compared to placentas from lean women. Lipotoxicity, inflammation and endothelial dysfunction affecting the maternal and placental compartments, are most likely involved in the pathophysiology of obesity related complications [305]. The mechanism behind the high incidence of LGA infants in the non-diabetic population was elucidated in a in a recent publication from Sweden. This study including 22 non-diabetic women and their newborns, demonstrated that 1/3 of the variance in fetal weight is accounted for by maternal glucose production. 60% of the variance in maternal glucose production was in turn explained by maternal insulin resistance, closely associated with maternal fat mass [307].

Clinical studies evaluating weight loss programs in pregnancy have been rather disappointing. Losing weight in pregnancy is difficult and there is no consensus regarding what weight loss that is safe in pregnancy. Based on current knowledge it seems important to encourage women with T1DM planning a pregnancy to reach normal BMI before conception.

PATIENT EDUCATION

Pre conception counselling and patient education emerges as extremely important features in trying to prevent complications in T1DM pregnancies. Over the last decades, leading diabetologists in Sweden have regularly offered diabetes teams to participate in educational programs. An important cornerstone in these programs is the undisputable need of patient education. Much effort is put into patient education aiming at making the patient herself the expert of her own disease. This process is initiated already at the paediatric clinic and is reinforced at every visit with the diabetes team. The same group of enthusiastic diabetologists has also developed several brochures with information and guidelines for patients. The effort to communicate the latest guidelines to all teams working with T1DM pregnancy has been successful and pregnancy outcome for women with T1DM in Sweden is encouraging. We could also demonstrate in study I, that the incidence of major outcomes of T1DM pregnancies did not differ with geographical areas in Sweden [248]. In light of this, it is of importance that health care personnel working with diabetes and pregnancy are continued to be offered national educational programs, including recent data on maternal and perinatal outcome. Information for patients needs to be continuously updated. Aiming at individualized programs of care for each T1DM patient is important to enable favourable outcome.

IMPLICATIONS AND FUTURE RESEARCH

Pregnancy outcome for women with T1DM has never been as favourable as today. Major improvements have been made in the care for the pregnant woman with T1DM, new techniques for insulin administration and glucose monitoring are in use and the understanding of pathophysiological mechanisms behind adverse outcomes in T1DM pregnancies is increasing rapidly. However, there rates of complications are still significantly increased and it is plausible that the goal set by the St Vincent declaration in 1989 cannot be achieved with current techniques for diabetes treatment.

The results of the present thesis will hopefully contribute to the increasing knowledge of pregnancy in T1DM. Large epidemiological studies like the ones included in this thesis may be helpful in assessing trends of complication rates and may also generate new hypotheses. Our data indicate improved outcome over time with decreasing national rates of stillbirth and perinatal mortality in T1DM pregnancies (IUFD 1991-2003:1.5% and 0.81% in 1998-2007, PMR: 2% in 1991-2003 and 1.2% in 1998-2007) but also increasing rates of fetal macrosomia. In study II, we demonstrate that there is a gender difference in size at birth in T1DM offspring, giving rise to the hypothesis that female fetuses accrete more fat in utero than their male counterparts. We intend to investigate this hypothesis in a future clinical study. It can be discussed if customized growth charts for offspring to T1DM mothers should be used. From our results in study II, we conclude that the distribution of BWSDS in T1DM offspring is unimodal and significantly shifted to the right of the normal reference. This implies that all fetuses to mothers with T1DM are more or less growth promoted and that the cut-off for an LGA outcome in T1DM offspring is higher than in infants to non-diabetic mothers. In line with this, T1DM offspring who are small for gestational age, according to the normal reference, are likely to be more severely growth restricted than SGA infants to non-diabetic mothers. Customized birth weight percentiles for T1DM offspring could perhaps better indicate which infants, in particular those in the left tail of the birth weight distribution that are at increased risk of adverse outcome.

The increasing understanding of the pathophysiology behind the elevated risk of stillbirth and preeclampsia in T1DM pregnancies will hopefully soon enable new strategies for prevention of these adverse outcomes. Long-term follow-up of T1DM women with preeclampsia could perhaps further increase the understanding of pathophysiological mechanisms involved. Measurement of amniotic erythropoietin levels at the end of theT1DM pregnancy has been associated with declining rates of stillbirth in Finland [20] and introduction of this management program should be considered in Sweden. Investigating the impact of other factors, besides glucose, for the risk of stillbirth in T1DM pregnancies could also be helpful in order to decrease the incidence of fetal demise. Also, randomized trials investigating the use of insulin pumps and continuous glucose monitoring in pregnancy on the risk of different complications are important.

The importance of preconception care and education of medical staff and patients cannot be emphasized too much. Patients with T1DM planning a pregnancy should be encouraged to optimize metabolic control, strive towards normal BMI and to stop smoking. Information regarding the risk of hypoglycaemia in pregnancy should be provided the patient and her family. Moderate amounts of physical activity are most likely very beneficial also in pregnant women with T1DM, increasing insulin sensitivity and keeping body weight under control. Thus, continued effort to provide all women with T1DM pre conception counselling is important as well as frequent visits with the diabetes team throughout pregnancy. Outcome of T1DM pregnancies is favourable in Sweden. This is most likely partly a reflection of the comparatively good socioeconomic situation in Sweden with free health care for all citizens, including free insulin/test strips etc. In the present thesis, we were not able to investigate the impact of socioeconomic factors on the risk of adverse pregnancy outcome and there are few studies investigating this association. However, in a recent publication from the UK it was demonstrated that social disadvantage significantly decreased the risk for LGA in both type 1 and type 2 diabetic pregnancies, and was not identified as a risk factor for major malformations or perinatal mortality [8]. The influence of maternal ethnicity on pregnancy outcome is also interesting. Comparing the risk of adverse outcome in T1DM women of Nordic origin with that of T1DM women of non-Nordic origin revealed a significantly increased risk of an LGA outcome in the Nordic group, even after taking differences in maternal height into account. There was however, no difference in the risk of preeclampsia, perinatal mortality or major malformations between the two groups (data not shown).

Further research regarding fetal growth regulation in T1DM pregnancies is needed. The pathophysiological mechanism behind the high incidence of fetal macrosomia is not completely understood. It is also important to find markers for early detection of fetuses at risk of macrosomia as well as to elucidate potential gender differences in fetal growth and body composition. Detailed body composition analyses with respect to total amount and distribution of fat mass in T1DM offspring are warranted as well as investigation of the impact of “new” growth factors such as leptin. LGA as a dichotomous outcome variable is often a too crude estimate as infant body composition may be significantly abnormal with increased amounts of body fat and thickening of the interventricular septum of the heart, even in cases of normal birth weight. Hence, analysing body composition may give more accurate information regarding the infant´s risk of acute and long term complications. It is also of great interest to study the postnatal growth pattern of T1DM offspring with different birth size, not only with respect to weight and height but also with regard to the different compartments of fat mass: i.e. subcutaneous and visceral fat mass. It is possible that the postnatal growth pattern differs between infants who were disproportionate /overweight at birth as compared with proportionate newborns. Characterization of postnatal growth patterns in T1DM offspring may increase our understanding of the enhanced risk of long term

complications such as obesity, metabolic syndrome and cardiovascular disease observed in this group. Increased knowledge of fetal and postnatal growth and body composition of type 1 diabetic offspring is a prerequisite for future preventive measures.

ACKNOWLEDGEMENTS

During the writing of this thesis, I have received advice and encouragement from many. First, I would like to thank my supervisors: Mikael Norman, Ulf Hanson, Magnus Westgren and Dharmintra Pasupathy. I have benefited greatly from your expertise in medicine and research and I highly value the strong personal commitment that you have shown to my work. All of these collaborations were both intellectually rewarding and enjoyable. I regard you all as my dear friends.

I owe special thanks to Mikael, my main supervisor. Your unfailing helpfulness and support have been essential for completion of this thesis. I appreciate your always constructive advice and constant encouragement. I could not have wished for a more devoted supervisor.

I want to thank Ulf, my co-supervisor, for introducing me to research and for generously sharing your data with me. I have always enjoyed our discussions on different aspects of research and your knowledge on diabetes has been invaluable.

Magnus, I want to express my sincere thanks for your strong support and enthusiasm and for your belief in me and my capacity. I am very grateful to you for introducing me to Mikael, my main supervisor. I also owe you many thanks for introducing me to Dharmintra Pasupathy and Lucilla Poston at King´s College.

Dharmintra, I thank you for sharing your great knowledge in epidemiology and statistics with me and for introducing me to the Academic Unit of Maternal and Fetal Medicine at King´s College.

Lucilla Poston, thank you for cordially inviting me to your research department at Kings' College.

I would also like to express my gratitude to Gunnar Lilja for always defending my interests, for encouraging my ideas and wish to work with research.

I am also very grateful to Per Sandstedt, Eva Berggren-Boström and Eva Östblom for giving me the opportunity to work with my thesis.

Anders Åhlin, my mentor on the PhD program and dear friend. Thank you for your constant encouragement and always positive attitude and for sharing your great enthusiasm for paeditrics.

Birger Winbladh and Bonna Dahl - thank you for introducing me to paediatrics. You have all been important role models for me in my clinical work.

I thank Anna Gunnerbeck, Karolina Lindström , Lisa Örtquist and Eva Åndell – my dear friends and companions on the PhD program.

I would like to thank all colleagues and friends at the Sachsska Children's Hospital for creating a permissive and friendly atmosphere at work. Fredrik Stenius, thanks for always making me laugh.

In particular I would like to thank my beloved family: Jens, Emil, Linus, Nisse, Ulla, Bengt, Björn and Ester.

I am also grateful to Swedish Order of Freemasons, the Samariten Order, Stockholm County Council for the support of this work.

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