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Trends in Obstetric and Perinatal Outcomes of Women with Type 1 Diabetes During 1988-2011

A Finnish Population-Based Observational Study



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TRENDS IN OBSTETRIC AND PERINATAL OUTCOMES OF WOMEN WITH TYPE 1 DIABETES DURING 1988-2011

A Finnish population-based observational study

Miira Klemetti

Academic dissertation

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To Ante, Molly and Mona

To women with type 1 diabetes and their babies

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ABSTRACT

Background: Dr. Priscilla White, a pioneer in the care of diabetes (DM) in pregnancy, recognized that the prognosis of pregnancy is not identical in all women with type 1 DM. To improve the prediction of risks, she published in 1949 a classification system for pregnant women with DM according to the age at onset, the duration of DM and the presence of diabetic vascular complications. Since then, great advances in diabetes care and obstetrics have been made, but adverse outcomes remain increased in type 1 DM pregnancies compared with background populations. Pregnancy-related metabolic and hemodynamic changes superimposed on the diabetic metabolic milieu and the diabetes-affected vasculature contribute to many of these complications. The increasing prevalence of obesity in women of reproductive age may result in additional obstetric challenges.

Aims. To analyze the trends in pre-pregnancy body mass index (BMI), glycemic control and blood pressure (BP) levels and their relations to obstetric and perinatal outcomes in women with type 1 DM during 1988-2011. To analyze the association of White's class with pregnancy outcomes in contemporary type 1 diabetic parturients and to evaluate whether White's classification provides predictive information in addition to measurement of first trimester glycated hemoglobin (HbA_{1c}) and BP.

Subjects and methods. The obstetric records of a population-based cohort of 1094 consecutive type 1 DM patients with a singleton childbirth during 1988-2011 at Helsinki University Hospital (HUH) were reviewed. The most recent childbirth of each woman was included. The patients were categorized based on White's classification as follows: 1) class B (n= 208): age at onset ≥ 20 years and DM duration < 10 years; 2) class C (n=282): age at onset 10-19 years or DM duration 10-19 years; 3) class D (n=375): age at onset < 10 years or DM duration ≥ 20 years or background retinopathy; 4) class R (n=121): diabetic proliferative retinopathy; and 5) class F (n=108): diabetic nephropathy.

Results. During 1988-2011, the pre-pregnancy BMI increased, with the exception of women with diabetic nephropathy. The frequencies of BMI 25-29.9 kg/m² and ≥ 30 kg/m² increased from 19% and 2%, respectively, in 1988-1991 to 37% and 10% in 2008-2011. Concurrently, pre-pregnancy and late pregnancy glycemic control deteriorated. Early pregnancy glycemic control remained suboptimal (mean HbA_{1c} $> 7\%$) in the total cohort and in patients with diabetic nephropathy it was particularly poor (median HbA_{1c} $> 8\%$). The proportion of women who exceeded the American Diabetes Association's definition of hypertension during pregnancy (BP $> 130/80$ mmHg) increased in all trimesters of pregnancy and the frequency of preeclampsia remained high (19-34%). In women with diabetic nephropathy, BP exceeded 130/80 mmHg in $> 60\%$ of patients in the first trimester and in $> 90\%$ of patients in the third trimester throughout the study period and the frequency of preeclampsia was 48%.

In the total cohort, the elective and the total cesarean section (CS) rates decreased from 58% and 74%, respectively, in 1988-1991 to 27% and 66% in 2008-2011. The emergency CS rate increased from 16% in 1988-1991 to 39% in 2008-2011. Deliveries before 37 weeks of gestation increased from 29% in 1988-1991 to 49% in 2008-2011, and deliveries before 32 weeks decreased from 4% in 1988-1991 to 2% in

2008-2011. Of patients with diabetic nephropathy, >70% delivered before 37 weeks of gestation and >90% delivered by CS throughout the study period.

Among the newborn infants, the frequency of fetal macrosomia remained high (27-39%). The frequencies of umbilical artery pH <7.15 and <7.05 increased from 4% and 1%, respectively, in 1988-1991 to 18% and 4% in 2008-2011. The frequency of neonatal hypoglycemia decreased from 66% in 1988-1991 to 55% in 2008-2011. Neonatal intensive care unit (NICU) admissions persisted above 15%. The perinatal mortality rate was 1.8% in the total cohort and 3.4% in diabetic nephropathy patients.

In multiple regression analyses exploring risk factors of adverse outcomes, poor glycemic control in early and late pregnancy was associated with delivery before 37 weeks of gestation, fetal macrosomia, and NICU admission. Poor glycemic control in late pregnancy was also associated with fetal acidemia at birth and neonatal hypoglycemia. Early pregnancy BP >130/80 mmHg was associated with delivery before 37 weeks, small-for-gestational age infant, NICU admission, and decreased risk of fetal macrosomia. Maternal overweight predicted fetal macrosomia. White's classes B to F predicted preeclampsia, independently of suboptimal glycemic control ($HbA_{1c} \geq 7\%$) and hypertension (BP $\geq 140/90$ mmHg) in early pregnancy, with odds ratios increasing stepwise from class B to F. White's classes R and F were associated with delivery before 37 weeks. Class F also predicted NICU admission and reduced risk of fetal macrosomia. White's class did not predict other perinatal outcomes.

Conclusions. Pre-pregnancy BMI has increased, glycemic control before pregnancy and during the second half of pregnancy has deteriorated, and BP levels during pregnancy have increased in type 1 diabetic parturients. The frequencies of most adverse obstetric and perinatal outcomes have either persisted at high levels or increased. The results call for an intensified therapeutic approach in type 1 DM women, both before and during pregnancy. White's classification is useful in estimating the risk of preeclampsia but its contemporary utility in predicting other pregnancy outcomes of women with type 1 DM appears limited when information on first trimester HbA_{1c} , BP and diabetic microvascular complications is available.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

- I Klemetti M, Nuutila M, Tikkanen M, Kari MA, Hiilesmaa V, Teramo K. Trends in maternal BMI, glycaemic control and perinatal outcome among type 1 diabetic pregnant women in 1989-2008. *Diabetologia* 2012;55:2327-34.
- II Klemetti MM, Teramo K, Nuutila M, Tikkanen M, Hiilesmaa V, Laivuori H. Blood pressure levels but not hypertensive complications have increased in type 1 diabetes pregnancies during 1989-2010. *Diabet Med* 2013;30:1087-93.
- III Klemetti MM, Laivuori H, Tikkanen M, Nuutila M, Hiilesmaa V, Teramo K. Obstetric and perinatal outcome in type 1 diabetes patients with diabetic nephropathy during 1988-2011. *Diabetologia* 2015;58:678-86.
- IV Klemetti MM, Laivuori H, Tikkanen M, Nuutila M, Hiilesmaa V, Teramo K. White's classification and pregnancy outcome in women with type 1 diabetes: a population-based cohort study. *Diabetologia* Oct 2015 [Epub ahead of print] doi: 10.1007/s00125-015-3787-1

The publications are published with permission from the publishers and are referred to in the text by their Roman numerals.

ABBREVIATIONS

ADA	American Diabetes Association
ACOG	American College of Obstetricians and Gynecologists
BMI	Body mass index
BP	Blood pressure
CS	Cesarean section
CEMACH	Confidential Enquiry into Maternal and Child Health
DCCT	Diabetes Control and Complications Trial
DM	Diabetes mellitus
DKA	Diabetic ketoacidosis
EASD	European Association for the Study of Diabetes
EDIC	Epidemiology of Diabetes Interventions and Complications
EPO	Erythropoietin
ESC	European Society of Cardiology
GFR	Glomerular filtration rate
HbA _{1c}	Glycated hemoglobin A _{1c}
HELLP	Hemolysis, elevated liver enzymes, low platelet count
HUH	Helsinki University Hospital
IUGR	Intrauterine growth restriction
LGA	Large-for-gestational age
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
OR	Odds ratio
PROM	Preterm rupture of membranes
RDS	Respiratory distress syndrome
SGA	Small-for-gestational age
SMBG	Self-monitoring of blood glucose

1 INTRODUCTION

Adverse outcomes remain increased in pregnancies of women with type 1 diabetes (DM) compared with the general population (Boulot et al. 2003; CEMACH 2005; Evers 2004; Hawthorne et al. 1997; Jensen et al. 2004; Lapolla et al. 2008b; Macintosh 2006; Murphy et al. 2011; Penney et al. 2003a; Persson et al. 2009; Teramo 2010; Verheijen et al. 2005; Väärasmäki et al. 2000). During pregnancy, type 1 diabetic women are at an increased risk of acute DM complications, such as severe hypoglycemia, progression of diabetic long-term complications and hypertensive disorders of pregnancy (Colatrella et al. 2010; Hawthorne 2011; Kaaja 2011). Typical perinatal complications include congenital malformations, abnormal fetal growth, chronic fetal hypoxia, preterm birth, shoulder dystocia, and perinatal death (Boulot et al. 2003; CEMACH 2005; Evers 2004; Hawthorne et al. 1997; Jensen et al. 2004; Lapolla et al. 2008b; Macintosh 2006; Penney et al. 2003a; Persson et al. 2009; Secher et al. 2015; Teramo et al. 2004a; Väärasmäki et al. 2000; Verheijen et al. 2005). Pregnancy-related metabolic and hemodynamic changes superimposed on the diabetic metabolic milieu and the diabetes-affected vasculature contribute to many of these complications. Glycemic control and BP levels during pregnancy as well as underlying diabetic complications are important determinants of pregnancy outcomes in type 1 DM (Kitzmilller et al. 2008).

Obesity and the associated insulin resistance, dyslipidemia and other metabolic disturbances may complicate the achievement of good glycemic control and normotension in diabetic pregnancies (Catalano 2010; Jarvie et al. 2010). Poor glycemic control as well as high BMI are risk factors of preeclampsia as well as other adverse pregnancy outcomes such as malformations, fetal macrosomia and CS deliveries in women with pre-gestational DM (Holmes et al. 2011; Persson et al. 2012). Little evidence exists regarding the possible impacts of the ongoing obesity pandemic on the trends in glycemic control, BP levels as well as obstetric and perinatal outcomes in type 1 DM pregnancies.

Diabetic nephropathy, caused by long-term deleterious effects of chronic hyperglycemia and related abnormal metabolism on the renal glomeruli, is associated with a particularly high risk of hypertensive disorders of pregnancy, preterm birth, intrauterine growth restriction (IUGR) and perinatal mortality (Biesenbach et al. 2000; Damm et al. 2013; Dunne et al. 1999; Gordon et al. 1996a; Kitzmilller et al. 1981; Reece et al. 1988). Its prognosis has improved with modern care (Marshall 2012), but recent large reports analyzing temporal changes in the glycemic control, BP levels, markers of renal function as well as obstetric and perinatal outcomes of women with diabetic nephropathy are lacking.

An American pioneer in the care of diabetic pregnant women, Dr. Priscilla White, recognized that considerable variation exists in the prognosis of pregnancies among type 1 DM patients. In 1949, she introduced a classification system for pregnant women with DM according to the age at onset, duration of DM and the presence of diabetic vascular complications (White 1949, White 1965, Hare and White 1977). Recently, the usefulness of this classification has been questioned based on studies involving mainly women with type 2 and gestational DM and low numbers of women with severe diabetic vascular complications (Cormier et al. 2010; Cormier et al. 2009; Sacks and Metzger 2013). The American Diabetes Association (ADA) has proposed

that type 1 and type 2 DM pregnant women should be classified simply as “without vascular complications” or “with vascular complications” (ADA 2010). The original cohort of White included predominantly women with type 1 DM, many of whom were diagnosed with DM in their childhood or teenage years and had a long disease duration (White 1949). There is a paucity of recent studies examining the relevance of White’s classification in type 1 DM pregnancies with or without vascular complications.

Active monitoring and evaluation of the quality of care, including reviews of hospital records, are needed to plan and target interventions aiming to improve outcomes in diabetic pregnancies. In the present study, recent trends in pre-gestational BMI, glycemic control and BP levels during pregnancy, as well as obstetric and perinatal outcomes and risk factors, were investigated in a large population-based cohort of Finnish type 1 DM women with and without vascular complications. In addition, the current utility of White’s classification in the prediction of adverse obstetric and perinatal outcomes in type 1 DM pregnancies was assessed.

2 REVIEW OF THE LITERATURE

2.1 Type 1 diabetes

2.1.1 Etiology and pathogenesis

Type 1 DM is a chronic, progressive disease in which autoimmune antibodies selectively destroy the pancreatic β -cells leading to lack of insulin secretion and hyperglycemia (Pugliese 2013). Its precise etiology and pathogenesis are still unknown, but both underlying genetic susceptibility and environmental triggers, such as infectious or nutritional agents or factors affecting the gut microbiome, are likely required to initiate the disease (Knip and Simell 2012). The asymptomatic preclinical period from the first appearance of DM-associated autoantibodies in the blood to overt type 1 DM is heterogeneous, ranging from months to decades (Knip and Simell 2012; Kulmala 2003). The incidence of type 1 DM peaks in adolescence (Simell et al. 2010), but marked individual variation exists in the disease progression and tendency to develop specific long-term complications, reflecting the multifactorial pathogenesis (Pugliese 2013; Tuomilehto 2013).

2.1.2 Prognosis

Since insulin was discovered in 1921, significant advances have been made in the management of type 1 DM, including the development of glycated hemoglobin (HbA_{1c}) measurement, devices for the self-monitoring of blood glucose (SMBG) and insulin delivery, as well as insulin analogues enabling the imitation of normal insulin secretion. Despite these advances, less than half of insulin-treated DM patients achieve the recommended level of glycemic control <7% (<53 mmol/mol) (Stark Casagrande et al. 2013). Mortality remains elevated in type 1 DM patients compared with non-diabetic individuals (Harjutsalo et al. 2011; Jørgensen et al. 2013), diabetic nephropathy and cardiovascular diseases accounting for much of this excess mortality (Jørgensen et al. 2013; Livingstone et al. 2015). Compared with men with type 1 DM, type 1 diabetic women have a 40% higher excess risk of death from any cause, and a doubly elevated risk of fatal cardio- or cerebrovascular events (Huxley et al. 2015). Recent observations suggest that survival of Finnish patients with DM onset before 15 years of age has improved and deaths due to chronic DM complications have reduced since the 1980's, but the survival of those with later disease onset has deteriorated and lethal acute complications have increased (Harjutsalo et al. 2011). Social disadvantage, e.g. long-term unemployment, low income as well as alcohol-, drug and mental health related issues, is associated with excess mortality in Finnish type 1 DM (Forssas et al. 2010; Forssas et al. 2012; Harjutsalo et al. 2011).

2.1.3 Prevalence in Finnish parturients

Annually approximately 350 Finnish women with type 1 DM give birth, which is approximately 0.6% of all Finnish childbirths (Väärasmäki et al. 2012; Vuori and Gissler 2013). The incidence of type 1 DM in Finnish children is among the highest in the world and has been constantly increasing until recent times (Harjutsalo et al. 2008; Harjutsalo et al. 2013). In 2008, it was estimated that the number of new cases diagnosed before the age of 15 will double in the following 15 years and the incidence

will increase in particular in the age group of children under five years (Harjutsalo et al. 2008). Similar increasing incidences of type 1 DM have been recorded worldwide (Onkamo et al. 1999; Patterson et al. 2012) and various environmental factors have been suspected to contribute to these trends (Tuomilehto 2013). The most recent Finnish and Swedish reports suggest that after a period of steep increase, the incidence of type 1 DM among children under 15 might be plateauing (Berhan et al. 2011; Harjutsalo et al. 2013), although this could also be due to year-to-year random variations in the incidence (Tuomilehto 2013). Nevertheless, it can be expected that, in the next decades, a growing number of women at reproductive age have long-standing type 1 DM and are predisposed to the obstetric and perinatal complications associated with maternal hyperglycemia and chronic complications of DM.

2.2 Micro- and macrovascular complications in type 1 diabetes

2.2.1 Mechanisms of diabetic vascular damage

Chronic hyperglycemia and associated metabolic disturbances that characterize type 1 DM have detrimental effects on the human vasculature (Nathan 1993; Paneni et al. 2013). The mechanisms by which micro- and macrovascular damage occurs are not completely known, but at least endothelial dysfunction, inflammation and oxidative stress due to hyperglycemia are implicated (Giacco and Brownlee 2010). Other risk factors include hypertension, dyslipidemia and genetic susceptibility (Paneni et al. 2013). As a result of hyperglycemia, intracellular concentrations of glucose metabolites in endothelial cells are elevated leading to mitochondrial dysfunction, increased oxidative stress, activation of various cellular pathways associated with diabetic complications (e.g. the polyol pathway, advanced glycosylation end product formation, inhibition of endothelial vasodilators and antiatherosclerotic enzymes (Brownlee 2005; Giacco and Brownlee 2010; Rask-Madsen and King 2007). In addition to chronic hyperglycemia, acute hyperglycemic episodes, epigenetic mechanisms and biomechanical forces such as disturbed blood flow, and hypertension may contribute to endothelial dysfunction and diabetic vascular complications (Ceriello et al. 2009; Gordin et al. 2007; Reddy and Natarajan 2011). In line with the progressive nature of the disease, the likelihood of clinically manifest complications increases with DM duration as vascular damage accumulates.

2.2.2 Categories of diabetic vascular complications

The chronic vascular complications of type 1 DM can be grouped into microvascular diseases, such as diabetic retinopathy, diabetic kidney disease, and diabetic neuropathy, as well as macrovascular diseases, such as coronary heart disease, peripheral arterial disease and cerebrovascular complications. In addition, the occurrence of chronic hypertension is approximately doubled in DM compared to the general population (Epstein and Sowers 1992). Hypertension in DM results from a multitude of different pathogenetic mechanisms, e.g. renin-angiotensin-aldosterone and sympathetic nervous system activation, excess sodium retention, oxidative stress and endothelial dysfunction (Van Buren and Toto 2011). It accelerates the progression of all diabetic vascular complications (Epstein and Sowers 1992).

Aiming for normoglycemia is of fundamental importance in attempts to prevent or delay the progression of all diabetic micro- and macrovascular complications. A large landmark study, Diabetes Control and Complications Trial (DCCT), and its 20-year follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC), demonstrated that achievement of good glycemic control by intensive insulin treatment early in the course of DM provides long-lasting protection against the development or progression of retinopathy, nephropathy and neuropathy (DCCT Research Group 1993, DCCT/EDIC Research Group 2014; Lachin et al. 2008; Martin et al. 2006; Writing team for the DCCT/EDIC Research Group 2002) as well as macrovascular disease (Nathan et al. 2005).

Good management of all cardiovascular risk factors is also important in the primary and secondary prevention of diabetic long-term complications. A cornerstone of treatment is stringent BP control (Chobanian et al. 2003; Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) et al. 2014). The ADA recommends a BP level <130/80 mmHg (ADA 2011) and the Finnish Current Care Guidelines <140/80 mmHg (Diabetes: Current Care Guideline 2013) for individuals with type 1 DM. Treatment of lipids to target levels is also recommended (Collins et al. 2006; ESC et al. 2014). In addition to pharmacologic therapies, a healthy diet and a physically active lifestyle should be encouraged (Buse et al. 2006; Chimen et al. 2011; ESC et al. 2014). Physical activity may aid in the prevention and control of obesity and other features of the metabolic syndrome, which has been associated with micro- and macrovascular complications in type 1 DM (Metascreen Writing Committee 2006; Price et al. 2014; Thorn et al. 2009).

2.2.2.1 Diabetic retinopathy

Diabetic retinal damage can be divided into pre-proliferative retinopathy (i.e. background retinopathy) and proliferative retinopathy. Microaneurysms, exudative changes and hemorrhages, ischemic changes, and intraretinal microvascular abnormalities are typical findings in background retinopathy (Mohamed et al. 2007; 2012). Background retinopathy may regress with intensive treatment (Klein et al. 2008) or, with worsening retinal ischemia, progress towards proliferative retinopathy characterized by abnormal formation of new blood vessels on the optic disk and the surface of the retina, fibroblast proliferation, and vitreous hemorrhage (Antonetti et al. 2012). Diabetic macular edema may be diagnosed at non-proliferative or proliferative stages of diabetic retinopathy (Mohamed et al. 2007).

Diabetic retinopathy is among the most prevalent diabetic long-term complications. Almost all type 1 DM patients with DM diagnosis before age 30 are affected by it to some degree after 20 years' DM duration (Diabetic retinopathy: Current Care Guideline 2014; Klein et al. 2008). Risk factors include poor glycemic control and HbA_{1c} variability, hypertension, dyslipidemia, albuminuria and long DM duration (Kilpatrick et al. 2008; Klein et al. 2008; Lyons et al. 2004; Porta et al. 2001). The incidence of proliferative retinopathy seems to be decreasing, but it is still diagnosed in over 20% of type 1 DM patients after 25 years' DM duration (Nordwall et al. 2004) and prevails as the most common cause of blindness in working-age adults (Ciulla et al. 2003).

The most important treatment of proliferative diabetic retinopathy is focal or pan-retinal laser photocoagulation (Mohamed et al. 2007), which may also be performed

during pregnancy if needed. Since permanent loss of eye sight can be prevented or delayed with prompt treatment, regular monitoring with biomicroscopy and fundal photographs is essential in type 1 DM patients from age 10 forward (Diabetic retinopathy: Current Care Guideline 2014).

2.2.2.2 Diabetic kidney disease

Diabetic kidney disease develops progressively, with gradually increasing albuminuria, hypertension and declining glomerular filtration rate (GFR), at worst leading to end-stage renal disease and need for dialysis and kidney transplantation. Microalbuminuria, defined as total urinary albumin excretion of 30-299 mg/24h, or nocturnal albuminuria of 20-199ug/min, or albumin/creatinine ratio of 2.5-25 mg/mmol (men) or 3.5-35 mg/mmol (women), in a spot urine sample is the first functional sign of diabetic kidney disease (ADA 2004a; Metsärinne et al. 2007). Total urinary albumin excretion of ≥ 300 mg/24 hours, or nocturnal albuminuria ≥ 200 ug/min, or albumin/creatinine ratio of >25 mg/mmol (men) or >35 mg/mmol (women), are classified as macroalbuminuria (ADA 2004a; Metsärinne et al. 2007). Histologic findings such as increased glomerular membrane thickness, mesangial cell expansion, nodular sclerosis (Kimmelstiel-Wilson lesions) and global glomerulosclerosis denote diabetic nephropathy and are verified by kidney biopsy (Tervaert et al. 2010). In type 2 DM, also more heterogenous, atypical patterns of renal lesions and disease progression may be seen (Nosadini et al. 2000; Tervaert et al. 2010). However, in the present study involving type 1 DM patients exclusively, the term diabetic nephropathy will be used to describe the progressive kidney disease of type 1 DM patients, characterized by macroalbuminuria in the absence of non-diabetic renal diseases based on clinical assessment or kidney biopsy.

European studies have reported 8-19% cumulative incidences of diabetic nephropathy in patients with DM duration exceeding 15-29 years, with the lowest proportions observed in the most recent cohorts (Bojestieg et al. 1994, Dahlqvist et al. 2001; Harvey et al. 2001; Hovind et al. 2003; Nordwall et al. 2004). Persistent microalbuminuria has been reported to affect 6-20% of patients with DM duration of 10-31 years (Bojestieg et al. 1994; Dahlqvist et al. 2001; Harvey et al. 2001; Nordwall et al. 2004). The incidence of diabetic nephropathy increases in type 1 DM patients progressively up to 20 years after DM diagnosis, after which it declines suggesting individual differences in susceptibility to diabetes-induced kidney damage (Harjutsalo et al. 2004). Poor glycemic control, hypertension, smoking, male sex, and certain genetic factors are associated with increased risk (Rossing et al. 2002b; Scott et al. 2001). Besides indicating nephropathy, micro- and macroalbuminuria signify a markedly increased risk of cardiovascular diseases (Cirillo 2008). Mortality in type 1 DM patients with diabetic nephropathy is increased significantly, both due to end-stage renal disease and cardiovascular events (Harjutsalo et al. 2011).

In addition to optimizing glycemic control, strict treatment of hypertension is crucial to slow the progression of diabetic kidney disease. The currently recommended target BP for diabetic patients with either micro- or macroalbuminuria is $\leq 130/80$ mmHg (Wheeler and Becker 2013). Drugs inhibiting the renin-angiotensin aldosterone system are particularly important in diabetic kidney disease and decrease the risk of its progression even in normotensive patients (Mathiesen 1999; Gross et al. 2005). Smoking cessation is essential (Scott et al. 2001).

2.2.2.3 Diabetic neuropathy

The pathogenesis and clinical manifestations of diabetic neuropathy are multifaceted (Albers and Pop-Busui 2014). Many of the complex pathological mechanisms affecting neuronal functions resemble those implicated in diabetic microvascular complications (Albers and Pop-Busui 2014). According to current views, in addition to hyperglycemia, various components of the metabolic syndrome, e.g. insulin resistance and dyslipidemia, contribute to the development of diabetic neuropathy, in particular in type 2 DM (Callaghan et al. 2012b; Tesfaye et al. 2005). Apparently both neuronal metabolic abnormalities and ischemia are involved. Typical diabetic polyneuropathy is chronic, symmetrical, length-dependent, primarily sensorimotor polyneuropathy, which starts in the feet and progresses proximally (Callaghan et al. 2012b; Tesfaye et al. 2010). It is associated with a significant burden of morbidity and disabilities, such as chronic pain, numbness, susceptibility to limb fractures, ulcerations and amputations (Callaghan et al. 2012b; Vincent et al. 2011). Autonomic diabetic neuropathy may be clinical or subclinical, and may manifest as impaired function of various organ systems, e.g. cardiovascular, gastrointestinal, genitourinary, sudomotor or ocular.

Diabetic neuropathy in its various forms may affect over half of type 1 DM patients aged 30 or over (Maser et al. 1989). Diabetic autonomic neuropathy affects approximately 40% of patients with type 1 DM (Freccero et al. 2004; Low et al. 2004). Apart from aiming at overall good DM management, including glycemic, hypertension and lipid control and avoidance of smoking, no specific treatment against diabetic polyneuropathies exist (Callaghan et al. 2012a). Anticonvulsants and antidepressants may be utilized to alleviate neuropathic pain (Callaghan et al. 2012b).

2.2.2.4 Macrovascular complications

Several aspects of diabetic metabolism promote or accelerate the development of atherosclerosis (Libby 2005; Paneni et al. 2013). Furthermore, DM seems to reduce the protective effects of female sex against cardiovascular diseases, resulting in excess cardiovascular morbidity and mortality in diabetic women (Recarti et al. 2015). Endothelial dysfunction and early atherosclerotic changes can be seen already in children and adolescents with type 1 DM (Heilman et al. 2009; Jarvisalo 2004). Because of the atherosclerosis-promoting effects of DM, careful control of all cardiovascular risk factors, such as hypertension, dyslipidemia and overweight, and the avoidance of smoking, are important in DM (ESC et al. 2014).

2.2.3 Diabetic vascular complications in pregnant women with type 1 diabetes

Retinopathy. In European multicenter or population-based studies, reported frequencies of diabetic retinopathy among parturients with type 1 DM range between 20-35% (Bell et al. 2012; Boulot et al. 2003; Hiilesmaa et al. 2000; Lapolla et al. 2008a). Diabetic retinopathy is associated with an increased risk of preeclampsia, pre-term delivery, SGA infant, and CS delivery (Haeri et al. 2008; Hiilesmaa et al. 2000).

Diabetic kidney disease. Overt diabetic nephropathy affects 2.5-5% of type 1 diabetic pregnancies (Bell et al. 2012; Damm et al. 2013; Landon 2007). Less data is available regarding the prevalence of microalbuminuria in pregnancy, but small Danish cohorts have reported prevalences of 4.5-11% (Damm et al. 2013; Ekbom et al. 2001).

Diabetic kidney disease is linked to high risks of maternal and fetal complications associated with maternal impaired kidney function, hypertension and endothelial dysfunction, e.g. maternal nephrotic-level proteinuria, preeclampsia and fetal growth restriction (Biesenbach et al. 2000; Carr et al. 2006; Damm et al. 2013; Ekblom et al. 2001; Glinianaia et al. 2012b; Kimmmerle et al. 1995).

Neuropathy. Reports on the prevalence of peripheral or autonomic neuropathy in pregnant women with type 1 DM are scarce. A British population-based register study showed a 2.1% prevalence of diabetic neuropathy in parturients with type 1 DM (Bell et al. 2012). Pregnancy symptoms, such as nausea, vomiting and constipation, may be similar to those of gastrointestinal autonomic neuropathy and complicate its diagnosis during pregnancy (Kitzmilller et al. 2008). Since the autonomic nervous system is involved in maternal circulatory adaptation to pregnancy, autonomic neuropathy may result in poor tolerance of pregnancy-related hemodynamic changes (Airaksinen et al. 1986; Hagay and Weissman 1996). Severe hypoglycemia tendency and impaired physiological responses to hypoglycemia may also follow (Kitzmilller et al. 2008). Diabetic gastroparesis may be exacerbated during pregnancy and lead to severe maternal morbidity (pulmonary edema, aspiration pneumonia, severe malnutrition, septic infections, deep vein thrombosis, burst abdomen, constant vomiting) and fetal complications (growth restriction, preterm birth, fetal death) and overall poor prognosis of pregnancy (Hagay and Weissman 1996).

Macrovascular complications. Data on macrovascular complications in type 1 DM pregnancies are limited (Gordon et al. 1996b). In population-based studies in the United States, maternal DM has been shown to be a significant risk factor of stroke (James et al. 2005) and acute myocardial infarction in pregnancy (James et al. 2006). Coronary heart disease has been reported to affect 1/350 of DM pregnancies (Leguizamon et al. 2015). Type 1 DM women aged >35 years, or aged >25 years with DM duration >15 years, with retinopathy or nephropathy, with signs or symptoms of peripheral arterial disease, or with risk factors for coronary heart disease, are considered to be at an increased risk for underlying cardiovascular diseases (ADA 2004b; Gordon et al. 1996b). This should be borne in mind when examining women planning pregnancy or in early pregnancy (Kitzmilller et al. 2008). Pregnancy-associated hemodynamic and metabolic alterations may result in increased strain and oxygen consumption of the myocardium, poor cardiovascular tolerance of pregnancy, myocardial infarction, and even maternal or perinatal death (Gordon et al. 1996b). Data on diabetic cardiomyopathy and peripheral arterial disease prevalence in diabetic pregnant women are lacking.

2.3 Type 1 diabetes in pregnancy

2.3.1 Historical perspectives

Before the invention of insulin treatment in 1922, the death of both the mother and the fetus was the usual outcome among the few diabetic women who were able to conceive (Jorgensen 1977). At the Elliot Joslin's diabetes clinic in Boston, fetal mortality was 40% and maternal mortality 66% in 108 parturients during 1898-1917 (Hare and White 1977), possibly in women with milder forms of DM. An American

internist, Dr. Priscilla White, was among the first to initiate research and develop clinical care of DM in pregnancy. In 1924, she started working at the Joslin clinic, closely monitoring large numbers of diabetic children, adolescents and pregnant women for decades. She recognized that the best outcomes are achieved by striving for as good a glycemic control as possible during pregnancy with frequent administration of small doses of insulin to minimize hypoglycemic events (Dunn 2004). She emphasized the pivotal role of careful supervision of the diabetic parturient by an internist and an obstetrician in cooperation (Dunn 2004). She also promoted basic research, e.g. concerning pancreatic β cell transplantation, as well as called attention to the psychosocial aspects of DM (Dunn 2004). Among her important observations was that the prognosis of pregnancy in all diabetic women is not the same. To improve the prediction of diabetic pregnancy complications, she published a classification system based on the prepregnancy characteristics of the mother: age at DM diagnosis, DM duration and the presence of diabetic vascular complications (White 1949). Several versions of this classification have been published (White 1965; Hare and White 1977; White and Hare 1980).

Although the invention of insulin treatment improved the survival of pregnant women with type 1 DM and their possibilities to become pregnant, perinatal mortality related to maternal DM remained high for decades (Pedersen 1977, Hare and White 1977). A Swedish physician, Lars Hagbard, showed in 1956, before modern fetal surveillance methods were available, that the risk of fetal death increased linearly from approximately 5% at 32 weeks of gestation up to 20% at term (Hagbard 1956). At the time, preterm infants were at very high risk of death, with above 60% neonatal death rate among those born before 32 weeks (Hagbard 1956). After 36 weeks, stillbirths were observed to exceed neonatal deaths, which led to a clinical policy of inducing labor around 37 weeks of gestation in pregestational DM pregnancies (Pedersen 1977). Since the available methods of predicting stillbirths in DM pregnancies continue to be limited, this practice prevails in modern obstetrics.

Another pioneer in the field of DM in pregnancy was a Danish professor in internal medicine, Jorgen Pedersen, who opened the Copenhagen center for Pregnant Women in Diabetes in 1946. In the 1960's, he formulated a hypothesis stating that fetal overgrowth in DM pregnancies is due increased transplacental transfer of glucose, causing hypertrophy of fetal pancreatic β cells and insulin hypersecretion, leading to greater fetal utilization of glucose (Pedersen 1977). Similarly to White, Pedersen underlined the importance of multidisciplinary cooperation and centralization in the care of diabetic parturients (Pedersen 1977). During 1946-1972, perinatal mortality fell at his Copenhagen clinic from 22% to 7% (Pedersen et al. 1974).

2.3.2 Management of type 1 diabetes before and during pregnancy

The pregnancy of a woman with type 1 DM should be well planned in order to optimize outcomes. During pregnancy, active glycemic and BP management is crucial, as well as monitoring of the status of possible diabetic complications, with prompt adaptation to the changing metabolic and physiological conditions of pregnancy (Kitzmiller et al. 2008; Ringholm et al. 2012a). In addition to medical care, an individualized healthy food plan and adequate carbohydrate counting skills are important, and nutritional therapy should be provided if needed (Kitzmiller et al. 2008; McCance 2011; Ringholm 2012a). At least half an hour of moderate intensity

physical activity with no risk of trauma on most days of the week is recommended for diabetic women without complications (Kitzmilller et al. 2008).

2.3.2.1 Pre-pregnancy care

Observational studies have demonstrated that attendance in pre-pregnancy care is associated with lower early pregnancy HbA_{1c} values and reduced frequencies of congenital malformations in type 1 diabetic pregnancies (Evers et al. 2004; Fuhrmann et al. 1983; Leguizamon et al. 2007; Ray et al. 2001; Steel et al. 1990). Pre-pregnancy counseling to all women of reproductive age should be included in routine DM control visits in primary or specialist clinics (McCance 2011; Varughese et al. 2007; Väärasmäki et al. 2012). If pregnancy is not wished, reliable contraception should be ensured (Ringholm et al. 2012a). Unfortunately, only 30-50% of pregnancies in type 1 DM patients are planned (CEMACH 2005; Holing et al. 1998; Murphy et al. 2011).

As part of pre-pregnancy care, an obstetrician and/or an internist should collect information regarding age at DM diagnosis, DM duration, glycemic and BP control, possible long-term complications, associated conditions such as thyroid disorders and celiac disease, smoking, medications and reproductive history (Kitzmilller et al. 2008; McCance 2011; Ringholm et al. 2012a). Medications with teratogenic potential (e.g. statins, renin-angiotensin-adoosterone system inhibitors) should be discontinued and replaced with drugs which are safe in pregnancy (Ringholm et al. 2012a; 2014). Screening for possible complications of DM and associated disorders is essential (ACOG 2005). A retinal examination should be done if one has not been performed within the last 6-12 months (Väärasmäki et al. 2012). Possible proteinuria should be screened for and/or quantified and renal function assessed (Kitzmilller et al. 2008). Simple clinical tests to screen for peripheral neuropathy should be performed (Gabbe and Graves 2003; Kitzmilller et al. 2008). Electro- and echocardiogram and other cardiovascular investigations may also be indicated in selected cases with symptoms of macrovascular disease, hypertension or albuminuria (Kitzmilller et al. 2008).

Table 1 shows the pre-pregnancy HbA_{1c} and SMBG targets recommended by the International Diabetes Federation as well as expert organizations in Australia, Great Britain, Canada, Finland and the United States. Achievement of near-normoglycemia already before pregnancy is important because diabetes-related malformations commonly develop before the seventh week of gestation (Mills et al. 1979). This is particularly crucial in patients with diabetic retinopathy, since rapid improvements in glycemic control during pregnancy may cause progression of retinal changes (Kitzmilller et al. 2008; Laatikainen et al. 1987). However, glycemic targets should be individually tailored. Even slight improvements in HbA_{1c} levels decrease the risk of congenital malformations (Inkster et al. 2006; Suhonen et al. 2000). In addition to good glycemic control, folic acid supplementation is important to prevent neural tube defects, which are increased in DM pregnancies. Folic acid may also have other antiteratogenic effects due to its antioxidant functions (Eriksson 2009).

A woman with type 1 DM planning pregnancy should be educated about the specific prognosis and risks associated with her pregnancy (McCance 2011). However, unnecessary discouragement or negative attitude towards pregnancy hopes should be avoided (Holing et al. 1998). In case of poor glycemic control or DM complications that require treatment before pregnancy, contraception should preferably be continued

Table 1. Targets for glycaemic control in the pre-pregnancy period and during pregnancy as recommended by international and national guidelines.

Organization	Pre-pregnancy targets	Pregnancy targets
NICE, UK ^a	HbA _{1c} <7.5% (<58 mmol/mol) Pre-prandial blood glucose 4-7 mmol/l Post-prandial blood glucose <9 mmol/l	HbA _{1c} <6.5% (<47.5 mmol/mol) Fasting blood glucose <5.3 mmol/l 1 hour postprandial blood glucose <7.8 mmol/l 2 hours postprandial blood glucose <6.4 mmol/l
Canadian Diabetes Association ^b	HbA _{1c} <7% (<53 mmol/mol) or “as close to normal as can safely be achieved”	Fasting blood glucose <5.3 mmol/l 1 hour postprandial blood glucose <7.5 mol/l 2 hour postprandial blood glucose <6.7 mmol/l.
Finnish Diabetes Association ^c	HbA _{1c} <7% (<53 mmol/mol)	HbA _{1c} 7–7.5% (53–58 mmol/mol) (Early pregnancy recommendation <7%, “but the risk of hypoglycemia needs to taken into account”)
International Diabetes Federation ^d	HbA _{1c} <7% (<53 mmol/mol) Fasting blood glucose <5.5 mmol/l Postprandial blood glucose <8.0 mmol/l	HbA _{1c} <6% (<42 mmol/mol) or lower if safe and acceptable. Action points for treatment adjustment: Fasting glucose ≥ 5.5 mmol/l 1 hour postprandial blood glucose ≥8.0 mmol/l 2 hour postprandial blood glucose ≥7.0 mmol/l
American Diabetes Association ^e	HbA _{1c} <7% (<53 mmol/mol)	HbA _{1c} <6.0% (<42 mmol/mol) Fasting blood glucose 3.4–5.5 mmol/l Postprandial blood glucose 5.5–7.1 mmol/l
Australasian Diabetes in Pregnancy Society ^f	HbA _{1c} <7% (<53 mmol/mol) or “as close as possible to the reference range”	HbA _{1c} “within the normal range” Fasting and preprandial blood glucose 4.0–5.5 mmol/l 1 hour postprandial blood glucose <8.0 mmol/l 2 hour postprandial blood glucose <7 mmol/l

^aNational Collaborating Centre for Women’s and Children’s Health 2015

^bCanadian Diabetes Association Clinical Practice Guidelines Expert Committee 2013

^cVääräsmäki et al. 2012

^dInternational Diabetes Federation Clinical Guidelines Task Force 2009

^eKitzmiller et al. 2008

^fMcElduff et al. 2005

until improved status has been achieved (National Collaborating Centre for Women's and Children's Health 2015; Suhonen et al. 2000). In case of advanced renal insufficiency, coronary heart disease or severe autonomic neuropathy, a nephrologist, cardiologist or other specialists should be consulted before pregnancy is attempted (Gordon et al. 1996b; McElduff et al. 2005; National Collaborating Centre for Women's and Children's Health 2015).

2.3.2.2 Pregnancy care

A pregnant woman with type 1 DM should be referred for antenatal follow-up to a hospital providing specialist pregnancy and childbirth care for women with pregestational DM. Provision of patient-centered care by multidisciplinary DM teams may be beneficial in optimizing treatment compliance and success in the management of type 1 DM before and during pregnancy (Funnell et al. 2011; Ilanne-Parikka 2015; Kitzmiller et al. 2008). These teams may ideally involve, in addition to obstetricians and internists, e.g. DM nurses, registered dietitians and specialists of self-management education and psychosocial strategies (Funnell et al. 2011; Ilanne-Parikka 2015; Kitzmiller et al. 2008).

2.3.2.2.1 Glycemic control

In healthy non-diabetic women, maternal glucose metabolism adapts progressively to optimize the flow of nutrients to the fetus (Butte 2000). The mechanisms of this adaptation are not fully known, but a complex interplay of hormones, cytokines and growth factors is likely involved (Butte 2000; Kirwan et al. 2002). The first trimester is characterized by the development of increased insulin response to glucose, increased glycogen storage as well as normal or slightly improved insulin sensitivity (Butte 2000). Fasting glucose concentrations fall and remain slightly lower than before pregnancy until delivery, although in overweight women this phenomenon may be attenuated (Mills et al. 1998). In the second trimester, a gradually increasing insulin resistance emerges (Butte 2000; Kirwan et al. 2002). Insulin action has been demonstrated to be 50-70% lower during normal late pregnancy compared with the non-pregnant state (Butte 2000). Concurrently, post-prandial glucose values increase gradually as the pregnancy progresses compared to those measured outside pregnancy (Siegmond et al. 2008). In parturients with type 1 DM, a particularly prolonged postprandial hyperglycemia has been demonstrated in late pregnancy, due to impaired glucose disposal (Murphy et al. 2012). An increased insulin response to glucose persists until the end of pregnancy (Buchanan et al. 1990; Butte 2000; Catalano et al. 1991). Within hours after the delivery of the placenta, the levels of pregnancy hormones fall and insulin sensitivity returns to the same level as before pregnancy (Achong et al. 2014).

Taking into account this continuously transforming maternal metabolic environment, a watchful and active attitude toward monitoring and management of glycemic control in type 1 DM parturients is required. National recommendations concerning glycemic control in type 1 DM pregnancies vary somewhat between centers and countries, as shown in Table 1. Daily SMBG with multiple capillary pre- and postprandial measurements forms the basis for glycemic control. Continuous glucose monitoring has not so far been demonstrated to improve outcomes in diabetic pregnancies (Murphy et al. 2008; Murphy 2013).

Insulin treatment can usually be carried out with the same long- and short-acting human insulin or insulin analogues as the patient has used before pregnancy (Lambert and Holt 2013). In addition to the standard method of multiple daily injections, continuous subcutaneous insulin infusion can be used, particularly if the woman is accustomed to using an insulin pump (de Valk and Visser 2011; Väärasmäki et al. 2012). However, so far, studies have not demonstrated additional benefit from continuous subcutaneous insulin infusion compared with multiple daily injections (de Valk and Visser 2011).

Due to the hypoglycemia risk in early pregnancy, insulin doses may need to be decreased slightly at weeks 8-16 when the risk of hypoglycemia is highest (García-Patterson et al. 2009; Ringholm et al. 2013). Thereafter, insulin requirements usually increase, so that by late gestation doses 3-4 times higher than before pregnancy may be needed (de Valk and Visser 2011; García-Patterson et al. 2009). In parturients who receive antenatal glucocorticoid medication to improve fetal lung maturity, insulin doses need to be increased for a few days due to the hyperglycemia-inducing effects of steroids (Ringholm et al. 2012a; Väärasmäki et al. 2012).

During labor, maternal blood glucose should be kept at 4-7 mmol/l by frequent capillary glucose measurements, an intravenous glucose-insulin infusion and additional insulin doses if needed (Ringholm et al. 2012a; Stenninger et al. 2008). Maternal hyperglycemia during labor increases the risk of neonatal hypoglycemia (Schwartz and Teramo 2000). After delivery, maternal insulin doses need to be reduced due to increased insulin sensitivity and hypoglycemia risk (Achong et al. 2014). Breastfeeding reduces insulin requirements even further (de Valk and Visser 2011).

2.3.2.2.2 Blood pressure control

Normal pregnancy is characterized by hemodynamic and metabolic changes that affect BP. In diabetic parturients, these changes are superimposed on a vascular system variably damaged by the long-lasting diabetic metabolism as well as possible disturbances of the autonomic nervous system due to diabetic neuropathy.

Research evidence regarding optimal BP treatment targets in diabetic pregnancies is insufficient. The Finnish Diabetes Association recommends aiming at levels below 140/90 mmHg during pregnancy (Väärasmäki et al. 2012). Because of the well-known benefits of aggressive hypertension treatment in the prevention of vascular complications outside pregnancy (Chobanian et al. 2003), the ADA recommends treatment of BP to levels $\leq 130/80$ mmHg also during pregnancy in women with pre-gestational DM (Kitzmilller et al. 2008). Available evidence supports strict control of BP at least in pregnancies with diabetic vascular complications. Hypertension is associated with progression of diabetic retinopathy during pregnancy (Rosenn et al. 1992) and with preterm delivery in patients with diabetic nephropathy (Carr et al. 2006). Danish observational studies suggest that starting intensive antihypertensive treatment with BP $\geq 135/85$ mmHg in patients with micro- or macroalbuminuria in early pregnancy reduces preterm deliveries and preeclampsia in this group of patients (Damm et al. 2013; Nielsen et al. 2009).

In diabetic parturients, a combination treatment with several antihypertensive drugs may be required to achieve BP targets, due to chronic diabetic hemodynamic changes, such as increased peripheral vasoconstriction (Carr et al. 2006; Nielsen et al. 2009; Van Buren and Toto 2011). Safe antihypertensive medications during pregnancy include labetalol, long-acting calcium antagonists and methyldopa (Kitzmilller et al. 2008).

2.3.2.2.3 Monitoring of maternal diabetic complications

Retinopathy. Both the British NICE guidelines and the ADA recommend that diabetic parturients without retinopathy have a retinal examination in the first and the third trimesters of pregnancy (National Collaborating Centre for Women's and Children's Health 2015). The NICE guidelines suggest an additional retinal examination at 16-20 weeks to those with retinopathy and the ADA specifies that mild background retinopathy or laser-treated proliferative retinopathy should be controlled in every trimester but severe background or untreated proliferative retinopathy monthly (Kitzmilller et al. 2008; National Collaborating Centre for Women's and Children's Health 2015)

Nephropathy. A careful baseline screening for albuminuria and assessment of kidney function before and/or in early pregnancy is important in type 1 DM in order to identify women needing stricter BP control and to better distinguish the possible development of preeclampsia from worsening nephropathy in late pregnancy. Urine albumin-creatinine ratio and dipstick methods can be used to screen for albuminuria before and during pregnancy, but a 24-hour urine collection to determine total protein excretion in urine as well as tests of renal function should be carried out if screening tests are positive, micro- or macroalbuminuria has been diagnosed before pregnancy, or DM duration exceeds 10 years (Gabbe and Graves 2003; Kitzmilller et al. 2008).

Physiological changes related to pregnancy, such as hemodilution and renal hyperfiltration, may complicate the interpretation of markers of renal function. Estimated GFR tends to yield an underestimate during pregnancy (Smith et al. 2008 Ahmed et al. 2008). Cystatin C levels increase in late pregnancy, due to unknown etiology, and the currently available evidence does not support its use as a marker of GFR during pregnancy (Akbari et al. 2005; Saxena et al. 2012). Although pregnancy causes a decrease in serum and plasma creatinine levels, in lack of better indicators, serum or plasma creatinine concentrations and the 24-hour creatinine clearance are currently recommended for monitoring of kidney function during pregnancy (Kitzmilller et al. 2008; Koetje et al. 2011).

Neuropathy. Screening for symmetric distal polyneuropathy and autonomic neuropathy is not a part of routine follow up during pregnancy. Because autonomic nervous system function is modified by pregnancy, possible screening tests for autonomic neuropathy may be unreliable and should be repeated postpartum (Hagay and Weissman 1996).

Macrovascular complications. Obtaining a careful patient history is central in determining the risk of macrovascular disease in pregnant women with type 1 DM. Symptoms of cardiovascular disease may be atypical in DM, particularly in women (Stephen et al. 2008). Screening for macrovascular complications is not routinely

performed during pregnancy. However, the ADA recommends investigations like electro- and/or echocardiography and stress tests in high-risk cases, e.g. in parturients with age ≥ 35 years, DM duration ≥ 15 years, symptoms of coronary heart disease, cardiac autonomic neuropathy or peripheral arterial disease (Kitzmilller et al. 2008).

2.3.2.2.3 Obstetric monitoring

Strong research evidence showing the superiority of any specific obstetric monitoring or antenatal testing protocol in type 1 diabetic pregnancies does not currently exist (Mathiesen 2011; McCance 2011). Early pregnancy ultrasonography should be performed to date the pregnancy accurately, since assessment of fetal size with respect to gestational weeks later in pregnancy is particularly important in diabetic pregnancies (McCance 2011). Trisomy screening is offered as in non-diabetic pregnancies. Due to the increased risk of fetal malformations, a comprehensive ultrasound examination of fetal morphology is important at 18-20 weeks of gestation, with particular focus on possible cardiovascular abnormalities (Albert et al. 1996).

In the second half of pregnancy, close attention should be paid to monitoring BP, proteinuria, fetal growth and signs of fetal distress, due to the increased risks of hypertensive disorders as well as fetal macrosomia, growth restriction and chronic hypoxia. Possible methods of fetal surveillance include cardiotocography, biophysical profiling with assessment of amniotic fluid volume by ultrasonography and umbilical artery Doppler velocimetry in cases of intra-uterine growth restriction (IUGR) or maternal vasculopathy (ACOG 2000; Maulik et al. 2002; Reece et al. 1994). Many experts consider the initiation of fetal surveillance at 32-34 weeks of gestation appropriate for most type 1 DM patients (Gabbe and Graves 2003; Ringholm et al. 2012a), but in high-risk pregnancies it may be started at 26-28 weeks (ACOG 2000). The British NICE guidelines do not recommend routine surveillance of fetal well-being before 38 weeks of gestation in diabetic pregnancies unless there is a risk of fetal growth restriction, e.g. in maternal micro- or macrovascular complications (National Collaborating Centre for Women's and Children's Health 2015). Measurement of amniotic fluid erythropoietin (EPO) levels can be used to diagnose chronic fetal hypoxia to facilitate the timing of delivery (Teramo and Widness 2009).

2.3.2.3 Labor and delivery

An individualized approach is required in order to choose the optimal time and route of delivery in a type 1 DM pregnancy. The high frequencies of fetal growth abnormalities and chronic hypoxia, maternal morbidities such as exacerbation of diabetic long-term complications and preeclampsia, as well as the neonatal risks related to premature birth are issues to be weighted (Gabbe and Graves 2003). CS rates among women with type 1 DM commonly exceed 40-50% (Table 2) (CEMACH 2005; Haeri et al. 2008; Howarth et al. 2007).

A challenge in diabetic pregnancies is to identify those fetuses that cannot be safely delivered vaginally because of the risk of shoulder dystocia. The problems related to diagnosing fetal macrosomia and assessing fetal body composition are discussed in section 2.3.6.3.1. Evidence regarding the advantages of elective induction of labor or CS in the prevention of adverse obstetric and perinatal outcomes when fetal macrosomia is suspected is limited and partly conflicting (ACOG 2005; Kjos et al.

1993). The Finnish Diabetes Association and the ACOG recommend an elective CS due to suspected fetal macrosomia if the estimated fetal weight exceeds 4500g in a diabetic pregnancy (ACOG 2005; Vääräsmäki et al. 2012). The most recent British NICE guidelines do not specify a fetal weight estimate cut-off above which delivery by an elective CS is advisable (National Collaborating Centre for Women's and Children's Health 2015). Instrumental vaginal deliveries are not encouraged due to the increased risk of shoulder dystocia (ACOG 2005).

Another challenge is to identify the fetuses that need to be intensively followed and delivered early due to chronic fetal hypoxia. These fetuses at risk of intrauterine death may be macrosomic, growth-restricted or normal weight (Teramo 2010). The British NICE guidelines recommend an elective induction of labor or CS between 37+0 and 38+6 weeks of gestation in a type 1 DM pregnancy, or earlier in case of metabolic or other maternal or fetal complications (National Collaborating Centre for Women's and Children's Health 2015). The ACOG outlines that early delivery may be considered in parturients with vasculopathies, poor glycemic control and previous fetal death, but the pregnancies of women with well-controlled DM and normal findings in antenatal surveillance could be allowed to continue until term but not beyond (ACOG 2005).

2.3.2.4 Post-partum care

Breastfeeding should be encouraged in women with type 1 DM due to its multiple beneficial metabolic and other effects for both the diabetic mother and her child (Feig et al. 2011). Planning of appropriate antihypertensive treatment and other medications suitable for use during lactation is important. Education regarding the importance of pre-pregnancy care should be provided. Intensified retinal monitoring is needed during the first post-partum year because of the transient risk of retinopathy progression due to pregnancy (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee et al. 2013; DCCT Research Group 2000). Due to the high risk of thyroid disorders in type 1 DM, thyroid stimulating hormone levels should be assessed at 6-8 weeks postpartum (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee et al. 2013).

2.3.3 Acute maternal complications in type 1 diabetic pregnancies

2.3.3.1 Hypoglycemia

The risk of iatrogenic hypoglycemia is a major limiting factor in attempts to achieve near euglycemia during pregnancy (DCCT Research Group 1997; Nielsen et al. 2008; Ringholm et al. 2012b). Severe hypoglycemia is defined as a hypoglycemic event during which an individual requires the assistance of another person (ADA 2005). Approximately 17-45% of type 1 DM women experience an episode of severe hypoglycemia during pregnancy (DCCT Research Group 1997; Evers et al. 2002a; Nielsen et al. 2008, Ringholm et al. 2012b).

As a result of the changes in maternal glucose metabolism in the first trimester, severe hypoglycemia occurs three to five times more often in early pregnancy than immediately before pregnancy (Ringholm et al. 2012b). In the third trimester, the risk of hypoglycemia is lower than before pregnancy (Ringholm et al. 2012b). Asymptomatic hypoglycemia, which may be life threatening particularly during night, is common in parturients with type 1 DM (Hellmuth et al. 2000; Leinonen et al.

2001). Risk factors of severe hypoglycemia include history of severe hypoglycemic events, low HbA_{1c} level, impaired ability to recognize symptoms of hypoglycemia and long duration of DM (Evers et al. 2002a; Nielsen et al. 2008). Late evening blood glucose level <6.0 mmol/l predicts nocturnal hypoglycemia (Hellmuth et al. 2000). Research evidence regarding fetal effects of maternal severe hypoglycemia is insufficient, but available reports suggest that recurrent or severe hypoglycemia is not associated with fetal malformations or perinatal complications (Braak et al. 2002).

2.3.3.2 Ketoacidosis

Increasing insulin resistance, lipolysis and ketone bodies increase the risk of diabetic ketoacidosis (DKA) in particular in the second half of pregnancy (Carroll and Yeomans 2005; Kitzmiller et al. 2008). DKA in pregnancy is a life-threatening acute complication for both the mother and the fetus. Approximately 2-9% of women with type 1 DM experience DKA during pregnancy (Guo et al. 2008). Risk factors of DKA include acute infections, vomiting, dehydration, diabetic gastroparesis, poor compliance to insulin treatment and the use of sympathicomimetics and glucocorticoid medications for obstetric indications. Due to the above-mentioned metabolic changes that occur in pregnancy, DKA may develop during pregnancy at lower glucose levels than in non-pregnant individuals and even during normoglycemia (Guo et al. 2008; Hawthorne 2011; Kitzmiller et al. 2008). Hence, the possibility of DKA should thus be always borne in mind when examining pregnant women with type 1 DM suffering from nausea, vomiting and dehydration.

2.3.4. Progression of diabetic long-term complications during pregnancy

The physiological changes associated with pregnancy, such as hypervolemia, insulin resistance, hypercoagulopathy and inflammation could be expected to contribute to the development and progression of diabetic micro- and macrovascular complications (Kaaja 2011). However, it seems that experiencing one or more pregnancies is not an independent risk factor for the accelerated development of microalbuminuria, retinopathy or neuropathy (DCCT Research Group 2000; Verier-Mine et al. 2005)

Retinopathy. A temporary progression of diabetic retinopathy may occur during pregnancy, but the lesions usually regress to the level preceding pregnancy (DCCT Research Group 2000; Verier-Mine et al. 2005). Pregnancy does not seem to enhance the progression of retinopathy (Arun and Taylor 2008). Risk factors for long-term progression of retinopathy during pregnancy include long DM duration, poor glycemic control, rapid improvement of glycemic control, hypertension, moderate or severe retinopathy in early pregnancy, nephropathy and preeclampsia (Kaaja 2011; Laatikainen et al. 1987; Loukovaara et al. 2003; Rosenn et al. 1992; Temple et al. 2001). Proliferative retinopathy should be treated with laser photocoagulation before pregnancy to reduce the risks of progression (Gabbe and Graves 2003).

Nephropathy. Pregnancy does not seem to accelerate long-term decline of kidney function in women with diabetic nephropathy who enter pregnancy with normal serum creatinine levels (Rossing et al. 2002a). However, in women with micro- or macroalbuminuria before pregnancy, considerable (3-20g) transient increase in proteinuria may develop by late pregnancy (Kitzmiller et al. 2008). The appearance of mild macroalbuminuria below 500mg/24h during pregnancy may reflect pregnancy-associated changes in nephrons rather than actual development of overt nephropathy.

It should be kept in mind that in women with moderate-to-severe diabetic renal insufficiency, pregnancy has been associated with accelerated deterioration of kidney function in as many as 40% (Purdy et al. 1996).

Neuropathy. Prospective studies examining the effect of pregnancy on the progression of diabetic nephropathy are not available. A small nested case-control study suggested that pregnancy may accelerate the development of diabetic polyneuropathy in the short-term but does not result in excess prevalence among parous women in the long-term (Hemachandra et al. 1995). A Finnish cross-sectional study showed that a previous pregnancy does not seem to be a risk factor for the decline in autonomic nervous function and the development of autonomic neuropathy in type 1 diabetic women (Airaksinen and Salmela 1993).

Macrovascular diseases. The impact of pregnancy on the long-term progression of macrovascular diseases is not clear. Future research should investigate the roles of glycemic, BP and lipid control, albuminuria, oxidative stress and sub-clinical inflammation during pregnancy on the development of macrovascular diseases in diabetic women (Kitzmilller et al. 2008).

2.3.5 Hypertensive complications in pregnancy

Preeclampsia-eclampsia, chronic hypertension with superimposed preeclampsia and gestational hypertension complicate almost half of all type 1 DM pregnancies (Colatrella et al. 2010; Cundy et al. 2002). Hypertensive disorders in pregnancy are associated with an increased likelihood of preterm delivery, CS, SGA infant and NICU admission (Buchbinder et al. 2002; Colatrella et al. 2010).

Preeclampsia is a vascular disorder of pregnancy characterized by new-onset hypertension and proteinuria that develop after mid-pregnancy (ACOG Committee on Obstetric Practice 2002). Different subtypes of the preeclampsia syndrome, with possibly differing pathogeneses, are considered to exist (Staff et al. 2013a). It may be associated with complications such as HELLP (i.e. a syndrome of hemolysis, elevated liver enzymes and low platelet count) and eclampsia, which can be life-threatening for both the mother and the fetus. Preeclampsia rates in type 1 diabetic pregnancies in European population-based studies are shown in Table 2. The risk of preeclampsia in type 1 DM is strongly affected by the presence of diabetic vascular complications. Preeclampsia has been reported to affect 6-20% of patients with normoalbuminuria before pregnancy, over 40% of women with microalbuminuria, and over 50-60% of women with diabetic nephropathy (Colatrella et al. 2010; Evers 2004; Hanson and Persson 1998; Hiilesmaa et al. 2000; Holmes et al. 2011; Jensen et al. 2009a; Persson et al. 2009; Sibai et al. 2000a). In diabetic nephropathy, the diagnosis is commonly based on some measure of further increase in chronically hypertensive BP levels and proteinuria (Gordon et al. 1996a; Kimmerle et al. 1995; Nielsen et al. 2009). In addition to the vascular complications of DM, risk factors of preeclampsia in DM pregnancies include nulliparity, long DM duration, obesity, chronic hypertension and poor glycemic control (Hanson and Persson 1998; Hiilesmaa et al. 2000; Holmes et al. 2011; Howarth et al. 2007). Since the only currently available cure is the delivery of the placenta, preeclampsia is a major cause of preterm deliveries and the associated neonatal morbidity and mortality (Jensen et al. 2009a; Sibai et al. 2000b).

Gestational hypertension is defined as new-onset hypertension after mid-pregnancy without the presence of proteinuria (Roberts et al. 2003). It is 2-3 times more frequent in diabetic women compared to non-diabetic women (Evers 2004; Hanson and Persson 1998; Holmes et al. 2011; Persson et al. 2009) and its severe forms are associated with adverse perinatal outcomes such as preterm birth and fetal growth restriction (Buchbinder et al. 2002). Risk factors of gestational hypertension include nulliparity, long duration of DM and diabetic retinopathy (Colatrella et al. 2010; Hiilesmaa et al. 2000). It appears that glycemic control during pregnancy is not a risk factor of gestational hypertension (Hanson and Persson 1998; Hiilesmaa et al. 2000).

Recent studies have revealed interesting linkages between hypertensive pregnancy complications in type 1 diabetic pregnancies and the progression and development of diabetic vascular complications. During pregnancy, preeclampsia and hypertension are risk factors of retinopathy progression (Lövestam-Adrian et al. 1997; Rahman et al. 2007). Concerning the postpartum incidence of microvascular complications, Gordin et al. showed recently in Finnish women with type 1 DM that prior gestational hypertension is associated with later development of proliferative retinopathy (Gordin et al. 2012) and prior preeclampsia with later development of diabetic nephropathy (Gordin et al. 2007). Insulin resistance, endothelial dysfunction, inflammation, oxidative stress, which are typical features of diabetic metabolism, may contribute to these associations, since they are thought to be involved in the pathogenesis of both hypertensive pregnancy disorders and long-term complications of DM (Agatista et al. 2004; Colatrella et al. 2010; Gordin et al. 2014; Kaaja et al. 1999; Kaaja et al. 1995).

2.3.6 Perinatal complications in type 1 diabetic pregnancies

2.3.6.1 Fetal malformations and spontaneous abortions

Maternal hyperglycemia in early pregnancy during fetal organogenesis increases the risk of fetal malformations (Bell et al. 2012; Hanson et al. 1990; Jensen et al. 2009b; Suhonen et al. 2000), which are 2-6 times more frequent in pre-gestational diabetic pregnancies than in background populations (Bell et al. 2012; Eidem et al. 2010; Feig et al. 2014; Murphy et al. 2011; Suhonen et al. 2000). Rates of congenital malformations reported in European population-based studies are given in Table 2. The rate of spontaneous abortions is similarly affected by maternal glycemic control (Hanson et al. 1990). Maternal early pregnancy HbA_{1c} levels show a continuous positive correlation with the frequency of fetal malformations, without a specific threshold and with even slightly increased levels associating with increased risk (Nielsen et al. 2006; Suhonen et al. 2000). An HbA_{1c} level exceeding 10% during fetal organogenesis is associated with a significantly increased risk of both fetal anomalies and spontaneous abortions (Hanson et al. 1990). Lack of pre-pregnancy care is a risk factor for congenital malformations in type 1 diabetic pregnancies as it is linked to poor glycemic control in early pregnancy (Murphy et al. 2011). In a recent population-based study, the risk of congenital anomalies was particularly high in type 1 DM patients with diabetic nephropathy (Bell et al. 2012).

The pathogenesis of diabetes-associated fetal malformations appears to be multifactorial (Eriksson et al. 2003). Experimental studies in vitro and in vivo suggest that similar pathogenetic mechanisms as implicated in diabetic microvascular complications may contribute to diabetic embryopathy in humans (Eriksson 2009). The teratogenic effects of maternal DM most frequently affect fetal cardiovascular,

musculo-skeletal and central nervous systems (Garne et al. 2012; Macintosh et al. 2006).

2.3.6.2 Preterm delivery

Prematurity is among the most important causes of neonatal morbidity and mortality in the offspring of type 1 diabetic women. Preterm delivery rates of 19-41% before 37 weeks of gestation have been reported in European population-based studies on parturients with type 1 DM (Table 2). Risk factors of preterm delivery in pregestational diabetic pregnancies include poor glycemic control, retinopathy, nephropathy, gestational hypertension and preeclampsia (Boulot et al. 2003; Lepercq et al. 2004). Most of the preterm births are indicated due to maternal or fetal complications, but also spontaneous preterm deliveries are more common in diabetic compared to non-diabetic pregnancies (Lepercq et al. 2004; Sibai et al. 2000b). The exact mechanism by which maternal DM predisposes to spontaneous preterm birth is not known. Poor glycemic control, polyhydramnios and urogenital infections may play a role, and hyperglycemia-induced oxidative stress leading to impaired nitric-oxide dependent relaxation of the uterus has been speculated to be a possible etiological factor (Kovilam et al. 2002; Lepercq et al. 2004).

2.3.6.3 Abnormal fetal growth

2.3.6.3.1 Fetal macrosomia

Fetal macrosomia, i.e. fetal overgrowth, is the hallmark complication of a diabetic pregnancy. The definitions of macrosomia and large-for-gestational age (LGA) vary between countries, the most common being relative birth weight >2 SD units above the mean of a reference population, relative birth weight $>90^{\text{th}}$ (>1.28 SD units) percentile of a reference population and absolute birth weights $>4000\text{g}$ or $>4500\text{g}$ (Sacks 2007). In European population-based studies, frequencies of relative birth weight >2 SD units range from 20 to 36%, and those for relative birth weight $>90^{\text{th}}$ percentile from 55% to 63%, in the offspring of type 1 DM women (Table 2).

The pathogenesis of fetal macrosomia is not fully understood, but it is known that both maternal chronic hyperglycemia and fetal hyperinsulinemia are major causative factors. Glucose crosses the placenta by concentration gradient-dependent carrier-mediated transport (Hay 1991) and high glucose concentrations in the maternal blood lead to high concentrations of glucose in the fetal circulation. Fetal insulin secretion starts in mid-pregnancy, resulting in fetal hyperinsulinemia in response to the excessive glucose loads supplied by the mother (Hay 2006). On the other hand, studies in fetal rhesus monkeys have shown that chronic fetal hyperinsulinemia causes fetal macrosomia also during maternal euglycemia (Susa et al. 1979). Thus, fetal hyperglycemia and hyperinsulinemia independently promote fetal overgrowth and fat accumulation, leading to an abnormal body composition characterized by excess adipose tissue and organomegaly (Hay 2011). Studies in fetal sheep have demonstrated that peaks of high glucose are particularly effective in stimulating fetal insulin production (Hay 2006). This is in agreement with the association of postprandial hyperglycemia with fetal overgrowth in humans (Combs et al. 1992). In diabetic parturients with strict glycemic control, a relatively weak correlation between HbA_{1c} levels and macrosomia, and a strong correlation between fetal hyperinsulinemia and macrosomia, have been demonstrated (Lepercq et al. 2001;

Schwartz et al. 1994). HbA_{1c} values used in the monitoring of glucose control do not reflect glucose variability, which may explain, at least partly, why fetal macrosomia sometimes develops in parturients whose HbA_{1c} values are within the recommended range (Evers et al. 2002b). In addition to glucose, increased fluxes of other substrates, such as lipids and amino acids, to the fetus may contribute to fetal macrosomia (Catalano and Mouzon 2011; Hay 2011).

Fetal macrosomia is associated with many obstetric and perinatal risks, such as shoulder dystocia, birth trauma, chronic fetal hypoxia, birth asphyxia and perinatal death (Jaffe 2002; Teramo 2010, Hay et al. 2012). Despite the development of modern fetal imaging methods, the identification of fetuses at risk for shoulder dystocia remains a challenge. An ultrasound estimate of fetal weight is associated with a possibility of 10-15% error (Schwartz and Teramo 1999). Measurement of relative abdominal circumference by ultrasonography at 36 weeks may provide some assistance in the prediction of shoulder dystocia (Secher et al. 2015), but, all in all, fetal biometry by ultrasound gives inadequate information on fetal body composition. In the future, fetal magnetic resonance imaging techniques may bring advancements in this field (Spörri et al. 2002; Tukeyva et al. 2001). Suspected macrosomia is a common indication for CS in type 1 DM since it practically eliminates the risk of shoulder dystocia (Lepercq et al. 2010). Considering the many short- and long-term adverse effects of CS deliveries (Pallasmaa et al. 2010; Pallasmaa et al. 2015), better methods for diagnosing fetal macrosomia and abnormal body composition are greatly needed.

2.3.6.3.2 *Intrauterine growth restriction*

Small-for-gestational age (SGA) is commonly defined as relative birth weight <2.0 SD units or <10th percentile, or absolute birth weight below 2500g. However, it should be noted that birth weights in type 1 DM pregnancies are normally distributed and some fetuses with normal birth weights might have been SGA without the growth-promoting effects of DM (Bradley et al. 1989; Haeri et al. 2008). Teramo et al. showed increased amniotic fluid EPO concentrations not only in macrosomic fetuses, but also in those with relative birth weight under -0.6 SD units, suggesting that birth weights falling below this limit could be considered “growth-restricted” (Teramo et al. 2004a). This underlines the need to consider the whole picture of risk factors, not only the fetal weight estimate, when making clinical decisions about the timing and mode of delivery.

Maternal systemic vasculature and its function are profoundly affected by long-standing DM. Possible diabetic autonomic neuropathy may further hinder the hemodynamic adaptations to pregnancy. It is logical that also placental circulation is often affected in these cases leading to substrate deprivation in the fetus (Jaffe 2002). Maternal diabetic vascular complications, which strongly associate with hypertensive pregnancy disorders, significantly increase the risk of IUGR in diabetic pregnancies (Haeri et al. 2008; Howarth et al. 2007; Sibai et al. 2000a). Haeri et al. (2008) reported frequencies of relative birth weight <10th percentile of 12% in parturients with diabetic proliferative retinopathy, 32% in those with diabetic nephropathy, and 50% in those with both diabetic nephropathy and retinopathy.

2.3.6.4 Fetal hypoxia

Several pieces of research evidence support the hypothesis that maternal DM contributes to chronic fetal hypoxia (Madsen 1986; Teramo 2010). At worst, a fetal death occurs, typically in late pregnancy as observed already by Hagbard (1956). Animal studies in fetal sheep have revealed that fetal hyperglycemia as well as fetal hyperinsulinemia during constant glucose levels result in fetal oxidative hypermetabolism, with increased rates of glucose utilization, oxidation and oxygen consumption, leading to arterial hypoxemia (Hay and Mezmarich 1986; Milley and Papacostas 1989; Philipps et al. 1984). Findings in stillborn fetuses and newborn infants of diabetic mothers demonstrate abnormal iron distribution, depleted iron stores in the liver, heart and brain, as well as cardiac hypertrophy (Georgieff et al. 1990; Georgieff et al. 1992; Petry et al. 1992; Russell et al. 2008b). In clinical studies, pathological cardiotocography before and during delivery, low umbilical blood pH values at birth, polycythemia and hyperbilirubinemia are more common in diabetic than in non-diabetic pregnancies, particularly in those with poor glycemic control (Kariniemi et al. 1983; Salvesen et al. 1992; Teramo et al. 1983).

Studies examining amniotic fluid and cord blood EPO levels in the offspring of diabetic mothers also suggest chronic hypoxia (Teramo and Widness 2009). Tissue hypoxia stimulates the production of EPO in the fetus. Both fetal plasma and amniotic fluid EPO levels correlate negatively with umbilical artery pH and pO₂ levels at birth (Buescher et al. 1998; Rollins et al. 1993; Teramo et al. 1987). In diabetic pregnancies, amniotic fluid EPO levels correlate positively with the levels of oxidative and nitrosative stress biomarkers in the amniotic fluid (Escobar et al. 2013). Maternal HbA_{1c} levels measured in late pregnancy correlate positively with amniotic fluid EPO concentrations measured before birth and umbilical blood plasma EPO levels at birth (Teramo et al. 2004a; Widness et al. 1990). This suggests that maternal hyperglycemia is associated with fetal hypoxia. Amniotic fluid and fetal plasma insulin levels also correlate with fetal plasma EPO levels independently of maternal glucose levels (Widness et al. 1990). Thus, both fetal hyperglycemia and hyperinsulinemia seem to contribute to chronic fetal hypoxia in diabetic pregnancies. Moreover, Doppler velocimetry studies in pregnancies complicated by diabetic nephropathy have suggested that fetal hypoxia in these pregnancies is not due to decreased placental perfusion (Salvesen et al. 1993) Thus, it seems that fetal hypoxia in most DM pregnancies does not result from placental insufficiency (Teramo 2010).

High fetal EPO levels are associated with perinatal complications such as fetal macrosomia, obstructive cardiomyopathy, neonatal hypoglycemia and NICU admission in DM pregnancies, and with fetal growth restriction in hypertensive pregnancies (Teramo et al. 2004a; Teramo et al. 2004b). Thus, although fetal macrosomia is a risk factor of chronic fetal hypoxia, it occurs also in low and normal birth weight fetuses of diabetic mothers (Teramo 2010). Hypertensive disorders, which are frequent in diabetic pregnancies and may affect placental circulation, can further elevate the risk of fetal hypoxia (Teramo et al. 2004b). A u-shaped relationship has been demonstrated between relative birth weight and amniotic fluid EPO levels (Teramo et al. 2004a).

2.3.6.5 Perinatal mortality

Perinatal deaths include stillbirths and early neonatal deaths. Stillbirth is commonly defined as the death of a fetus after 22 completed weeks of gestation or with a birth weight of $\geq 500\text{g}$ (Eidem et al. 2011; Mathiesen 2011), but in some studies only fetal deaths after 24 completed weeks of gestation have been classified as stillbirths and earlier fetal losses as late miscarriages (Evers et al. 2004; Lauenborg et al. 2003; Macintosh et al. 2006; Tennant et al. 2014). Early neonatal death (postnatal death) is defined as the death of a newborn infant during the first week of life (Evers et al. 2004; Tennant et al. 2014). The risk of perinatal death is 3-6 times higher in pregnancies complicated by pre-gestational DM compared with background populations (Boulot et al. 2003; CEMACH 2005; Evers et al. 2004; Hanson and Persson 1993; Jensen et al. 2004; Macintosh et al. 2006; Persson et al. 2009). Perinatal mortality rates in type 1 DM pregnancies reported in European population-based studies during 1993-2011 are shown in Table 2. Fetal malformations contribute to approximately 30-40% of perinatal deaths in type 1 DM pregnancies (Schwartz and Teramo 2000). Other important causes include chronic intrauterine hypoxia as well as neonatal complications related to prematurity (CEMACH 2005; Mathiesen et al. 2011). Tennant et al. (2014) showed recently that the relative risks of stillbirth and early neonatal death related to maternal DM in normally formed offspring have not decreased when the time periods 1996-1999 and 2006-2008 were compared.

Stillbirths account for the majority of perinatal deaths in type 1 DM (Mathiesen et al. 2011). In a study by Lauenborg et al. (2003), type 1 DM patients with a stillbirth were characterized by poorer glycemic control in early and, in particular, in late pregnancy, as compared to those with a live birth. The same observation has been made by others (Hanson and Persson 1993; Tennant et al. 2014; Teramo 2010), consistent with the association of poor glycemic control with chronic fetal hypoxia (Teramo et al. 2004a). Other risk factors of stillbirths in type 1 DM pregnancies include diabetic nephropathy, smoking and low social status (Lauenborg et al. 2003). Hypertrophic cardiomyopathy, associated with maternal poor glycemic control, may compound susceptibility to chronic hypoxia (Russell et al. 2008b; Sardesai et al. 2001).

Active fetal surveillance with ultrasonography, Doppler velocimetry or cardiotocography in late gestation is common practice in attempts to prevent stillbirths in diabetic pregnancies (Mathiesen et al. 2011). However, it does not guarantee a live birth, even if the testing is repeated several times a week, since the condition of a fetus suffering from chronic hypoxia may deteriorate rapidly in a few days (Teramo et al. 2004a, Teramo et al. 2004b). Hence, the development of new methods to diagnose fetal hypoxia before delivery is necessary. Repeated measurements of the amniotic fluid EPO level by amniocentesis, combined with the assessment of fetal lung maturation, may be useful in determining the appropriate time for delivery (Teramo and Widness 2009).

2.3.6.6 Neonatal complications

Hypoglycemia, often defined as blood glucose $< 2.6\text{ mmol/l}$ during the first days of life (Maayan-Metzger et al. 2009), is among the most common neonatal complications in type 1 diabetic pregnancies. The fetus of a diabetic mother develops pancreatic beta-cell hyperplasia and hyperinsulinemia in response to maternal

hyperglycemia. At birth, the maternal glucose supply abruptly stops. However, high insulin concentration in the infant's blood continues to promote increased glucose utilization, decreased glycogenolysis and decreased availability of alternate substrates, such as free fatty acids or ketone bodies (Hay 2011). Maternal poor glycemic control immediately before delivery and especially hyperglycemia during delivery increase the risk of neonatal hypoglycemia (DCCT Research Group 1996). Fetal macrosomia is a risk factor of neonatal hypoglycemia, but also growth-restricted infants are at an increased risk due to depleted hepatic glycogen stores (Nold and Georgieff 2004).

Respiratory problems, such as transient tachypnea, respiratory distress syndrome (RDS) and pulmonary hypertension, are common in the neonates of diabetic mothers, particularly in case of poor maternal glycemic control. The high frequency of preterm births in diabetic pregnancies contributes to the high frequency of RDS, but maternal DM is also an independent risk factor of RDS (Robert et al. 1976), as hyperglycemia inhibits surfactant production by pneumocytes (Gewolb and O'Brien 1997). Hyperviscosity due to polycythemia and chronic fetal hypoxia may lead to pulmonary hypertension and a CS without labor to neonatal transient tachypnea (Hay 2011).

Hypertrophic cardiomyopathy of various degrees of severity is found in as many as 40% of infants born to type 1 DM mothers and may occur also in cases where maternal glycemic control has been good (Gandhi et al. 1995; Russell et al. 2008a). It results in symptoms in 5% of these infants and may feature septal hypertrophy, thickened myocardium, outflow tract obstruction and congestive heart failure (Russell et al. 2008b). Usually the symptoms disappear in the first weeks of life and ultrasound findings in the first six months of life, but whether it has any long-term effects on the hearts of infants of diabetic mothers is poorly known (Hay 2011).

Polycythemia, i.e. hematocrit exceeding 65%, affects 20-40% of newborn infants of diabetic mothers (Schwartz and Teramo 2000). It results from chronic fetal hypoxia, which leads to increased EPO-induced production of red blood cells (Hay 2011; Schwartz and Teramo 2000). Polycythemia may lead to hyperbilirubinemia and predispose to thrombotic complications (Hay 2011).

Hypocalcemia and/or hypomagnesemia affect up to 50% of infants of diabetic mothers (Nold and Georgieff 2004; Schwartz and Teramo 2000), and may be associated with agitation, irritability and decreased myocardial contractility (Hay 2011). Hypocalcemia is thought to result from magnesium deficiency of the diabetic mother due to glycosuria, leading to fetal hypomagnesemia and transient hypoparathyroidism (Hay 2011; Mimouni et al. 1990b). Risk factors of neonatal hypocalcemia include preterm birth and birth asphyxia (Mimouni et al. 1990a). Maternal good glycemic control is associated with a lower frequency of neonatal hypocalcemia (Demarini et al. 1994).

Table 2. Obstetric and perinatal outcomes (%) of women with type 1 diabetes in European population-based studies published 1993-2011.

	Hansson and Persson 1993	Vääräsmäki et al. 2000	Penney et al. 2003a	Evers et al. 2004	Jensen et al. 2004	Persson et al. 2009	Murphy et al. 2011
Pregnancies, <i>n</i>	491	296	273	323	1215	5089	323
Preeclampsia	20.6 ^a	NA	NA	12.7	18.1	14.0	NA
Cesarean section	45.2	51.7	NA	44.3	55.9	46.0	63.5
Preterm delivery <37 weeks	24.6	18.9	NA	32.2	41.7	21.0	37.1
Large-for-gestational age	20.0 ^b	20.0 ^b	55 ^c	28.4 ^b	62.5 ^c	31.0 ^c	35.7 ^b
Congenital malformations	NA	5.4	6.0	8.8	5.0	4.7	4.2
Perinatal mortality	3.1 ^d	3.0	2.8	2.8 ^e	3.1 ^e	2.0 ^d	2.5

^aGestational hypertension or preeclampsia

^bRelative birth weight >2 SD units (>97.7th percentile)

^cRelative birth weight >90th percentile

^dBirths before 28 gestational weeks were excluded

^eBirths before 24 weeks were excluded

3 AIMS OF THE STUDY

I To analyze temporal trends in pre-pregnancy BMI, glycemic control during pregnancy, delivery mode and perinatal outcome among type 1 DM patients with a singleton childbirth at HUH during 1989-2008.

II To analyze temporal trends in BP levels during pregnancy as well as frequencies of hypertensive pregnancy complications in type 1 DM patients with a singleton childbirth at HUH during 1989-2010.

III To analyze temporal changes in glycemic control, BP levels, markers of renal function as well as obstetric and perinatal outcomes of women with type 1 DM and diabetic nephropathy (White's class F) during 1988-2011.

IV To analyze the association of White's class with obstetric and perinatal risk factors and outcomes in type 1 DM patients with a singleton childbirth at HUH during 1988-2011. To evaluate whether White's classification provides predictive information in addition to measurement of first trimester HbA_{1c} and BP.

4 SUBJECTS AND STUDY DESIGN

4.1 Ethical aspects

A research permit of the HUH Department of Obstetrics and Gynecology was obtained for the study protocol. The study was carried out in accordance with the Declaration of Helsinki.

4.2 Study design and setting

This study is a retrospective analysis of the obstetric records of a population-based cohort of type 1 DM patients who delivered at HUH during 1988-2011. This hospital is the only centre treating pregnant type 1 diabetic patients in the greater Helsinki area and serves a population of about 1.6 million.

4.3 Study population

The obstetric records of a total of 1094 consecutive type 1 DM patients with a singleton childbirth during 1988-2011 at HUH were analyzed. Only the most recent childbirth of each woman during the study period was included in the analyses. Multiple pregnancies (29 sets of twins and one set of triplets) as well as patients with maturity onset diabetes of the young were excluded. However, when calculating the perinatal mortality rates, the total number of singleton infants (n=1697) was used. The type 1 DM patients were categorized based on White's classification outlined in Table 3 (Hare and White 1977; White 1965; White 1949). Only four patients had coronary heart disease (White's class H); two of these patients were categorized as White's class D and two patients as White's class F. One patient had undergone renal transplantation prior to pregnancy (White's class T), but was excluded from the study due to a twin pregnancy.

Diabetic proliferative retinopathy was defined as laser photocoagulation treatment of diabetic retinopathy before, during or immediately after pregnancy.

Diabetic nephropathy was defined as total protein excretion in urine ≥ 0.3 g/24h or dipstick-positive proteinuria in each trimester of pregnancy, in the absence of non-diabetic kidney diseases based on clinical appraisal and/or kidney biopsy

Table 3. A modified version of the 1949 White's classification. Class E (calcified pelvic vessels on x ray) omitted and class R (diabetic retinopathy) included (White 1949, White 1965, Hare and White 1977).

White's class	Definition
B	Age at onset ≥ 20 years and DM duration < 10 years
C	Age at onset 10-19 years, or DM duration 10-19 years
D	Age at onset < 10 years, or DM duration ≥ 20 years, or background retinopathy
R	Diabetic proliferative retinopathy
F	Diabetic nephropathy
T	Renal transplantation prior to pregnancy
H	Atherosclerotic ischemic heart disease

5 METHODS

5.1 Obstetric follow-up

Type 1 DM patients were referred from primary health care centers and local hospitals to the HUH as soon as the pregnancy had been diagnosed, usually at 6 to 10 weeks of gestation. The duration of pregnancy was confirmed by sonography at 11-13 weeks of gestation in the majority of pregnancies. During pregnancy, the patients visited the antenatal clinic every 2-4 weeks and more frequently during the last trimester. Maternal BP was measured and urine dipstick analysis was performed at each visit. Fetal weight was estimated by ultrasound after 24 weeks of gestation at each visit.

5.2 Monitoring of glycemic control

The patients measured their fasting blood glucose and all pre- and postprandial values at least twice per week and took at least 3-5 daily glucose measurements on other days of the week. HbA_{1c} was assessed by the same high-performance liquid chromatography method (Diamat, Bio-Rad Laboratories, Hercules, CA, USA) throughout the study period. Four values were analyzed in this study: the last value measured within 12 months before pregnancy, the first value measured in the first trimester, one value measured in the second trimester between 18+0 to 22+0 weeks of gestation, and the last value recorded before delivery. If two HbA_{1c} values had been measured between 18+0 and 22+0 weeks of gestation, the average was used.

5.3 Collection of maternal, obstetric and perinatal data

Information on smoking, prepregnancy weight and height, DM duration, DM complications, past obstetric history, and the index pregnancy and delivery were collected from the maternity care cards and hospital records. The second highest systolic and diastolic BP values in each trimester were recorded.

Data on gestational age at birth, birth weight, the lowest blood glucose value of the newborn infant, and neonatal intensive care unit admission (NICU) were obtained from hospital records. Umbilical artery samples were analysed at birth for pH using Ciba-Corning, Rapidlab 800 (Bayer Siemens) and ABL (Radiometer) pH/blood gas analysers.

Hypertension during pregnancy according to the ACOG criteria was defined as systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg (ACOG Committee on Obstetric Practice 2002; Roberts et al. 2003), Hypertension during pregnancy according to the ADA criteria was defined as systolic BP > 130 mmHg and/or diastolic BP > 80 mmHg (Kitzmiller et al. 2008). Patients with BP below the criteria of the ACOG were classified as normotensive. For a few patients data on BP was not

available for the time period before 20 weeks of gestation. In these cases, if BP values $\geq 140/90$ mmHg were recorded after 20 weeks of gestation, it was assumed that the patient had been normotensive in the first half of pregnancy.

Gestational hypertension was defined as hypertension meeting the ACOG criteria occurring after 20 weeks of gestation in a previously normotensive woman, without the presence of proteinuria.

Chronic hypertension was defined as systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg detected before 20 weeks of gestation.

Preeclampsia was defined as hypertension meeting the ACOG criteria occurring after 20 weeks of gestation in a previously normotensive woman, combined with new-onset proteinuria of ≥ 0.3 g/24 h. (ACOG Committee on Obstetric Practice 2002; Roberts et al. 2003)

Superimposed preeclampsia was defined as chronic hypertension combined with new-onset proteinuria of ≥ 0.3 g/24 h after 20 weeks of gestation (ACOG Committee on Obstetric Practice 2002; Roberts et al. 2003).

Preeclampsia in patients with diabetic nephropathy was defined as worsening of hypertension (≥ 15 mmHg increase in systolic and/or diastolic BP) with a proteinuria level of ≥ 5 g/24 h after 20 weeks of gestation.

Eclampsia was defined as the presence of new-onset grand mal seizures in a woman with preeclampsia (ACOG Committee on Obstetric Practice 2002; Roberts et al. 2003).

Fetal macrosomia was defined as birth weight >2.0 SD units (>97.7 th percentile) using a Finnish standard population (Pihkala et al. 1989).

Small-for-gestational age (SGA) was defined as birthweight <-2.0 SD units (<2.3 th percentile) using a Finnish standard population (Pihkala et al. 1989).

Mild fetal acidosis at birth was defined as an umbilical artery pH <7.15 (Ruth and Raivio 1988).

Severe fetal acidosis at birth was defined as an umbilical artery pH <7.05 (Knutzen et al. 2015).

Neonatal hypoglycemia was defined as blood glucose <2.6 mmol/l in the early neonatal period.

5.4 Statistical methods

Continuous variables were compared with the Student's *t* test, the Mann-Whitney *U* test, the paired-samples *t* test and the Kruskal-Wallis test. The Chi-square and the Fisher's exact tests were used in the analysis of categorical variables. Trends were

tested with linear regression analysis, the Jonckheere-Terpstra trend test or the Mantel–Haenszel linear-by-linear association Chi-square test. The associations of continuous or categorical variables with categorical outcomes were studied with multiple logistic regression analysis. P-values <0.05 were considered statistically significant. The statistical software used was IBM® SPSS® Statistics 21.0-22.0.

6 RESULTS

6.1 Maternal characteristics

6.1.1 Time-trends (Studies I, II and III)

All parturients with type 1 DM. Maternal characteristics of the whole study population for the period 1988-2011 are presented in Table 4. Maternal age, age at DM diagnosis, DM duration and the proportion of parturients who smoked during pregnancy did not change during the study period, but the frequency of nulliparous parturients increased marginally over time. The trends of pre-gestational BMI, overweight and obesity were increasing. The frequencies of patients in White's classes C and F decreased and those in White's class D increased during 1988-2011.

The mean HbA_{1c} levels in each trimester of pregnancy during 1988-2011 are also shown in Table 4. The trend of the last HbA_{1c} level measured within 12 months before pregnancy was increasing. The first HbA_{1c} measured in the first trimester remained unchanged during 1988-2011, but the mid-trimester HbA_{1c} levels and the last HbA_{1c} values before delivery increased. The first HbA_{1c} value in the first trimester correlated positively with the last HbA_{1c} before delivery ($r=0.54$, $p<0.001$).

Parturients with diabetic nephropathy. When the time periods 1988-1999 ($n=43$) and 2000-2011 ($n=65$) were compared, the median (range) duration of DM increased from 19 years (10-34) to 24 years (12-33) ($p=0.01$). The median age at diagnosis of DM, pregestational BMI or the frequency of nulliparity did not differ between the two study periods. The frequencies of smoking during pregnancy (26% vs. 29%, $p=0.78$) and proliferative retinopathy (51% vs. 65%, $p=0.14$) remained high.

In patients with diabetic nephropathy, the median (range) HbA_{1c} levels remained high in the prepregnancy period, being 8.2% (5.7–12.5) in 1988-1999 and 8.5% (6.1–13.5) in 2000-2011 ($p=0.16$). The median (range) first trimester HbA_{1c} values were 8.3% (5.7–11.8) in 1988-1999 and 8.4% (5.6–13.7) in 2000-2011, $p=0.67$. In both time periods, the median (range) HbA_{1c} decreased by mid-pregnancy, being 6.7% (4.7–9.3) in 1988-1999 and 6.9% (5.1–9.0) in 2000-2011, $p=0.11$. The median (range) last HbA_{1c} levels before delivery were 6.7% (4.6–10.0) in 1988-1999 and 6.8% (5.3–9.3) in 2000-2011 ($p=0.67$).

6.1.2 Trends across White's classes (Study IV)

Table 5 shows the maternal characteristics for the entire study population categorized by White's class. No trends were seen in maternal age across White's classes, age at DM diagnosis or DM duration across White's classes D, R and F. The age at diagnosis of DM did not differ between White's classes D, R and F. The duration of DM was somewhat longer in White's class R than in classes D ($p=0.01$) and F ($p=0.003$). There were more nulliparous women in White's class F compared to classes B to R ($p=0.01$) and in White's class R compared to classes B to D ($p=0.01$). The frequency of smoking during pregnancy was similar in White's classes B to R, but high in class F ($p<0.001$ for F vs. B to R).

Table 4. Time-trends in background characteristics of 1094 women with type 1 diabetes who delivered at Helsinki University Hospital during 1988-2011.

Maternal characteristic	1988-1991	1992-1995	1996-1999	2000-2003	2004-2007	2008-2011	p for trend ^a
<i>n</i>	147	140	146	146	195	320	
Age (years)	30 (5.3)	31 (4.8)	31 (4.6)	31 (5.2)	31 (5.0)	30 (5.1)	0.94
Age at diabetes diagnosis (years)	15 (1-37)	14 (1-41)	14 (1-34)	15 (2-39)	15 (1-37)	14 (1-39)	0.24
Diabetes duration (years)	15 (1-33)	16 (1-32)	17 (1-34)	16 (1-33)	17 (0-36)	16 (0-36)	0.38
White's class B	27 (18.4)	29 (20.7)	31 (21.2)	25 (17.1)	37 (19.0)	59 (18.4)	0.70
White's class C	53 (36.1)	35 (25.0)	31 (21.2)	41 (28.1)	45 (23.1)	77 (24.1)	0.04
White's class D	29 (19.7)	41 (29.3)	54 (37.0)	45 (30.8)	71 (36.4)	135 (42.2)	<0.001
White's class R	15 (10.2)	13 (9.2)	10 (6.8)	22 (15.1)	28 (4.4)	33 (10.3)	0.37
White's class F	23 (15.6)	22 (15.7)	20 (13.7)	13 (8.4)	14 (7.2)	16 (5.0)	<0.001
Smokers	24 (16.4) [146]	22 (15.7) [140]	21 (14.4)	29 (20.1) [144]	25 (13.3) [188]	35 (11.0) [314]	0.08
Nulliparous	56 (38.1)	47 (33.6)	56 (38.4)	61 (41.8)	70 (35.9)	150 (46.9)	0.03
Pre-pregnancy BMI (kg/m ²)	23.2 (2.8) [144]	23.6 (2.9) [133]	24.2 (3.5) [140]	24.3 (3.2) [145]	25.3 (4.0) [193]	24.4 (3.9) [318]	<0.001
Overweight (BMI 25-29.9 kg/m ²)	28 (19.4) [144]	40 (30.1) [133]	47 (33.6) [140]	58 (40.0) [145]	93 (48.2) [193]	116 (36.5) [318]	<0.001
Obesity (BMI ≥30 kg/m ²)	3 (2.1) [144]	6 (4.5) [133]	11 (7.9) [140]	4 (2.8) [145]	24 (12.4) [193]	33 (10.4) [318]	<0.001
Pre-pregnancy HbA _{1c} (%)	7.8 (1.8) [45]	7.6 (1.6) [58]	7.5 (0.9) [62]	7.7 (1.2) [48]	7.9 (1.4) [95]	8.0 (1.4) [201]	0.03
Pre-pregnancy HbA _{1c} (mmol/mol)	61.7 (14.2)	59.6 (12.6)	58.5 (7.0)	60.7 (9.5)	62.8 (11.1)	63.9 (11.1)	
First trimester HbA _{1c} (%)	7.8 (1.6) [114]	7.5 (1.3) [126]	7.4 (1.1) [134]	7.7 (1.1) [132]	7.6 (1.3) [182]	7.6 (1.2) [295]	0.77
First trimester HbA _{1c} (mmol/mol)	61.7 (12.7)	58.5 (10.1)	57.4 (7.2)	60.7 (7.4)	59.6 (7.1)	59.6 (7.8)	
Mid-trimester HbA _{1c} (%)	6.6 (1.0) [101]	6.4 (1.1) [107]	6.4 (0.8) [125]	6.6 (0.8) [121]	6.7 (0.8) [159]	6.9 (0.9) [257]	<0.001
Mid-trimester HbA _{1c} (mmol/mol)	48.6 (7.4)	46.4 (8.0)	46.4 (5.8)	48.6 (5.9)	49.7 (5.9)	51.9 (6.8)	
Last HbA _{1c} before delivery (%)	6.7 (1.2) [146]	6.7 (1.1) [138]	6.7 (0.9) [146]	6.9 (1.0) [146]	6.9 (0.9) [190]	7.0 (1.0) [314]	<0.001
Last HbA _{1c} before delivery (mmol/mol)	49.7 (7.9)	49.7 (7.2)	49.7 (6.7)	51.9 (7.5)	51.9 (6.8)	53.0 (7.6)	

Data are mean (SD), median (range) or *n* (%).

The number of subjects is presented in square brackets if different.

^aLinear regression analysis, Jonckheere-Terpstra trend test or Mantel-Haenszel linear-by-linear association Chi-square test

Table 5. Trends across White's class groups in maternal characteristics of 1094 type 1 diabetes patients with a singleton delivery at Helsinki University Hospital during 1988-2011.

Maternal characteristic	White B	White C	White D	White R	White F	p for trend ^a
<i>n</i> (%)	208 (19)	282 (26)	375 (34)	121 (11)	108 (10)	
Age (years)	31.5 (4.4)	29.7 (5.4)	30.8 (5.2)	31.6 (4.4)	30.0 (4.9)	0.66
Age at diabetes diagnosis (years)	27 (20-41)	16 (10-32)	9 (1-35)	8 (1-23)	8 (1-21)	0.42 ^b
Duration of diabetes (years)	4 (0-9)	13 (2-19)	22 (6-36)	24 (11-36)	20 (10-34)	0.82 ^b
Prepregnancy BMI (kg/m ²)	23.9 (3.8) [207]	23.9 (3.5) [278]	24.6 (3.7) [371]	24.6 (3.3) [116]	24.2 (3.3) [101]	0.05
Smokers	30 (14.6) [206]	38 (13.6) [279]	44 (11.9) [371]	15 (12.5) [120]	29 (27.1) [107]	0.06
Nulliparous	68 (32.7)	109 (38.7)	147 (39.2)	60 (49.6)	56 (51.9)	<0.001

Data are mean (SD), median (range) or *n* (%).

The number of subjects is presented in square brackets if different.

^aLinear regression analysis, Jonckheere-Terpstra trend test or Mantel-Haenszel linear-by-linear association Chi-square test

^bp values from comparisons of White's classes D, R and F

In the total cohort, 73% of patients had been diagnosed with DM before the age of 20 years and 74% had DM duration of over 10 years. Among White's class D patients, 43% (163/375) had background retinopathy. Among White's class F patients, 56% (61/108) had proliferative retinopathy. Of all patients, 26% (284/1094) had either background or proliferative retinopathy without diabetic nephropathy.

The prepregnancy and the first trimester HbA_{1c} levels increased across White's classes from B to F (p for trend <0.001 for both) but the trends of the mid-pregnancy HbA_{1c} and the last HbA_{1c} values before delivery were not significant across classes B to F (Figure 1). The HbA_{1c} values decreased from the prepregnancy to the first trimester level (p=0.02 for class B, p=0.001 for class R and p<0.001 for classes C, D and F) and from the first trimester to the second trimester level (p<0.001 for all White's classes). In White's classes B to R, the last HbA_{1c} values before delivery were slightly higher than those measured in the second trimester (p<0.001 for classes B, C and D, p=0.004 for class R), but in class F no such increase was seen (p=0.07).

6.2 Hypertension during pregnancy and preeclampsia

6.2.1 Time-trends (Studies II and III)

All parturients with type 1 DM. The mean systolic BP in the first trimester and the mean diastolic BP in all trimesters of pregnancy increased over the study period in normotensive women with type 1 DM (Table 6). The proportion of type 1 DM parturients who fulfilled the ADA hypertension criteria (BP >130/80 mmHg) increased, but no change was observed in the proportion of those who fulfilled the ACOG hypertension criteria (\geq 140/90 mmHg) (Table 7). The frequency of preeclampsia (19-34%) did not change during 1988-2011 (Table 7).

Parturients with diabetic nephropathy. In White's class F parturients, BP exceeded 130/80 mmHg in 62% and 61% (p=0.87) of patients in the first trimester, and in 95% and 93% (p=0.69) of patients in the third trimester, during 1988-1999 and 2000-2011, respectively. In the same group of patients, BP \geq 140/90 mmHg was recorded in 38% and 47% in the first trimester (p=0.39) and in 87% and 81% in the third trimester (p=0.40), during 1988-1999 and 2000-2011, respectively. The use of antihypertensive medication use increased in this group of parturients before pregnancy (34% vs. 65%, p=0.002) and in the second trimester (25% vs. 47%, p=0.02) and in the third trimester of pregnancy (36% vs. 61%, p=0.01) when the two time periods were compared.

Also in type 1 DM patients with diabetic nephropathy, preeclampsia frequencies remained high when the time periods 1988-1999 and 2000-2011 were compared (52% vs. 42%, respectively, p=0.29). One case of eclampsia occurred in 1993.

6.2.2 Trends across White's classes (Study IV)

Table 8 shows the trends across White's classes in the frequencies of hypertension during pregnancy during 1988-2011. The frequency of women with BP fulfilling the ACOG criteria of hypertension during pregnancy (systolic BP \geq 140 mmHg and/or diastolic BP \geq 90 mmHg) and the proportion of women exceeding the ADA criteria of hypertension during pregnancy (systolic BP >130 mmHg and/or diastolic BP >80

Figure 1. Mean HbA_{1c} levels by White's class in the prepregnancy period (red bars), first trimester (blue bars), midtrimester (yellow bars) and before delivery (green bars) in 1094 type 1 diabetes patients with a singleton childbirth at Helsinki University Hospital during 1988-2011. Error bars represent ± 1 SD.

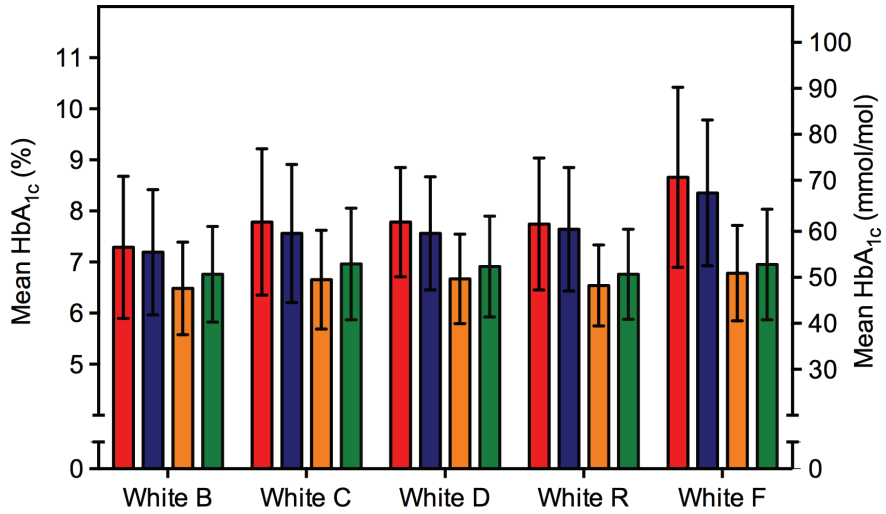


Table 6. Time-trends in the mean (SD) systolic (SBP) and diastolic (DBP) blood pressure levels during pregnancy in 591 normotensive (blood pressure <140/90 mmHg throughout pregnancy) type 1 diabetes patients with a singleton childbirth at Helsinki University Hospital during 1988-2011.

	1988-1991	1992-1995	1996-1999	2000-2003	2004-2007	2008-2011	p for trend^a
SBP (mmHg)							
1 st trimester	540 114.1 (9.1)	540 112.6 (8.6)	540 113.7 (9.7)	540 113.8 (9.9)	540 116.7 (9.5)	540 116.8 (10.4)	0.001
2 nd trimester	574 115.8 (8.0)	574 116.6 (8.8)	574 115.2 (7.9)	574 118.2 (10.3)	574 118.7 (8.7)	574 115.7 (9.9)	0.64
3 rd trimester	579 122.7 (8.6)	579 121.5 (8.7)	579 121.9 (8.3)	579 122.7 (9.8)	579 124.0 (8.3)	579 122.6 (9.5)	0.49
DBP (mmHg)							
1 st trimester	540 69.8 (6.9)	540 68.9 (7.1)	540 67.5 (7.8)	540 70.4 (8.4)	540 70.9 (6.9)	540 72.8 (7.5)	<0.001
2 nd trimester	574 70.2 (6.4)	574 70.7 (7.1)	574 69.0 (6.5)	574 71.5 (7.1)	574 73.0 (5.6)	574 71.3 (6.9)	0.01
3 rd trimester	579 76.9 (6.0)	579 74.4 (6.9)	579 74.8 (7.2)	579 75.5 (6.4)	579 77.2 (5.2)	579 77.2 (6.7)	0.02

^aLinear regression analysis

Table 7. Time-trends in the frequencies of hypertension during pregnancy and preeclampsia among 1094 type 1 diabetes patients with a singleton childbirth at Helsinki University Hospital during 1988-2011.

	1988-1991	1992-1995	1996-1999	2000-2003	2004-2007	2008-2011	p for trend ^c
<i>n</i>	147	140	146	146	195	320	
SBP > 130 mmHg or DBP > 80 mmHg ^a							
1 st trimester	34 (26.0) [131]	27 (21.1) [128]	36 (27.1) [133]	42 (30.0) [140]	64 (35.4) [181]	91 (31.4) [290]	0.019
2 nd trimester	32 (22.1) [145]	38 (27.9) [136]	37 (26.4) [140]	64 (45.4) [141]	78 (40.6) [192]	95 (31.4) [302]	0.006
3 rd trimester	85 (56.1) [146]	77 (57.0) [135]	90 (62.5) [144]	96 (66.7) [144]	132 (68.8) [192]	210 (66.5) [316]	0.005
SBP ≥140 mmHg and/or DBP ≥90 mmHg ^b							
1 st trimester	24 (18.3) [131]	15 (11.7) [128]	21 (15.8) [133]	20 (14.3) [140]	25 (13.8) [181]	31 (10.7) [290]	0.09
2 nd trimester	24 (16.6) [145]	26 (19.1) [136]	24 (17.1) [140]	31 (22.0) [141]	32 (16.7) [192]	34 (11.2) [302]	0.06
3 rd trimester	63 (43.2) [146]	66 (48.9) [135]	74 (51.4) [144]	67 (46.5) [144]	87 (45.3) [192]	123 (38.9) [316]	0.09
Preeclampsia	36 (24.5)	48 (34.3)	36 (24.7)	28 (19.2)	42 (22.1)	69 (21.8) [317]	0.05

Data are mean (SD) or *n* (%). The number of subjects is presented in square brackets if different.

^aAmerican Diabetes Association's criteria

^bAmerican College of Obstetricians and Gynecologists' criteria

^cMantel-Haenszel linear-by-linear association Chi-square test

Table 8. Trends in the frequencies of hypertension during pregnancy and preeclampsia across White's classes among 1094 type 1 diabetes patients with a singleton childbirth at Helsinki University Hospital during 1988-2011.

	White B	White C	White D	White R	White F	p for trend^c
<i>n</i>	208 (19)	282 (26)	375 (34)	121 (11)	108 (10)	
SBP \geq140 mmHg and/or DBP \geq90 mmHg^a						
1 st trimester	11 (5.7) [194]	21 (8.3) [252]	42 (12.2) [343]	20 (17.7) [113]	42 (41.6) [101]	<0.001
2 nd trimester	17 (8.3) [204]	26 (9.7) [269]	49 (13.6) [361]	25 (21.2) [118]	54 (51.4) [105]	<0.001
3 rd trimester	53 (26.2) [202]	97 (35.4) [274]	160 (42.8) [374]	80 (66.1)	90 (84.5) [106]	<0.001
SBP >130 mmHg and/or DBP >80 mmHg^b						
1 st trimester	39 (20.0) [195]	47 (18.7) [252]	100 (29.2) [343]	46 (40.7) [113]	62 (61.4) [101]	<0.001
2 nd trimester	46 (22.5) [204]	69 (25.7) [269]	108 (29.9) [361]	51 (43.2) [118]	70 (66.7) [105]	<0.001
3 rd trimester	95 (47.0) [202]	155 (56.6) [274]	239 (63.9) [374]	98 (81.0)	100 (94.3) [106]	<0.001
Preeclampsia	17 (8.2)	54 (19.3) [280]	93 (24.9) [374]	44 (36.5)	52 (48.1)	<0.001

Data are mean (SD) on or *n* (%). The number of subjects is presented in square brackets if different.

^aAmerican College of Obstetricians and Gynecologists' criteria

^bAmerican Diabetes Association's criteria

^cMantel-Haenszel linear-by-linear association Chi-square test

mmHg) increased in all trimesters of pregnancy from White's class B to F (Table 8). The frequency of preeclampsia increased stepwise from White's class B to F (Table 8). When analyzed separately, the trends of preeclampsia frequencies from White's class B to D ($p < 0.001$) and D to F ($p < 0.001$) were both significant.

6.3 Delivery mode

6.3.1 Time-trends (Studies I and III)

All parturients with type 1 DM. The elective CS rate decreased (p for trend < 0.001) and the emergency CS (p for trend < 0.001) and vaginal delivery (p for trend < 0.001) rates increased during 1988-2011 (Figure 2). The total CS rate decreased from 74% in 1988-1991 to 66% in 2008-2011 (p for trend < 0.001). The rate of assisted vaginal deliveries (vacuum extraction) did not change.

Parturients with diabetic nephropathy. Among parturients with diabetic nephropathy, the elective, emergency and total CS rates were 71% and 45% ($p = 0.01$), 29% and 48% ($p = 0.05$), and 100% and 93% ($p = 0.06$), in 1988-1999 and 2000-2011, respectively.

6.3.2 Trends across White's classes (Study IV)

Delivery mode trends across White's classes are depicted in Figure 3. Vaginal delivery rates decreased from White's class B (50%) to White's class F (3.7%) (p for trend < 0.001). Elective CS rates increased from White's class B (25%) to White's class F (60%) (p for trend < 0.001). Emergency CS rates were high (25%-36%) in all White's classes (p for trend = 0.08).

6.4 Gestational age at delivery

6.4.1 Time-trends (Studies I and III)

All parturients with type 1 DM. Deliveries before 32 weeks of gestation became less frequent during 1988-2011 but births before 37 gestational weeks increased (Table 9). The frequencies of preterm deliveries before 37 gestational weeks were 41%, 50% and 51% in normal weight, overweight and obese parturients, respectively ($p = 0.018$) during 1988-2011.

Parturients with diabetic nephropathy. The median (range) gestational age was 253 days (186-275) among the 108 diabetic nephropathy patients during 1988-2011. The percentages of deliveries before 32 (14% vs. 21%, $p = 0.33$) and 37 gestational weeks (71% vs. 77%, $p = 0.49$) remained high when the periods 1988-1999 and 2000-2011 were compared. Two (3.1%) patients in 1988-1999 and one (2.3%) in 2000-2011 delivered before 28 gestational weeks.

6.4.2 Trends across White's classes (Study IV)

The median gestational age at birth decreased and the frequency of deliveries before

Figure 2. Time-trends in delivery mode frequencies among 1094 type 1 diabetes patients with a singleton childbirth at Helsinki University Hospital during 1988-2011.

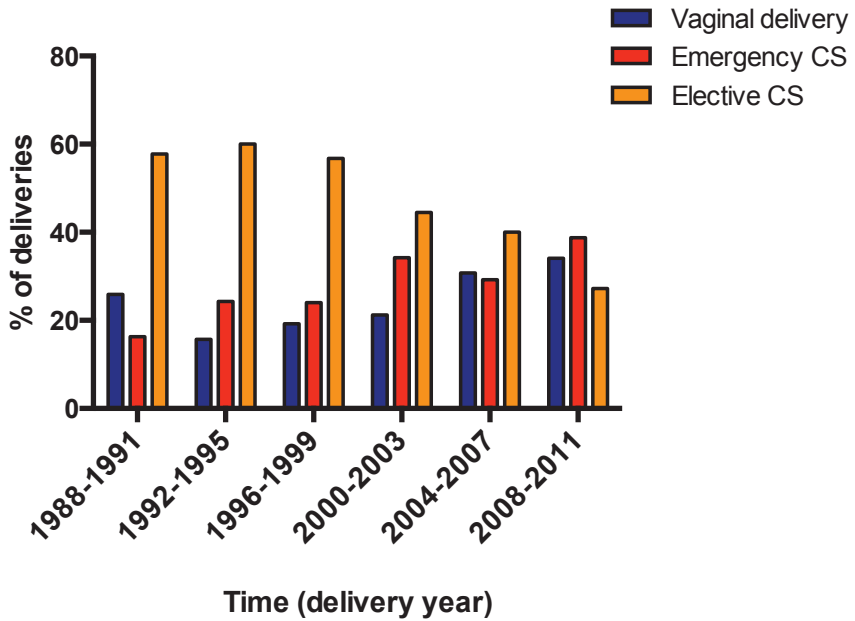


Figure 3. Trends in delivery mode frequencies across White's classes among 1094 type 1 diabetes patients with a singleton childbirth at Helsinki University Hospital during 1988-2011.

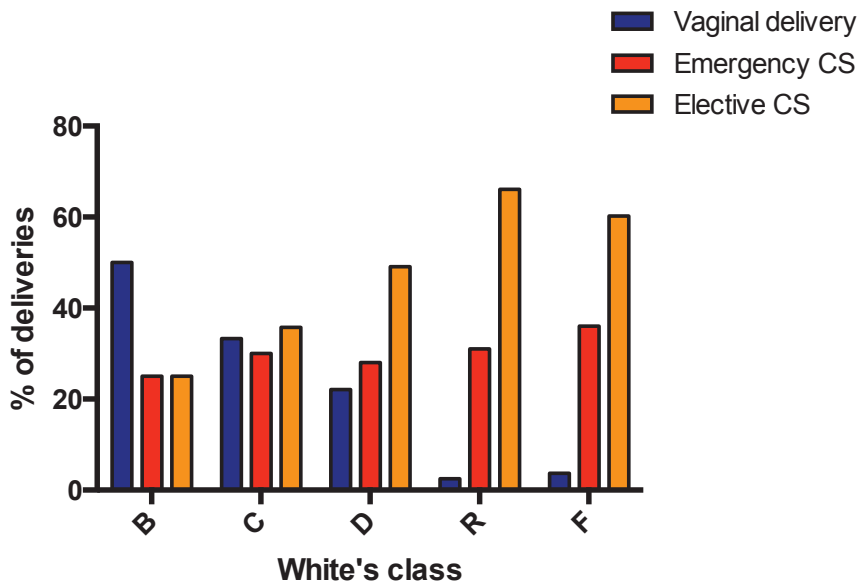


Table 9. Time-trends in the perinatal outcomes of 1094 type 1 diabetes patients with a singleton childbirth at Helsinki University Hospital in 1988-2011.

Perinatal outcome	1988-1991	1992-1995	1996-1999	2000-2003	2004-2007	2008-2011	p for trend ^a
<i>n</i>	147	140	146	146	195	320	
Perinatal mortality rate ^b	7 (2.7) [258]	7 (2.7) [258]	2 (0.8) [243]	2 (0.8) [246]	5 (1.5) [324]	8 (2.2) [368]	0.47
Gestational age (days)	259 (186-284)	255 (166-278)	254 (190-277)	253 (182-277)	259 (169-281)	258 (192-285)	0.30
Delivery <37 weeks of gestation	42 (28.6)	62 (44.3)	72 (49.3)	78 (53.4)	73 (37.4)	156 (48.8)	0.009
Delivery <32 weeks of gestation	6 (4.1)	13 (9.3)	9 (6.2)	11 (7.5)	3 (1.5)	5 (1.6)	0.001
Birth weight (g)	3597 (857)	3619 (1042)	3465 (924)	3473 (876)	3604 (711)	3689 (695)	0.17
Relative birth weight (SD units)	1.1 (1.7)	1.6 (2.1)	1.3 (2.0)	1.4 (1.8)	1.2 (1.6)	1.6 (1.6)	0.06
Birth weight >2.0 SD units	46 (31.3)	54 (38.6)	50 (34.2)	47 (32.2)	52 (26.7)	126 (39.4)	0.50
Birth weight <-2.0 SD units	3 (2.0)	6 (4.3)	5 (3.4)	3 (2.1)	4 (2.1)	3 (0.9)	0.08
Birth weight >90 th percentile	70 (47.6)	75 (53.6)	77 (52.7)	78 (53.4)	94 (48.2)	185 (57.8)	0.14
Birth weight < 10 th percentile	12 (8.2)	9 (6.4)	14 (9.6)	9 (6.2)	11 (5.6)	14 (4.4)	0.06
Umbilical artery pH <7.05	1 (0.8) [124]	1 (0.7) [136]	0 (0) [145]	4 (2.8) [143]	8 (4.2) [191]	12 (3.9) [307]	0.002
Umbilical artery pH <7.15	5 (4.0) [124]	11 (8.1) [136]	7 (4.8) [145]	10 (7.0) [143]	28 (14.7) [191]	55 (17.9) [307]	<0.001
NIICU admission	9 (6.2) [146]	24 (17.4) [138]	26 (17.9) [145]	39 (26.9) [145]	35 (18.0) [194]	51 (16.2) [315]	0.06
Neonatal hyglycemia	96 (66.2) [145]	80 (58.0) [138]	74 (51.0) [145]	86 (59.3) [145]	96 (49.7) [193]	172 (54.6) [315]	0.03

Data are means (SD), medians (range) or frequencies (%). The number of subjects is presented in square brackets if different.

^aLinear regression analysis, Jonckheere-Terpstra trend test or Mantel-Haenszel linear-by-linear association Chi-square test

^bCalculated from the total number of singleton offspring of type 1 diabetes patients during 1988-2011 (*n*=1697)

37 weeks increased from class B to F (Table 10). However, the trend of preterm deliveries from White's class B to D was not significant when analyzed separately. Deliveries before 32 gestational weeks were more frequent in White's class F (16.7%) compared with the other classes (0.8-4.3%) ($p < 0.001$ for F vs. B to R).

6.5 Absolute and relative birth weight and abnormal fetal growth

6.5.1 Time-trends (Studies I and III)

All parturients with type 1 DM. No change in absolute or relative infant birth weight was observed during 1988-2011 (Table 9). Fetal macrosomia rates remained high (27-39%) throughout the study period (Table 9). The frequencies of fetal macrosomia were 32%, 41% and 35% in normal weight, overweight and obese mothers, respectively ($p = 0.03$). No statistically significant trend was observed in the frequency of SGA infants during 1988-2011.

Parturients with diabetic nephropathy. The mean (SD) absolute (g) and relative (SD units) birth weights among the infants of mothers with diabetic nephropathy were 2978 (971) and 2694 (1029) ($p = 0.15$) and 0.5 (1.8) and 0.3 (1.8) ($p = 0.50$) during 1988-1999 and 2000-2011, respectively. The frequencies of fetal macrosomia were 21.5% and 16.3% ($p = 0.50$), and those of SGA infants 7.7% and 4.0% ($p = 1.00$), during 1988-1999 and 2000-2011, respectively.

6.5.2 Trends across White's classes (Study IV)

The overall trends of absolute and relative birth weights and the frequency of fetal macrosomia decreased from White's class B to F and that of SGA infants increased from class B to F (Table 10). However, when analyzed separately, the trends from class B to D for fetal macrosomia or SGA infants were not statistically significant.

6.6 Umbilical artery pH, neonatal hypoglycemia and neonatal intensive care unit admission

6.6.1 Time-trends (Studies I and III)

All parturients with type 1 DM. The time-trends of umbilical artery pH < 7.05 and < 7.15 , neonatal hypoglycemia and NICU admission of the newborn infants of type 1 DM women during 1988-2011 are shown in Table 9. The frequencies of umbilical artery pH < 7.05 or < 7.15 increased during 1988-2011 among the infants of women with type 1 DM. The median (range) umbilical artery pH at birth decreased from 7.25 (7.12-7.37) in 1988-1991 to 7.19 (6.88-7.38) in 2008-2011 in infants born vaginally (p for trend < 0.001). The trend of umbilical artery pH was also decreasing among the parturients with a normal BMI (p for trend < 0.001), but not among overweight or obese parturients. The NICU admission rate remained high during 1988-2011.

Parturients with diabetic nephropathy. In a separate analysis of patients with diabetic nephropathy, no changes in the frequencies of umbilical artery pH < 7.05 (0% vs.

Table 10. Between-group differences and trends across White's class groups in perinatal outcomes of 1094 type 1 diabetes patients with a singleton childbirth at Helsinki University Hospital during 1988-2011.

Perinatal outcome	White B	White C	White D	White R	White F	p for trend ^a
<i>n</i> (%)	208 (19)	282 (26)	375 (34)	121 (11)	108 (10)	
Perinatal mortality rate ^b	6 (1.8) [333]	12 (2.6) [468]	7 (1.2) [587]	1 (0.6) [166]	5 (3.5) [143]	0.94
Gestational age (days)	262 (166-284)	260 (169-282)	260 (196-285)	258 (222-278)	253 (186-275)	<0.001
Delivery <37 weeks of gestation	75 (36.1)	112 (39.7)	155 (41.3)	62 (51.2)	79 (73.1)	<0.001
Delivery <32 weeks of gestation	9 (4.3)	10 (3.5)	9 (2.4)	1 (0.8)	18 (16.7)	0.002
Birth weight (g)	3875 (440-5440)	3735 (400-6140)	3740 (860-5335)	3580 (1600-4925)	2975 (740-4810)	<0.001
Relative birth weight (SD units)	1.5 (1.8)	1.6 (1.8)	1.5 (1.7)	1.3 (1.6)	0.4 (1.8)	<0.001
Birth weight >2.0 SD units	76 (36.5)	107 (37.9)	133 (35.5)	38 (31.4)	21 (19.4)	0.003
Birth weight <-2.0 SD units	4 (1.9)	3 (1.1)	5 (1.3)	3 (2.5)	9 (8.3)	0.002
Birth weight >90 th percentile	118 (56.7)	160 (56.7)	204 (54.4)	62 (51.2)	35 (32.4)	<0.001
Birth weight <10 th percentile	11 (5.3)	12 (4.3)	20 (5.3)	6 (5.0)	20 (18.5)	<0.001
Umbilical artery pH <7.05	4 (2.0) [201]	8 (3.0) [271]	9 (2.5) [358]	4 (3.5) [114]	1 (1.0) [102]	0.87
Umbilical artery pH <7.15	21 (10.4) [201]	33 (12.2) [271]	46 (12.8) [358]	9 (7.9) [114]	7 (6.9) [102]	0.30
NICU admission	32 (15.7) [204]	42 (15.1) [279]	53 (14.2) [373]	20 (16.5)	37 (34.9) [106]	0.001
Neonatal hypoglycemia	113 (55.4) [204]	155 (56.0) [277]	208 (55.8) [373]	67 (55.4)	61 (57.5) [106]	0.81

Data are means (SD), medians (range) or frequencies (%). The number of subjects is presented in square brackets if different.

^aLinear regression analysis, Jonckheere-Terpstra trend test or Mantel-Haenszel linear-by-linear association Chi-square test

^bCalculated from the total number of singleton offspring of type 1 diabetes patients during 1988-2011 (*n*=1697)

2.6%, $p=0.37$) or umbilical artery $pH < 7.15$ (4.7% vs. 10.5%, $p=0.42$), or neonatal hypoglycemia (60.0% vs. 53.7%, $p=0.52$) were observed when the periods 1988-1999 and 2000-2011 were compared. However, NICU admissions increased from 26% in 1988-1999 to 49% in 2000-2011 ($p=0.02$).

6.6.2 Trends across White's classes (Study IV)

There were no significant trends across White's classes regarding frequencies of umbilical artery $pH < 7.05$ or < 7.15 , neonatal hypoglycemia and NICU admissions (Table 10).

6.7 Perinatal deaths (Studies III and IV)

Time-trends (Table 9) and trends across White's classes (Table 10) were not statistically significant concerning perinatal mortality. Perinatal mortality in the total cohort during 1988–2011 was 1.8% (31/1697) in singleton pregnancies. In the offspring diabetic nephropathy patients, perinatal mortality was 3.4% (5/147).

6.8 Risk factors of adverse obstetric and perinatal outcomes (Studies I-IV)

All parturients with type 1 DM. Risk factors of common adverse obstetric and perinatal outcomes in type 1 diabetic pregnancies are shown in Table 11. In multiple logistic regression analysis, the last HbA_{1c} value before delivery $> 7\%$ was associated with preterm delivery, umbilical artery $pH < 7.15$ at birth, fetal macrosomia, neonatal hypoglycemia and NICU admission. First trimester BP $> 130/80$ mmHg was associated with preterm delivery before 37 weeks, SGA infant and NICU admission, and reduced risk of fetal macrosomia. Maternal pre-pregnancy BMI ≥ 25 kg/m² was associated with fetal macrosomia, delivery before 37 weeks and NICU admission, but the associations with preterm delivery and NICU admission disappeared after adjustments. Smoking was associated with SGA infant and decreased likelihood of fetal macrosomia. Nulliparity was associated with pre-term delivery before 37 weeks, SGA infant, and reduced risk of fetal macrosomia, but the association with SGA infant disappeared after adjustments. Maternal age was associated with decreased likelihood of NICU admission in univariate analysis but not after adjustments.

Parturients with diabetic nephropathy. Risk factors of adverse perinatal outcomes in parturients with diabetic nephropathy were studied separately with multiple logistic regression analysis, including maternal age (years), prepregnancy BMI (kg/m²), first trimester BP $> 130/80$ mmHg, second trimester proteinuria ≥ 3 g/24 h, and last HbA_{1c} before delivery (%) as independent variables. Only variables with $p < 0.2$ in the univariate analyses were entered into the multiple models. First trimester BP $> 130/80$ mmHg was associated with delivery before 37 weeks (adjusted OR [95% CI] 3.62 [1.24, 10.56]) and NICU admission (adjusted OR 3.18 [1.19, 8.53]). The last HbA_{1c} value before delivery was associated with delivery before 37 weeks (adjusted OR 2.26 [1.28, 3.98] per increment) and umbilical artery $pH < 7.15$ (adjusted OR 2.39 [1.05, 5.42] per increment). Second trimester proteinuria ≥ 3 g/24h was associated with SGA

infant (adjusted OR 19.52 [1.91, 199.65]) and NICU admission (adjusted OR 6.10 [2.07, 17.96]). Maternal BMI was associated with fetal macrosomia (adjusted OR 1.24 [1.05, 1.45] per increment) and maternal age with decreased likelihood of delivering an SGA infant (adjusted OR 0.76 [0.60, 0.96] per increment).

Association of White's class with adverse pregnancy outcomes. When the associations of White's class, first HbA_{1c} in the first trimester $\geq 7\%$ (≥ 53 mmol/mol) and first trimester hypertension with adverse pregnancy outcomes were studied with multiple logistic regression analysis, White's class predicted preeclampsia, with a stepwise increase in odds ratios (OR) from White's class B to F (Table 12). Also first trimester HbA_{1c} $\geq 7\%$ and BP $\geq 140/90$ mmHg were associated with preeclampsia. White's classes R and F as well as first trimester HbA_{1c} $\geq 7\%$ were associated with delivery before 37 weeks. First trimester BP $\geq 140/90$ mmHg was associated with preterm delivery in univariate analysis, but after adjustments the association disappeared (Table 12). First trimester HbA_{1c} $\geq 7\%$ predicted fetal macrosomia whereas White's class F and first trimester BP $\geq 140/90$ mmHg were associated with reduced likelihood of fetal macrosomia. White's class F and first trimester HbA_{1c} $\geq 7\%$ were associated with NICU admission. First trimester BP $\geq 140/90$ mmHg predicted NICU admission in univariate analysis but not after adjustments (Table 12).

Table 11. Maternal factors predicting adverse perinatal outcomes in 1094 type 1 diabetes patients with a singleton delivery at Helsinki University Hospital during 1988-2011.

Perinatal outcome	Maternal variable	Non-adjusted OR (95% CI)	Adjusted OR (95% CI) ^a
Delivery <37 weeks of gestation	Last HbA _{1c} before delivery >7%	2.81 (2.18-3.62)	2.94 (2.23-3.88)
	First trimester BP >130/80 mmHg	1.92 (1.46-2.53)	1.93 (1.43-2.60)
	Pre-pregnancy BMI ≥25 kg/m ²	1.44 (1.12-1.85)	1.19 (0.90-1.59)
	Nulliparity	1.31 (1.03-1.68)	1.36 (1.04-1.80)
Umbilical artery pH <7.15	Last HbA _{1c} before delivery >7%	1.57 (1.06-2.33)	1.67 (1.10-2.51)
Macrosomia (relative birth weight >2 SD units or >97.7 th percentile)	Last HbA _{1c} before delivery >7%	1.97 (1.53-2.56)	1.93 (1.46-2.57)
	Pre-pregnancy BMI ≥25 kg/m ²	1.38 (1.06-1.78)	1.39 (1.03-1.85)
	First trimester BP >130/80 mmHg	0.67 (0.50-0.90)	0.67 (0.48-0.92)
	Smoking	0.50 (0.34-0.75)	0.40 (0.25-0.62)
	Nulliparity	0.48 (0.37-0.63)	0.52 (0.39-0.69)
Small-for-gestational age (relative birth weight <-2 SD units or <2.3 th percentile)	Nulliparity	3.05 (1.29-7.18)	2.55 (0.99-6.60)
	First trimester BP >130/80 mmHg	3.02 (1.24-7.37)	3.30 (1.31-8.34)
	Smoking	2.68 (1.08-6.61)	2.98 (1.10-8.07)
NICU admission	Last HbA _{1c} before delivery >7%	2.39 (1.72-3.32)	2.06 (1.44-2.95)
	First trimester BP >130/80 mmHg	1.75 (1.24-2.47)	1.78 (1.23-2.57)
	Pre-pregnancy BMI ≥25 kg/m ²	1.74 (1.26-2.41)	1.04 (1.00-1.10)
	Maternal age (years) ^b	0.96 (0.93-0.99)	0.96 (0.93-1.00)
Neonatal hypoglycemia	Last HbA _{1c} before delivery >7%	2.39 (1.72-3.32)	2.30 (1.77-2.97)

^aIndependent variables used in the multiple logistic regression analyses: maternal age, BMI ≥25 kg/m², nulliparity, smoking, last HbA_{1c} before delivery >7% (>53 mmol/mol) and first trimester blood pressure (BP) >130/80 mmHg. All variables with p<0.2 in the univariate analyses were entered into the multiple model.

^bFor maternal age, odds ratios are presented per year.

Table 12. Associations of White's class, first HbA_{1c} in the first trimester $\geq 7\%$ (≥ 53 mmol/mol) and first trimester hypertension with adverse obstetric and perinatal outcomes in 1094 type 1 diabetes patients with a singleton delivery at Helsinki University Hospital during 1988-2011.

Outcome	Maternal variable	Non-adjusted OR (95% CI)	Adjusted OR (95% CI)
Preeclampsia	White C vs. B	2.69 (1.51, 4.79)	3.23 (1.60, 6.52) ^a
	White D vs. B	3.72 (2.15, 6.44)	4.53 (2.32, 8.83) ^a
	White R vs. B	6.42 (3.46, 11.92)	7.36 (3.51, 15.40) ^a
	White F vs. B	10.43 (5.59, 19.46)	8.65 (4.00, 18.70) ^a
	First trimester HbA _{1c} $\geq 7\%$	2.38 (1.66, 3.41)	1.92 (1.29, 2.85) ^b
	First trimester BP $\geq 140/90$ mmHg	3.78 (2.60, 5.51)	2.11 (1.36, 3.26) ^c
Delivery <37 weeks of gestation	White R vs. B	1.86 (1.18, 2.94)	1.79 (1.07, 2.96) ^a
	White F vs. B	4.83 (2.90, 8.05)	3.94 (2.16, 7.18) ^a
	First trimester HbA _{1c} $\geq 7\%$	2.49 (1.87, 3.32)	2.31 (1.69, 3.15) ^b
	First trimester BP $\geq 140/90$ mmHg	1.74 (1.21, 2.50)	1.03 (0.67, 1.59) ^c
Birth weight >2 SD units (>97.7 th percentile)	White F vs. B	0.42 (0.24, 0.73)	0.47 (0.25, 0.89) ^a
	First trimester HbA _{1c} $\geq 7\%$	1.70 (1.27, 2.28)	1.91 (1.39, 2.62) ^b
	First trimester BP $\geq 140/90$ mmHg	0.58 (0.38, 0.87)	0.62 (0.39, 0.98) ^c
NICU admission	White F vs. B	2.88 (1.66, 4.99)	2.54 (1.32, 4.89) ^a
	First trimester HbA _{1c} $\geq 7\%$	2.53 (1.65, 3.88)	2.12 (1.35, 3.34) ^b
	First trimester BP $\geq 140/90$ mmHg	2.11 (1.38, 3.21)	1.29 (0.78, 2.13) ^c

^aAdjusted for first trimester blood pressure (BP) $\geq 140/90$ mmHg, first trimester HbA_{1c} $\geq 7\%$ (≥ 53 mmol/mol), smoking, pre-pregnancy BMI (kg/m²).

^bAdjusted for White's class, first trimester BP $\geq 140/90$ mmHg, smoking and pre-pregnancy BMI (kg/m²).

^cAdjusted for White's class, first trimester HbA_{1c} $\geq 7\%$ (≥ 53 mmol/mol), smoking and pre-pregnancy BMI (kg/m²).

7 DISCUSSION

7.1 Main findings

The present study revealed that the pre-pregnancy weight of Finnish parturients with type 1 DM increased during 1988-2011, with the exception of parturients with diabetic nephropathy. At the same time, glycemic control deteriorated in the pre-pregnancy period and in late pregnancy and remained suboptimal in early pregnancy. The proportion of women fulfilling the ADA criteria for hypertension (>130/80 mmHg) during pregnancy increased. Hypertension frequencies remained particularly high in women with diabetic nephropathy, despite increased use of antihypertensive medications. In the total cohort, the elective CS rate decreased, the emergency CS rate increased, and the total CS rate decreased but remained above 60%.

Among the infants of type 1 DM parturients, fetal macrosomia frequencies persisted at high levels during 1988-2011, fetal acidosis at birth increased and neonatal hypoglycaemia decreased. NICU admission rates were high throughout the study period. The frequencies of preeclampsia and preterm deliveries remained markedly high, especially in pregnancies complicated by diabetic nephropathy.

In the analyses of risk factors of adverse perinatal outcomes, poor glycemic control in early and late pregnancy was associated with delivery before 37 weeks of gestation, fetal macrosomia, and NICU admission. Poor glycemic control in late pregnancy was also associated with fetal acidemia at birth and neonatal hypoglycemia. Early pregnancy BP >130/80 mmHg was associated with delivery before 37 weeks, SGA infant and NICU admission, and reduced risk of fetal macrosomia. Maternal overweight was associated with fetal macrosomia. White's classes B to F predicted preeclampsia independently of suboptimal glycemic control and hypertension, with odds ratios increasing stepwise from class B to F. However, the utility of White's classification in the prediction of perinatal complications was limited.

7.2 Strengths and limitations of the study

The sample size was large and the long study period enabled the analysis of temporal trends. The population-based design improved the generalizability of the results. On the other hand, certain changes in clinical practice may have influenced some results during the long study period. Furthermore, due to the retrospective study design, some data were not available systematically in all patients, e.g. SMBG measurements, insulin doses, or data on different markers of renal function in diabetic nephropathy patients. For the same reason, it was not possible to collect accurate information concerning episodes of maternal severe hypoglycemia or diabetic ketoacidosis, diet and other lifestyle factors, or total weight gain during pregnancy. Some patients may have had their HbA_{1c} levels controlled before pregnancy at private clinics or health care centers and these values could not be included in the data if they were not mentioned in admission notes. Although the sample size was large, the cohort did not include a sufficient number of patients with macrovascular DM complications or

diabetic neuropathy to permit statistical analyses regarding the associations of these complications with obstetric and perinatal outcomes.

7.3 Interpretation of results

7.3.1 Maternal background characteristics

Although the age at DM diagnosis and DM duration did not change during the study period, the frequency of patients belonging to White's class D increased and those in White's class F decreased over the last two decades (Study I). This is in line with the decreasing cumulative incidence of diabetic microangiopathy in type 1 DM patients (Hovind et al. 2003). In the total cohort, the percentages of patients with proliferative or background retinopathy are similar (Bell et al. 2012; Jensen et al. 2004) or somewhat lower (Boulot et al. 2003) than reported by other population-based studies, but variation in the definitions used may also affect the figures. The high proportions of nulliparous patients in White's classes R and F are likely explained by the mother's diabetic microangiopathy, which may influence family planning decisions.

Compared with the 15-17% smoking frequencies recorded in all Finnish pregnant women during 1988-2010 (Varis 2012), smoking in parturients with type 1 DM was slightly less prevalent in the last time period (Study I). In comparison, recent Swedish (Persson et al. 2009) and British (Bell et al. 2012) studies report 18% and 22% smoking prevalences, respectively, among type 1 diabetic parturients. In our cohort, the frequency of smoking among patients with diabetic nephropathy was particularly alarming (Study III), which may have contributed to the development of microvascular complications in some of these patients (Scott et al. 2001). All in all, considering the high risks of pregnancy complications and cardiovascular disease associated with type 1 DM, these results call for intensified antismoking counseling as part of DM care.

7.3.2 Maternal pre-pregnancy BMI

The increasing maternal pre-pregnancy BMI (Study I) parallels the on-going worldwide obesity epidemic, including non-diabetic Finnish women (Vartiainen et al. 2010). Nevertheless, the type 1 diabetic parturients of our cohort are still leaner than Finnish pregnant women on average, of whom every third is overweight and 13% are obese (Vuori and Gissler 2013). The BMI trend in our cohort is in line with the findings of Persson et al. (2009), who reported an increase in obese type 1 diabetic parturients from 13.2% in 1991-1997 to 18.4% in 1998-2003 in Sweden. Similarly, Conway et al. (2010) demonstrated in an 18-year follow-up study increases in the frequencies of overweight and obesity among non-pregnant adult type 1 DM patients from 28.6% and 3.4% in 1986-1988 to 42.0% and 22.7% in 2004-2007, respectively. These trends are a cause for concern, taking into account the association of the metabolic syndrome with progression of microvascular complications, cardiovascular morbidity and diabetes-related mortality in type 1 DM (Chillaron et al. 2014; Thorn et al. 2009).

Avoidance of overweight is also essential in order to minimize obstetric and perinatal complications in diabetic pregnancies. A Swedish population based cohort study

involving 3457 type 1 diabetic parturients and 764 498 non-diabetic parturients demonstrated that obesity is an independent risk factor in type 1 DM pregnancies and when obesity and type 1 DM occur together, the risks exceed those of either condition alone (Persson et al. 2012). The present study is in agreement with the findings of Persson et al. (2012) who showed that overweight and obesity in type 1 diabetic parturients increases the risk of preeclampsia, macrosomia and CS in comparison to normal weight type 1 DM parturients. Overweight or obesity did not predict preterm delivery in the study of Persson et al. (2012), despite their association with preeclampsia.

Overall, the increasing trend of BMI among women with type 1 DM underlines the need to invest in lifestyle counselling, such as medical nutritional therapy and physical activity advice, as part of multidisciplinary DM follow-up and care (Ilanne-Parikka 2015). The multiple daily injections approach using modern insulin analogues allows flexible choice of foods, both healthy and unhealthy, which may increase caloric intake and lead to weight gain if the patient's nutritional awareness is poor (Davison et al. 2014; DCCT Research Group 2001). Intensive insulin treatment, which has become more common in the recent decades, may also predispose to weight gain (Conway et al. 2010). Unfortunately, adequate data on insulin doses was not available to be analysed in the present study.

7.3.3 Glycemic control before and during pregnancy

The present study (Studies I-IV) contributes to the pre-existing large body of evidence on the association of maternal poor glycemic control with adverse pregnancy outcomes (Holmes et al. 2011; Karlsson and Kjellmer 1972; Lepercq et al. 2004; Maresh et al. 2015; Mialhe et al. 2013; Väärasmäki et al. 2000). During 1988-2011, the glycemic target for type 1 DM parturients treated at HUH was HbA_{1c} <7% before and during pregnancy, in line with international and national recommendations (Table 1). However, the observed pre-pregnancy and first trimester HbA_{1c} levels exceeded this target throughout the study period. The results are in agreement with a Finnish report showing no improvement in glycemic control among non-pregnant adults with type 1 DM since 1990's (Valle et al. 2010).

The observation that poor early pregnancy glycemic control correlates with poor late pregnancy glycemic control (Study I) and associates with various obstetric and perinatal complications (Studies II and IV) is consistent with previous studies (Hiilesmaa et al. 2000; Jensen et al. 2009b; Nielsen et al. 2006; Suhonen et al. 2000; Temple 2002). The results suggest that the most intensive therapeutic efforts should be focused on women with poor glycemic control before and in early pregnancy. Type 1 DM women who do not attend pre-pregnancy care are more likely to be socioeconomically disadvantaged and have a low educational status compared to women who plan their pregnancies (Glinianaia et al. 2014a; Holing et al. 1998; Tripathi et al. 2010). The increasing pre-pregnancy HbA_{1c}, the fact that the pre-pregnancy HbA_{1c} value was available for less than 50% of the patients, and the lack of improvement in the first trimester HbA_{1c} levels call for new strategies to promote utilization of pre-pregnancy care. Counselling on the importance of optimizing glycemic control before pregnancy, and ensuring reliable contraception in case pregnancy is not wished, could be incorporated into routine annual check-ups of female type 1 DM patients of reproductive age.

In all White's classes, glycemic control improved markedly by mid-pregnancy and the mean HbA_{1c} levels remained below 7% until the end of pregnancy. This suggests that better glycemic control could most likely be achieved with intensified follow-up and care already before pregnancy, even in women with the most severe DM complications. In late pregnancy, glycemic control deteriorated slightly in all but White's class F women, possibly because of increase in insulin resistance with advancing gestation (Ryan 2003). The lack of deterioration in glycemic control in White F patients could be due to the higher frequency of preterm deliveries in this group or more intensive DM management.

The increasing trend in the last HbA_{1c} levels measured before delivery (Study I) suggests that more attention should be paid to adjusting insulin dosages promptly according to SMBG and HbA_{1c} values. Intensified focus on diet during pregnancy and active referral to medical nutritional therapy, if needed, could also enhance glycemic control. A controlled diet and a structured program of light-to-moderate physical activity have been demonstrated to assist in the achievement of good glycemic control during pregnancy in type 1 DM (Kumareswaran et al. 2013). Maternal overweight and obesity cause further increase in insulin resistance and insulin requirements in type 1 DM women, particularly in the second half of pregnancy (García-Patterson et al. 2009). Thus, the increase in the pre-pregnancy BMI during 1988-2011 has possibly contributed at least somewhat to the observed deterioration of late-pregnancy glycemic control.

Overall, these results call for a more intensive follow-up and therapeutic approach among type 1 DM women of reproductive age, in the pre-pregnancy period and throughout pregnancy. A large population-based study from Northern England reported improvements in glycemic control and pregnancy outcomes among obstetric type 1 DM patients after amendments in the organization of care as well as in region-wide audit and feedback practices (Bell et al. 2008). Provision of sufficient self-management education is nowadays considered a central component of DM care (Funnell et al. 2011; Ilanne-Parikka 2015). Since pregnancy is an exceptional time in a woman's life, and not only metabolically but also in various other aspects, the provision of adequate psychosocial support to keep up patient compliance and motivation is pivotal (Ilanne-Parikka 2015).

7.3.4 Blood pressure and hypertension during pregnancy

In keeping with the results of numerous previous studies (Colatrella et al. 2010), the frequencies of chronic hypertension as well as hypertensive disorders of pregnancy were high in our study population of diabetic women (Studies I-IV). High rates of hypertension have also been reported in Finland among non-pregnant type 1 DM patients with and without albuminuria (Lithovius et al. 2014).

Despite the increasing trends in maternal pre-pregnancy BMI, only the frequencies of borderline hypertension exceeding the ADA definition of >130/80 mmHg increased during the study period (Study II). It is possible that no increasing trend in hypertensive pregnancy disorders was seen because the rates of overweight and obesity are still relatively low. Changes in the use of antihypertensive medications during the study period could also have affected the BP trends, but unfortunately data

on antihypertensive therapies in the patients without diabetic nephropathy have not been collected in the present study.

A lack of physiologic mid-pregnancy nadir in systolic and diastolic BP values in type 1 DM patients was apparent in all White's classes of type 1 DM patients in our cohort. This could reflect inadequate hemodynamic adaptation to pregnancy of the maternal diabetes-affected vasculature (Ayala and Hermida 2013; Foo et al. 2015). Similarly, the stepwise increase in BP levels during pregnancy from White's class B to F (Study IV) may indicate increasing degrees of diabetes-induced vasculopathy, such as endothelial dysfunction, in these patients (Ladeia et al. 2014).

Considering the high frequencies of hypertension, preeclampsia and preterm births in patients with diabetic nephropathy (Study IV), it is possible that intensified control of BP levels starting from early pregnancy could improve outcomes at least in some of these patients (Carr et al. 2006; Kimmmerle et al. 1995; Mathiesen et al. 2012). Antihypertensive therapy may alleviate endothelial dysfunction, impaired vasodilation, over-activation of the renin-angiotensin-aldosterone system and cardiac overload, which characterize preeclampsia in women with type 1 DM (Mathiesen et al. 2012). It has also been speculated that intensive BP control might be beneficial in parturients with diabetic nephropathy to prevent massive loss of protein leading to hypoalbuminemia, decreased intravascular volume and reduced uteroplacental flow (Kimmmerle et al. 1995). In patients with diabetic retinopathy, aiming at normotension is probably also beneficial in order to reduce the risk of retinopathy progression. In our cohort, the BP levels of patients with microvascular complications commonly exceeded 140/90 mmHg, calling for intensification of antihypertensive control.

Whether anti-hypertensive treatment should be intensified also in those pregnant diabetic women without retinopathy or albuminuria, but with BP exceeding the ADA criteria for hypertension during pregnancy, is currently unclear. Due to concerns that low maternal BP might restrict fetal growth (Magee et al. 2009), the ADA recommends that the BP of pregnant women with DM and chronic hypertension should be controlled to 110–130/65–80 mmHg (Kitzmilller et al. 2008). No recommendations have been issued regarding the anti-hypertensive medication of patients with type 1 DM and gestational hypertension <160/100 mmHg (Kitzmilller et al. 2008). However, a recent prospective randomized trial in non-pregnant women with chronic or gestational hypertension showed lower frequencies of severe maternal hypertension and no excess of adverse perinatal outcomes with tight control (target diastolic BP 85 mmHg) of hypertension compared with less tight control (target diastolic BP 100 mmHg) (Magee et al. 2015). In a small Danish prospective study of pregestational diabetic parturients with normal kidney function but with pregnancy-induced hypertension, treating BP to levels <135/85 mmHg did not result in changes in fetal hemodynamics measured by Doppler flow (Pedersen et al. 2015)

7.3.5 Preeclampsia

A common concept used to explain the complex syndrome of preeclampsia is to divide the pathological processes involved into “placental” and “maternal” (Redman 2005). The placental disease refers to impaired remodeling of uteroplacental spiral arteries, inadequate placental perfusion and function due to abnormal placentation, and subsequent placental and systemic oxidative stress and inflammation (Staff et al.

2013b). The maternal disease manifests in women with metabolic, vascular or autoimmune disorders (e.g. DM), predisposing to abnormal reactions to either these pathological placental processes or even those related to a normal pregnancy (Roberts and Bell 2013; Staff et al. 2013b). It has also been suggested that preeclampsia is an “accelerator-brake disorder” in which the impaired function of the body’s protective pathways exposed to the specific metabolic environment of pregnancy play a central role (Ahmed and Ramma 2015).

In agreement with our results (Studies II, III and IV), maternal overweight, poor glycemic control, chronic hypertension and microvascular complications have been previously associated with preeclampsia in patients with type 1 DM (Hiilesmaa et al. 2000; Holmes et al. 2011; Howarth et al. 2007; Persson et al. 2012). Preeclampsia rates have been shown to increase with increasing severity of DM according to White’s classification (Bennett et al. 2015; Hanson and Persson 1998; Hiilesmaa et al. 2000; Sibai et al. 2000a). Our results (Study IV) suggest that the association of White’s class with preeclampsia might be even more pronounced than that of suboptimal glycemic control and chronic hypertension. It is possible that White’s classification reflects a maternal constitution with increasing predisposition to develop preeclampsia (Roberts and Bell 2013), i.e. accumulating maternal diabetes-related vascular and metabolic dysfunction, possibly associated with impaired protective metabolic pathways (Ahmed and Ramma 2015). In classes B and C this vasculopathy and metabolic dysfunction could be related to DM duration. In classes D to F, with similar DM duration, additional genetic, environmental and other factors contributing to specific diabetic vascular complications could be implicated. Poor glycemic control may further influence the maternal metabolic predisposition. Research evidence suggests that glycemic control in the first half of pregnancy, in particular, is significant with respect to development of preeclampsia. Hiilesmaa et al. (2000) demonstrated that improvement in glycemic control before mid-pregnancy was linked to a reduced risk of preeclampsia whereas improvement in glycemic control in late pregnancy did not have this effect (Hiilesmaa et al. 2000).

Already Priscilla White (White 1949) observed the particularly high risk of preeclampsia in patients with diabetic nephropathy. Although it seems apparent that patients with diabetic nephropathy frequently have a severe form of preeclampsia spectrum disorder, the exact diagnosis of preeclampsia in nephropathy patients is challenging. Various preeclampsia criteria have been used previously (Gordon et al. 1996a; Jensen et al. 2009a; Kimmeler et al. 1995; Sibai et al. 2000a). A large proportion of our patients experienced further increase in hypertensive BP levels with concurrent development of massive proteinuria in the second half of pregnancy, commonly leading to preterm delivery. For this reason, a strict proteinuria criterion of ≥ 5 g/24 h was chosen, which has also been used to define severe preeclampsia in patients without nephropathy (ACOG 2002). Regardless of the criteria used, it may be impossible to exactly distinguish preeclampsia from worsening of nephropathy based on BP and proteinuria measurements (Kitzmilller et al. 1981). Even using our strict criteria, the preeclampsia incidence was high in our patients with nephropathy, which is in accordance with previous reports (Biesenbach et al. 2000; Ekblom et al. 2001; Gordon et al. 1996a; Grenfell et al. 1986; Miodovnik et al. 1996; Nielsen et al. 2009).

7.3.6 Delivery mode

Overall, CS rates were high among type 1 DM patients in this study (Studies I, III and IV), in keeping with reports from several other centers (Evers 2004; Haeri et al. 2008; Jensen et al. 2004; Lepercq et al. 2010). However, a Swedish population-based study involving type 1 DM parturients reported a 20 percentage points lower total CS rate compared to the 66% recorded at HUH during 2008-2011 (Persson et al. 2009). The decrease in the elective CS rate during the study period likely reflects changes in clinical policies concerning the obstetric management of type 1 DM parturients. Until the year 2000, the delivery mode of choice was an elective CS in patients belonging to White's classes D, R and F. The increasing frequency of obesity among type 1 DM patients may have influenced these trends by encouraging the avoidance of elective CS in some cases, as obesity is a risk factor for surgical complications. Maternal DM has been shown to further increase the already elevated risk of post-CS infections in obese parturients (Leth et al. 2011). On the other hand, a pre-pregnancy BMI ≥ 25 kg/m² has been associated with increased CS rates in nulliparous type 1 DM women in labor (Lepercq et al. 2010). In the same study, gestational weight gain exceeding 15 kg was associated with CS without labour (Lepercq et al. 2010). Thus, trends in gestational weight gain among type 1 DM patients may also have influenced the trends of delivery modes but unfortunately data on this risk factor was not available in the present study. Mialhe et al. (2013) showed that an HbA_{1c} level $\geq 6.4\%$ before delivery predicted an emergency CS due to an abnormal non-stress test after 32 weeks gestation, emphasizing the importance improving late pregnancy glycemic control in order to reduce high emergency CS rates.

On the whole, the concurrent increase in the emergency CS rate and the decreasing trend of mean umbilical artery pH in vaginal deliveries suggest room for improvement in the identification of those high-risk type 1 DM patients for whom vaginal delivery may not be the optimal choice. Considering the low rates of vaginal deliveries among patients with proliferative retinopathy (White's class R) and diabetic nephropathy (White's class F), and the maternal and fetal risks related to emergency CS deliveries, the present study suggests that elective CS should be preferred for these patients.

7.3.7 Preterm deliveries

The preterm birth rates before 37 weeks of gestation were 29-53% in the time periods studied, in agreement with the 38-42% reported among parturients with pre-gestational DM in other population-based or multicenter studies (Jensen et al. 2004; Lapolla et al. 2008a; Sibai et al. 2000b). In Sweden, somewhat lower rates of deliveries before 37 (21%) and before 32 (2.3%) weeks of gestation have been recorded for the period 1991-2003 (Persson et al. 2009). Also in patients with diabetic nephropathy, the preterm delivery rate was similar in the present study (Kitzmilller et al. 1981) (Biesenbach et al. 2000; Damm et al. 2013; Kimmerle et al. 1995; Nielsen et al. 2009, Piccoli et al. 2013) or somewhat higher (Dunne et al. 1999; Grenfell et al. 1986; Miodovnik et al. 1996; Reece et al. 1988) than in previous studies.

The association between preterm birth and early pregnancy hypertension is probably linked to the higher frequency of preeclampsia in parturients with chronic hypertension (Sibai et al. 2000b). As discussed earlier, a stricter BP control during pregnancy at least in patients with diabetic kidney disease might be beneficial to

reduce the high rates of preeclampsia and preterm deliveries (Mathiesen et al. 2012). Poor glycemic control was associated with preterm delivery in our cohort, as well as in previous studies (Jensen et al. 2009a; Lepercq et al. 2004; Maresh et al. 2015). Poor glycemic control predisposes to preeclampsia, fetal macrosomia and fetal chronic hypoxia, which are common causes of indicated preterm birth in diabetic pregnancies (Hiilesmaa et al. 2000; Jensen et al. 2009a; Teramo et al. 2004a). Measurement of amniotic fluid EPO levels by amniocentesis could assist in optimizing the time of delivery of fetuses at risk of chronic fetal hypoxia (Teramo et al. 2004a).

7.3.8 Fetal growth

The high rates of macrosomia recorded throughout the study period in our cohort are in agreement with previous reports from Finland (Väärasmäki et al. 2000), Sweden (Persson et al. 2009), the Netherlands (Evers et al. 2004) and the Great Britain (Murphy et al. 2011) (Table 2). The mean relative birth weight during the last half of the study period in our cohort (1.2-1.6 SD units) is similar to the 1.5 SD units recorded during 1990-1999 in a Scottish study, in which no decrease was observed in LGA rates during 1960-1999 (Johnstone et al. 2006).

A complex interplay of various maternal, fetal and placental factors determines infant birth weight (Sacks 2007). In accordance with the Pedersen hypothesis, poor glycemic control, in particular in late pregnancy, is a risk factor of fetal macrosomia (Studies I and IV) (Evers et al. 2002b; Glinianaia et al. 2012; Peck et al. 1991). Maresh et al. have recently shown that the risk of LGA infant (relative birth weight >90th percentile) increases significantly with HbA_{1c} ≥6.0 (42 mmol/mol) at 26 and 34 weeks of gestation (Maresh et al. 2015). Thus, the worsening of glycemic control in the second half of pregnancy (Study I), with the mean HbA_{1c} levels exceeding the above-mentioned thresholds in both mid- and late pregnancy, has most likely promoted fetal overgrowth in our cohort. Maresh et al. suggest that values <6.5% (<48 mmol/mol) or even <6.0% (<42 mmol/mol) could be aimed at during pregnancy, if safely achievable (Maresh et al. 2015). Nevertheless, it should be remembered that HbA_{1c} and SMBG levels explain only a fraction of birth weight and fetal overgrowth in diabetic pregnancies (Evers et al. 2002b; Hanson and Persson 1996; Peck et al. 1991; Penney et al. 2003b). High rates of fetal macrosomia have been reported to occur also in type 1 DM pregnancies with apparent good glycemic control (Evers et al. 2002b; Lepercq et al. 2001; Murphy et al. 2008), reflecting the complex etiology as well as the deficiencies of our current methods of monitoring maternal glycemia.

Maternal overweight is another important factor associated with increased risk of fetal macrosomia (Persson et al. 2012), as also shown in the present study (Study I). Persson et al. (2009) reported an increase in the rate of infants with relative birth weight ≥2.0 SD units from 27.6% in 1991-1997 to 35.0% in 1998-2003, in parallel with increasing maternal overweight. In comparison, the rates of fetal macrosomia in our cohort exceeded 30% already in 1988-1991, and were markedly high (39%) in the last time period, even though the average pre-pregnancy BMI of our parturients was lower than in the study by Persson et al. (2009). Differences in glycemic control between Finnish and Swedish parturients might account for these observations, but data on glycemia were not reported by Persson et al., disallowing comparisons.

Diabetic microvascular complications are associated with fetal growth restriction

(Studies III and IV) (Glinianaia et al. 2012; Haeri et al. 2008). In our cohort, despite the increasing pre-pregnancy BMI and late-pregnancy HbA_{1c} levels and the decreasing frequency of diabetic nephropathy, the frequency of fetal macrosomia did not increase and that of SGA infants did not decrease. The observed moderate increases in BP levels during pregnancy (Study II) and the high rates of preeclampsia (Studies II, III and IV) could be speculated to play some role. Furthermore, taking into account the very multifactorial basis of birth size, changes in various other factors, such as maternal gestational weight gain (Evers et al. 2002b; Secher et al. 2014), lipids (Catalano and Haguel-de-Mouzon 2011; Schaefer-Graf et al. 2008), and diet (Walsh and McAuliffe 2015), might also have affected the trends of fetal growth. However, data on these factors was unfortunately not available for analyses.

7.3.9 Fetal acidosis at birth

Maternal hyperglycemia in late pregnancy increases the risk of fetal chronic hypoxia (Teramo 2010). A positive correlation has been demonstrated between HbA_{1c} values before delivery and amniotic fluid or cord blood EPO concentrations as well as negative correlations between amniotic fluid EPO levels and umbilical artery pH and pO₂ levels at birth (Buescher et al. 1998; Rollins et al. 1993; Teramo et al. 2004a; Widness et al. 1990). Thus, it is possible that the observed deterioration in glycemic control in the latter half of pregnancy, although modest, has contributed to the increased frequency of fetal acidosis at birth (Study I).

HbA_{1c} levels reflect the average glucose level over the preceding 6-8 weeks and even small increments this average level may reflect phenomena, such as frequent spikes of high glucose, which may have adverse effects on the fetus. Hay (2006) showed in late-gestation fetal sheep that constant, sustained hyperglycemia combined with pulsatile hyperglycaemic peaks increases fetal insulin secretion, which in turn is associated with fetal macrosomia and chronic hypoxia. Postprandial blood glucose levels have been recognized to have particular importance in the development of macrosomia (Combs et al. 1992). Maresh et al. (2015) demonstrated, on the other hand, that third trimester preprandial glucose values 6.0-6.9 mmol/l are associated with a composite adverse neonatal outcome, suggesting the importance of high fasting and preprandial glucose. Therefore, the daily profile of the SMBG values of each patient should be carefully followed. A study by Kerksen et al. (2006) revealed that a minimum of ten SMBG measurements are needed to acquire sufficient information on daily variations in blood glucose. Thus, the frequency of SMBG measurements recommended to diabetic parturients at HUH might need to be reviewed.

Since the decreasing umbilical artery pH trend was limited to parturients with a vaginal delivery, it is likely that the observed decrease in elective CS deliveries has also influenced the rates of fetal acidosis at birth.

7.3.10 Neonatal hypoglycemia

The frequency of neonatal hypoglycemia was high in all White's classes (Study IV). In comparison, Väärasmäki et al. reported a neonatal hypoglycaemia frequency of only 16% in an older Finnish population-based cohort of type 1 diabetic parturients (Väärasmäki et al. 2000). However, a different definition of hypoglycemia (blood glucose concentration ≤ 1.7 mmol/l more than twice or once during administration of i.v. glucose) probably explains the lower frequency. Evers et al. (2004) reported a

neonatal hypoglycemia (plasma glucose < 2.6 mmol/mol) frequency of 64% among the infants of women with type 1 DM, which is in line with our results. In the present study, the high rates of fetal macrosomia in White's classes B to D, and the high frequencies of preterm and SGA infants in White's classes R and F, have probably contributed to these figures. The incidence of neonatal hypoglycemia decreased during the study period, although the last HbA_{1c} before delivery increased (Study I). This is likely due to advancements in the care of the newborn infants of type 1 DM patients, including active early feeding practices, frequent blood glucose measurements and prompt treatment.

7.3.11 Neonatal intensive care unit admission

Important advancements have been made in the care of newborn infants during 1988-2011. Surfactant treatment was started at HUH in 1991 and glucocorticoid administration to the mother in threatened preterm delivery in 1992. Nasal continuous positive airway pressure treatment became available in the neonatal monitoring unit of the labor ward in 2002. Despite these improvements, the decrease in the frequency of neonatal hypoglycemia and the unchanged rates of fetal macrosomia, SGA infants and preeclampsia, the NICU admission rate was high throughout the study period. Bell et al. reported an opposite trend, a decrease in neonatal admissions to special postnatal care from 69% in 1996-1998 to 35% in 2002-2004 among parturients with pregestational (type 1 or 2) DM (Bell et al. 2008). This trend was observed after region-wide development of audit and feedback practices in DM care and concurrent with improvement in glycemetic control during pregnancy.

In the present study, both the increased frequency of fetal acidosis at birth and the increase in the percentage of infants born before 37 weeks of gestation may have contributed to the high NICU admission rates in the recent years (Study I). The high emergency CS rates, associated with an elevated likelihood of fetal distress, may also have influenced the NICU admission frequencies. The positive association of maternal overweight with NICU admission is likely related to the high rates of fetal macrosomia among the infants of overweight type 1 diabetic women.

7.3.12 Perinatal deaths

In the early 1980's, the perinatal death rate among the offspring of type 1 DM patients was approximately 5% (Madsen 1986). During 1988-2008 at HUH, the perinatal mortality rate was 1.8% in type 1 diabetic pregnancies (Teramo 2010). Thus, the addition of the data for years 2009-2011 in the present study did not change the figure. In comparison, the CEMACH report in the United Kingdom revealed a perinatal mortality rate of 3.2% during 2003-2004 (CEMACH 2005). In a more recent British study, Tennant et al. (2014) reported a fetal mortality rate of 3% and a neonatal mortality rate of 0.7% in a population-based study of parturients with pregestational DM, with no evidence of decrease in either figure during 1996-2008. A perinatal mortality rate of 2% among the offspring of type 1 DM parturiens was reported by a Swedish population based study, but only births after 28 weeks of gestation were included in this figure (Persson et al. 2009).

The prediction of stillbirths is challenging, Teramo (2010) showed that over half of all stillbirths in our cohort during 1988-2008 occurred in fetuses with normal relative birth weight. Hypertensive pregnancy disorders may increase the risk of chronic fetal

hypoxia (Teramo et al. 2004b) and may be accompanied by fetal growth restriction that misleadingly “normalizes” fetal growth (Bradley et al. 1989; Haeri et al. 2008). Poor glycemic control is a strong risk factor of perinatal death (Lauenborg et al. 2003), but the risk seems to be increased even at periconceptional HbA_{1c} levels below 7% (Jensen et al. 2009b; Nielsen et al. 2006; Tennant et al. 2014). As the risk of stillbirth starts to increase as early as at 32 weeks of gestation in type 1 diabetic pregnancies (Hagbard 1956; Holman et al. 2014), the practice of inducing labor or performing a CS at 37-38 weeks of gestation is not sufficient to bring perinatal mortality down to the level of background populations. According to recent estimates, the relative risk of stillbirth in type 1 diabetic pregnancies between 32 and 34 weeks is 4.95 (95% CI 4.24–5.78) (Holman et al. 2014). All of the above supports the monitoring of amniotic fluid EPO concentrations (Teramo et al. 2010), which may be combined with the assessment of lung maturity, latest at 37 weeks, and in some cases as early as 32 weeks of gestation, in all type 1 diabetic pregnancies.

8. CONCLUSIONS

1. During 1988-2011, maternal pre-pregnancy overweight and obesity increased, glycemic control before pregnancy and during the second half of pregnancy deteriorated, and early pregnancy glycemic control remained suboptimal in women with type 1 DM. The frequencies of most adverse perinatal outcomes either persisted at high levels or increased. The results demonstrate that the care of reproductive-age women with type 1 DM should be intensified both before and during pregnancy.
2. Despite the increasing trend of pre-pregnancy BMI and the worsening of late pregnancy glycemic control in women with type 1 DM during 1988-2011, there was no concurrent increase in the frequency of hypertensive pregnancy disorders. However, the BP levels of type 1 DM parturients currently classified as normotensive increased. Furthermore, the proportion of all type 1 DM parturients who exceeded the ADA-recommended BP threshold of 130/80 mmHg during pregnancy increased.
3. Preeclampsia and preterm delivery rates remained high, and BP levels as well as early pregnancy glycemic control suboptimal, in parturients with diabetic nephropathy during 1988-2011. The high frequency of hypertension throughout pregnancy despite the increased use of antihypertensive medications calls for more attention to controlling BP in type 1 DM parturients with diabetic kidney disease.
4. White's classification is useful in estimating the risk of preeclampsia in early pregnancy independently of suboptimal glycemic control and hypertension. However, its contemporary utility in predicting other adverse pregnancy outcomes in women with type 1 DM seems limited when information on first trimester HbA_{1c}, BP and diabetic microvascular complications is available.
5. Future investigations should explore:
 - 1) Factors behind the persisting poor glycemic control among reproductive-age women with type 1 DM before and during pregnancy.
 - 2) Possible areas of improvement concerning the availability, accessibility and quality of care provided to type 1 DM women before and during pregnancy.
 - 3) Time-trends in the indications for CS deliveries in type 1 DM parturients.
 - 4) New methods for antenatal diagnosis of fetal hypoxia, assessment of fetal body composition and diagnosis of feto-pelvic disproportion to optimize the timing and mode of delivery in type 1 DM patients.
 - 5) Possible associations of hypertension of different degrees of severity during pregnancy, different targets of anti-hypertensive treatment, and different hypertensive complications of pregnancy, with short- and long-term outcomes in type 1 DM women and their offspring.
 - 6) Possible shared genetic and other risk factors between specific diabetic vascular complications and adverse pregnancy outcomes in type 1 DM.

6. Suggested actions:

1) Increasing the awareness of diabetic women of reproductive age, and that of health care providers, of the importance of optimizing glycemic control before pregnancy.

2) Ensuring the availability and accessibility of multidisciplinary and individualized DM care before and during pregnancy, including e.g. individually tailored follow-up by DM nurses, internists and obstetricians as well as sufficient self-management education, psychosocial support, physical activity advice and medical nutritional therapy.

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