

**CARE AND OUTCOME OF
FINNISH DIABETIC
PREGNANCY**

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OULU 2001



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DIABETIC PREGNANCY**

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Abstract

The aim of this study was to evaluate the treatment, course and outcome of pregnancy in Finland using two cohorts of diabetic women. The clinical cohort consisted of data from all 210 women with Type 1 diabetes and their 296 pregnancies managed between 1986 and 1995 in the two northernmost provinces of Finland. The register-based study population included all 1442 mothers with a singleton birth who had insulin treatment during pregnancy in 1991-1995 according to the Medical Birth Register. Of these mothers, 954 (66%) had pre-existing diabetes.

Insulin-treated diabetes complicated 4.5/1000 births in Finland in 1991-1995, the prevalence of Type 1 diabetes being 2.9/1000 in the whole country and 3.3/1000 in Northern Finland. In the 1990's the care of these women shifted from tertiary level only to include the secondary level hospitals as well, and was more often carried out on an out-patient basis. This care policy in association with the self-monitoring of blood glucose levels contributed to an obvious improvement in glycaemic control during pregnancy. Despite that, the high proportion (73%) of women entering pregnancy with unsatisfactory glycaemic control did not decrease during the study period.

Retinopathy complicated 134 (45.3%) diabetic pregnancies, while clinical nephropathy was found in 23 (7.8%) cases. Although retinopathy was more often aggravated during the first pregnancy, the occurrence of retinopathy or its severe form was not increased at the beginning of consecutive pregnancies. Of the mothers, 50 (16.9%) had pre-eclampsia during pregnancy, and in 28% of these cases it was classified as superimposed. It was found more often among primiparous than multiparous (25.6% vs. 11.0%, respectively), and its occurrence rose with the severity of diabetes.

In both cohorts, the rates of preterm deliveries, Caesarean sections and large for gestational age (LGA) infants were significantly ($p < 0.001$) higher in Type 1 diabetic pregnancies than in the background population. The rates of congenital anomalies (CA) were 540-629/10000 in two study populations, both being 2-3-fold as compared to the background population. Cardiac malformations were most common, with anomalies in the genitourinary tract and the musculoskeletal organs being next in frequency. Sixty-three percent of malformed infants were boys.

Though pregnancy itself was not found to worsen the prognosis of diabetes, at least in the short term, pregnancy in diabetic women still remains a high risk state with an increased rate of prematurity, operative deliveries, CAs and peri- and neonatal mortality. In order to decrease the mortality rate in diabetic births, attention should be directed at both the prevention of CA and at identifying the fetuses at risk for intrauterine death. The postneonatal mortality rate is also high, reflecting a shift in the deaths from the early neonatal period to a later age. Therefore, a combined mortality, including induced abortions, stillborns and infant deaths, would give a more realistic idea of the outcomes in diabetic pregnancies.

Keywords: congenital abnormalities, glycaemic control, infant mortality, perinatal mortality, pregnancy complications, pregnancy in diabetes

This book is dedicated to Sini and Olli

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Abbreviations

AGA	Appropriate for gestational age
ASD	Atrial septum defect
BMI	Body mass index
BPP	Biophysical profile
CA	Congenital anomaly
CDR	Cause Of Death Register
CI	Confidence interval
CNS	Central nervous system
CoA	Coarctation of aorta
CTG	Cardiotocography
GDM	Gestational diabetes mellitus
GHbA	Glycosylated haemoglobin A
GW	Gestational week
ICD	International Classification of Diagnosis
IDM	Infant of diabetic mother
IUGR	Intrauterine growth retardation
LGA	Large for gestational age
MBR	Medical Birth Register
MWC	Maternity welfare clinic
NST	Non-stress test
OGTT	Oral glucose tolerance test
OR	Odds ratio
PDA	Patent ductus arteriosus
PI	Pulsatility index
PIH	Pregnancy induced hypertension
PNM	Perinatal mortality rate
RCM	Register of Congenital Malformations
RDS	Respiratory distress syndrome
RI	Resistance index
RR	Relative risk

SD	Standard deviation
SGA	Small for gestational age
VSD	Ventricular septum defect
WHO	World Health Organisation

List of original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:

- I Vääräsmäki M, Hartikainen AL, Anttila M, Pirttiaho H (2000) Out-patient management does not impair outcome of pregnancy in women with type 1 diabetes. *Diab Res Clin Res* 47: 111-117.
- II Vääräsmäki MS, Hartikainen AL, Anttila M, Pramila S, Koivisto M (2000) Factors predicting peri- and neonatal outcome in diabetic pregnancy. *Early Hum Devel* 59: 61-70
- III Vääräsmäki M, Anttila M, Pirttiaho H, Hartikainen AL. Are recurrent pregnancies a risk in Type 1 diabetic pregnancy? Submitted.
- IV Vääräsmäki M, Gissler M, Hartikainen AL. A uniform regimen enables decentralized care of diabetic pregnancies. *Diabetic Med*, in press.
- V Vääräsmäki M, Gissler M, Ritvanen A, Hartikainen AL. Congenital anomalies and first life year surveillance in Type 1 diabetic births. Submitted.

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1 Introduction

The first recorded case of diabetic pregnancy was reported in 1823: the mother survived but a 12-lb (5.4 kg) baby died during delivery due to dystocia. The prognosis of diabetic pregnancy remained poor long thereafter, and even in 1913 obstetric textbooks recommended that pregnancy complicated by diabetes be terminated because of significant maternal and foetal risks - the maternal mortality was reported to be 50% and the overall pregnancy loss rate 41%. The discovery of insulin by Frederik Banting and his collaborators in 1921 dramatically changed the outcome of diabetic pregnancy: maternal mortality, mostly based on diabetic ketoacidosis, fell rapidly to 2% shortly thereafter. (Gabbe 1992) Insulin not only made possible successful pregnancy, but also restored regular menses and fertility. The improvement in neonatal outcome followed more slowly, mainly with a better comprehension of the pathophysiology of diabetes and the importance of maternal metabolic control.

With improved glycaemic control, the outcome of diabetic pregnancy has become significantly better during the past decades. Maternal mortality is uncommon, ketoacidosis infrequent, and with modern monitoring and treatment of glycaemic control, pregnancy does not appear to worsen the prognosis of diabetes (Chaturvedi *et al.* 1995, Hemachandra *et al.* 1995, Kaaja *et al.* 1996). Despite a favourable outcome in diabetic pregnancy, congenital anomalies (CA) and perinatal morbidity- and mortality rates are still significantly higher than in the background population. According to different definitions, CAs affect 2 - 10% of diabetic pregnancies, the proportion of major anomalies being especially increased (Cnattingius *et al.* 1994, Casson *et al.* 1997, Hawthorne *et al.* 1997, von Kries *et al.* 1997, Suhonen *et al.* 2000). These have also been reported to cause 30-40% of perinatal deaths in diabetic births (Schwartz & Teramo 2000). Perinatal mortality rates in diabetic pregnancies have recently varied from 2.4 to 4.8% (Hanson & Persson 1993, Nielsen & Nielsen 1994, Casson *et al.* 1997, Hawthorne *et al.* 1997, von Kries *et al.* 1997, Schwartz & Teramo 2000), rates being 3 - 5 times than that in the normal obstetric population. In 1967-1987, the PNM rate among insulin-treated diabetic women was 6.6% in Northern Finland (Anttila 1993). Adverse peri- and

neonatal outcome is mostly associated with maternal hyperglycaemia, especially hyperglycaemia in early pregnancy.

Today, diabetes is one of the most common chronic diseases complicating pregnancy, and its incidence is still rising (Bingley & Gale 1989). Its occurrence is especially high in Finland (Tuomilehto *et al.* 1995, Karvonen *et al.* 2000), and while the onset of diabetes still occurs at a younger age, more pregnant women have had diabetes long enough to develop diabetic vascular complications (Karvonen *et al.* 1999). Therefore, the care of pregnant diabetic women will put more and more of a strain on maternal care services in the future. In this study, we wanted to evaluate trends in the care of pregnant diabetic women in Finland. Apart from the outcome of pregnancy, the risk factors and causes for adverse neonatal events were also analysed.

2 Review of the literature

2.1 Diabetes mellitus

2.1.1 Classification of diabetes mellitus during pregnancy

Diabetes mellitus is defined as a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both (World Health Organisation (WHO) Study group 1998). Impairment of insulin secretion and defects in insulin action, frequently existing together, are the primary causes of hyperglycaemia. According to a recent report of the WHO Study group (1998) diabetes mellitus is divided aetiologically into four categories:

Type 1 including autoimmune and idiopathic form

Type 2 including insulin resistance and insulin secretory defects

Other specific types such as genetic defects of β -cell function or defects in insulin action, and endocrinopathies, diseases of the exocrine pancreas and drug- or chemical-induced diabetes

Gestational diabetes mellitus (GDM)

Priscilla White presented the classification of diabetes during pregnancy (White 1949, White 1978).

- A pregnant women with GDM
- B age over 20 years at onset, or duration of diabetes less than 10 years, no vascular lesions
- C age 10-19 years at onset or duration 10-19 years, no vascular lesions
- D age less than 10 years at onset or duration over 20 years. Hypertension or background retinopathy is found

<i>F</i>	nephropathy
<i>R</i>	proliferative retinopathy

In the original classification, class E included calcification of pelvic arteries but this class was later excluded. Classes A-F are original but class R was added in 1965. In 1977, classes C and D were divided into subgroups and classes G including many failures, H with cardiopathy and T with renal transplant, were added. (White 1978) Class A is often divided into classes A including GDM with only dietary therapy, and AB including insulin-treated GDM (Pedersen 1977).

2.1.2 Type 1 diabetes

Type 1 diabetes results from a destruction of the β -cells of the pancreas, usually leading to absolute insulin deficiency. Most often the reason is autoimmune mediated destruction. These patients require insulin for survival to prevent the development of ketoacidosis and coma (WHO Study group 1998). The rate of β -cell destruction is variable: children mainly present with a rapidly progressing diabetes, while some adults may retain residual β -cell function sufficient to prevent ketoacidosis for many years. There are some patients, mostly non-Europeans, with this form of diabetes with no evidence of autoimmune disorder. They are considered to represent an idiopathic form of Type 1 diabetes. (WHO Study group 1998)

The peak incidence of Type 1 diabetes is in childhood and adolescence. Genetic predisposition to the autoimmune destruction of β -cells has been demonstrated, and it has also been associated with environmental factors which are still poorly defined. Instead of the previously used diagnostic criteria for diabetes including fasting plasma glucose concentration ≥ 7.8 mmol/l, in the new diagnostic criteria the limit has been lowered to 7.0 mmol/l. The corresponding rates for whole blood are 6.7 mmol/l and 6.1 mmol/l, respectively. (WHO Study group 1998)

Type 1 diabetes is one of the most common pre-existing medical disorders during pregnancy, complicating approximately 0.2-0.4% of all pregnancies (Engelgau *et al.* 1995, von Kries *et al.* 1997). The prevalence of diabetes has increased in Finland recently, being 6.8/1000 in females aged 15-44 years in 1997 (National Social Insurance Institute 1997). The incidence of Type 1 diabetes in girls aged 0-14 years in Finland is at present one of the highest in Europe (36.0 per 100 000 per year), leading to the fact that its prevalence during pregnancy will also be higher than in the most other countries (Karvonen *et al.* 2000).

2.1.3 Type 2 diabetes

Type 2 diabetes is characterized by disorders of insulin action and secretion, either of which may be a predominant feature (WHO Study group 1998). Though it is the most common form of diabetes, it is seldom diagnosed in patients less than 40 years, and is therefore rare in women of childbearing age (Hare 1991, WHO Study group 1998). The risk of Type 2 diabetes increases with age, obesity and lack of physical activity, and it occurs more frequently in individuals with hypertension or dyslipidemia, or in women with previous GDM (WHO Study group 1998). Some degree of hyperglycaemia may be present for a long period before the detection of diabetes. While these patients often have an increased risk of developing vascular complications, it may be more important to identify and treat other risk factors such as dyslipidemia and hypertension, instead of mild hyperglycaemia. Although Type 2 diabetes is associated with a strong genetic predisposition, its genetics have not been defined. (WHO Study group 1998)

2.1.4 Gestational diabetes mellitus

In 1952, Jackson reported the reversible state of impaired glucose tolerance related to pregnancy, called the "prediabetic state of pregnancy" (Jackson 1952). Today, gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or initial recognition during pregnancy (Metzger & organizing committee 1998). It complicates 1 - 4% of all pregnancies (Amankwah *et al.* 1977, Stephenson 1993, Engelgau *et al.* 1995, Naylor *et al.* 1997) depending on the population studied. Its incidence in Finland was 1.3% in 1987-88, when diagnosis was set after exceeding two or more threshold values in the oral glucose tolerance test (OGTT) (Hyvönen 1991).

In Finland, the current practice is to screen for GDM pregnant women who have a clinical history or known risk factors for GDM, including a prior infant weighing more than 4500 g at birth, obesity (body mass index (BMI) ≥ 25 kg/m²), age ≥ 40 years, or glucosuria or macrosomic foetus (≥ 2 SD) in current pregnancy. When a BMI exceeding 24 kg/m² and glucosuria were used as indications for screening, 83% of all GDM cases were detected and OGTT should have been performed in 30 % of all pregnant women. (Hyvönen 1991)

According to WHO recommendations, GDM is diagnosed by OGTT using a 75 g oral dose of glucose after over-night fasting for women with anamnestic or clinical risk factors. The recommended cut-off levels in capillar blood and venous plasma in Finland are 4.8 mmol/l for fasting, 10.0 mmol/l at 1 h and 8.7 mmol/l at 2 h (Teramo *et al.* 1993). The present international cut-off levels are 5.3 mmol/l for fasting, 10.0 mmol/l after 1 h and 8.6 mmol/l after 2 h in venous plasma (Metzger & organizing committee 1998).

Glucose regulation will return to normal after delivery in the majority of cases. According to different studies, 40-60 % of women with previous GDM will develop Type 2 diabetes during the next 10-15 years (Teramo *et al.* 1993). Metzger *et al.* (1993) found insulin resistance and impaired β -cell function in GDM women conveying a high

risk (relative risk (RR) 8.0) for later diabetes development. By giving dietary advice, stabilizing weight, exercise and periodic glucose monitoring it is possible to prevent or delay the progression of diabetes and the development of its complications in women with previous GDM (Gregory *et al.* 1993).

2.2 Care of diabetes during pregnancy

2.2.1 Treatment of diabetes during pregnancy

Especially in Scandinavian countries, the findings of Jørgen Pedersen and his collaborators have had a great influence on the care of diabetic women during pregnancy (Pedersen 1967). Through centralised care carried out by a team of obstetricians, internists and paediatricians, they succeeded in realizing a significant decrease in perinatal mortality between 1946 and 1975. Regardless of the type of diabetes, diet is always a cornerstone of the treatment. Human insulin is mostly recommended to be used during pregnancy (Hare 1991, Teramo *et al.* 1993). In addition to previously used short-, intermediate- and long-acting form insulins, also rapid-acting insulin, insulin lispro, has lately been used successfully during pregnancy (Anderson *et al.* 1997, Jovanovic *et al.* 1999, Buchbinder *et al.* 2000).

Although insulin requirements mainly increase during pregnancy, they often decrease during the first weeks of pregnancy and near the estimated delivery time. The fasting hypoglycaemia at the beginning of pregnancy has been found to also occur in non-diabetic women, and may be due to placental hormonal restriction of gluconeogenic substrate availability. In addition, better dietary adherence or a more effective pattern of insulin administration may result in a decrease in insulin doses in diabetic women. (Hare 1991, Steel & Johnstone 1996) During the second trimester, there is nearly always an increase in insulin requirements due to insulin resistance produced by the increased production of pregnancy-related hormones oestrogen, progesterone, placental lactogen and prolactin (Steel & Johnstone 1996). Maternal insulin requirements may be decreased during the last weeks of pregnancy due to a continuous foetal siphoning of maternal fuels, which is more noticeable as foetal size increases. This decrease was previously misinterpreted to be a sign of placental-placental insufficiency, and needless preterm deliveries were induced. (Hare 1991)

During labor, intravenous 10% dextrose is given and insulin is administered subcutaneously according to blood glucose values measured every 2 hours (Teramo *et al.* 1993). Insulin requirements drop dramatically after labor and no insulin may be given in several hours. A state of relative hypopituitarism and blunted growth hormone secretion has been postulated to be the explanation for this (Hare 1991). Women with GDM do not need insulin after delivery.

2.2.1.1 Treatment of Type 1 diabetes

Most diabetic women use multiple daily insulin injections, which has been found to contribute to a more satisfactory glycaemic control than do twice daily injections (Nachum *et al.* 1999). The use of a continuous subcutaneous administration of insulin is recommended by some authors (Hare 1991), but not all, mainly due to the increased risk of ketoacidosis even after a short failure in the insulin pump system (Teramo *et al.* 1993). The current goal is to reach near euglycaemia without a significant risk of hypoglycaemic episodes. Fasting blood glucose values have previously been recommended to be maintained between 3.5 – 5.0 mmol/l and postprandial values 1.5 h after eating less than 7.3 mmol/l (Teramo *et al.* 1993), but today, 5.3 mmol/l for fasting values and 6.7 mmol/l 2 hours after eating in capillary blood are mostly used as cut-off levels (Metzger & organizing committee 1998).

2.2.1.2 Treatment of Type 2 diabetes and GDM

Nutritional counselling is the first line treatment for all women with GDM. Insulin treatment is recommended in cases when fasting glucose concentration is twice measured as over 5.5 mmol/l or once over 5.5 mmol/l combined with a postprandial value higher than 7.8 mmol/l. When these instructions are used, 10% of all GDM patients need insulin treatment in addition to dietary management. (Teramo *et al.* 1993) Because oral hypoglycaemic agents have been proscribed during pregnancy, women with Type 2 diabetes also use only insulin during pregnancy. Glyburide (glibenclamide) has lately been suggested to be an effective alternative to insulin therapy in women with GDM (Langer *et al.* 2000), but especially treatment with metformin during pregnancy is associated with an increased prevalence of pre-eclampsia and a high perinatal morbidity (Hellmuth *et al.* 2000a). At present, however, oral hypoglycaemic agents are not in routine use. The principles of insulin treatment in Type 2 diabetes and in GDM are similar to those in Type 1 diabetes. Insulin lispro might be a suitable option, especially for GDM women in the prevention of postprandial hyperglycaemia, which has been linked to increased rates of macrosomia (Jovanovic *et al.* 1999).

2.2.2 Monitoring of glucose metabolism during pregnancy

Glycaemic control during pregnancy is usually assessed by means of home glucose monitoring. Six or more glucose measurements each day may be required to optimise therapy (Jovanovic 2000). In Finland, 15-20 weekly measurements are recommended, but the need is always individual (Teramo *et al.* 1993). Telephone access to the physician, or in most cases, to a specialist nurse must always be available. Weekly contacts are usually adequate but in cases of illness, for example, extra tests and contacts are required.

Glucose binds irreversibly non-enzymatically to haemoglobin A, and its concentrations have been used to assess diabetic control. The previously used total level of glycosylated haemoglobin A1 (GHbA1) has today been displaced by its more relevant subfraction GHbA1c. Levels correlate with the mean glycaemia for the previous 4-6 weeks, with the best correlation to the more recent weeks (Hare 1991). A clear improvement or worsening in control is evident by GHbA values in 1-2 weeks and a more modest change is detectable within 1 month (Hare 1991). These values are usually checked every 4 to 6 weeks (Steel & Johnstone 1996). The measurement of fructosamine has also been used to determine glycosylated serum proteins (Negoro *et al.* 1988).

2.2.3 Pre-pregnancy care

Fuhrman *et al.* (1983) indicated that reasonable metabolic control started before conception and continued during the first weeks of pregnancy prevents malformations in infants of diabetic mothers. Although the importance of pre-pregnancy care has thereafter been demonstrated in several studies, glycaemic control is often unsatisfactory at the beginning of pregnancy. Jantz *et al.* (1995) reported that only one-third of women with established diabetes receive pre-conceptual care, and 61% of pregestational diabetic women present for prenatal care with suboptimal glycaemic control (Casele & Laifer 1998). A racial disparity in glycaemic control among Type 1 diabetic women entering prenatal care has also been found - according to a recent study, Caucasian women enter pregnancy with significantly more satisfactory GHbA levels than do African-American women (Holcomb *et al.* 2001). The best participation in pre-pregnancy care (75%) has been reported in a specialized centre in Denmark (Damm & Molsted-Pedersen 1989). The high number of un-planned pregnancies is not due to a lack of information: Holing *et al.* (1998) found that 79% of diabetic women who had delivered knew the importance of optimal periconceptual glycaemic control but only 41% of their pregnancies were planned. Attendance has not improved despite an intensive programme of education and information on the importance of good periconceptual metabolic control (Carron Brown *et al.* 1999). An on-going, positive doctor-patient-relationship seems to be most essential to increase the rate of planned pregnancies (Janz *et al.* 1995, Holing *et al.* 1998).

2.2.4 Follow-up protocols for diabetes mellitus during pregnancy

There is no consistent opinion as to whether the care of diabetic pregnancies should be centralized or not. Pedersen (1977) reported a significant decrease in perinatal mortality rate after the centralized care of pregnant diabetic women. Centralization is considered to be essential mostly in order to maintain and improve the clinical experience of diabetic pregnancies (Olofsson *et al.* 1984). The outcome of pregnancy has been found to be better in specialized centres (Traub *et al.* 1987, Hadden 1999), although good results

have also been reported in shared care. In Sweden, nearly 40 clinics are involved in the care of diabetic patients, and despite that the outcome of pregnancy is good. This is probably mainly due to an intensive education of personnel. (Cnattingius *et al.* 1994) Traub *et al.* (1987) compared the outcome of diabetic pregnancies managed in central referral hospital and in peripheral maternity units, and found that combined antenatal/endocrine care with a neonatal intensive care unit is essential when treating diabetic pregnancies. Hadden (1999) reported on the outcomes of over 800 diabetic pregnancies between 1985 - 1995 in Ireland managed in regional and peripheral clinics, and demonstrated that the obstetric risk was highest in those pregnancies referred to a specialized care centre during pregnancy from other clinics - the PNM rate was 2.6% in the special centre, 3.4% in peripheral hospital and 7.5% among referred cases. They postulate that centralization of care should therefore be begun in early pregnancy. Satisfactory glycaemic control in early pregnancy has been suggested to be more essential in the decrease of PNM rate in diabetic pregnancies than improved referral to tertiary centres (Connell *et al.* 1985).

At present, diabetic pregnant women are mainly monitored on an out-patient basis. Hanson *et al.* (1984) found no significant differences between either blood glucose values or in pregnancy complications in women who self-monitored their blood glucose at home or were in hospital care in the 32-36 gestational week (GW). Bourgeois and Duffer (1990) compared the 3-year period experience of an out-patient diabetic obstetric clinic with the results obtained at the same facility during the 5 previous years managed mainly on an in-patient basis. According to their findings, obstetric outpatient management efficiently decreased maternal morbidity without increasing infant mortality and morbidity.

2.3 Maternal diabetic complications and pregnancy

The long-term complications of diabetes can be divided into three categories: microvascular, macrovascular and neuropathic (Hare 1994). The development of these complications is related to not only the control of diabetes but also to its duration. Microvascular complications typically take 10 to 20 years to develop and therefore are quite often present during pregnancy. Macrovascular complications, on the other hand, including coronary artery-, peripheral vascular- and cerebral arterial diseases, seldom occur before middle age and therefore rarely complicate pregnancy (Hare 1994).

2.3.1 Retinopathy

Diabetic retinopathy is a disease of retinal microvasculature, and the structural changes during pregnant and non-pregnant state are identical. Damage to the retinal capillaries is a result of chronic hyperglycaemia (Davidorf & Chambers 1993). Retinopathy commonly

begins to develop after 5-10 years of diabetes and is nearly universal after a duration of 20 years (Hare 1994). Diabetic retinopathy can be divided into the non-proliferative and proliferative form (Davidorf & Chambers 1993), and an intermediate category known as pre-proliferative retinopathy is often also included (Elman *et al.* 1990, Jovanovic-Peterson & Peterson 1991). The first stage, called background retinopathy, consists of microaneurysms or punctate haemorrhages being visible with direct ophthalmoscopy. Hard exudates, lipid deposits in the retina, can also be seen as a consequence of capillary leakage. The second stage, pre-proliferative retinopathy, includes infarcts in the nerve layer called soft exudates. Third stage, vision-threatening proliferative retinopathy, is characterized by the growth of capillaries on the surface of the retina protruding into the vitreous matter. (Hare 1994)

Opinions as to the effect of pregnancy on the progression of retinopathy are controversial. It is difficult to evaluate whether the progression of retinopathy during pregnancy is due to natural course of diabetes, or to factors related to pregnancy. However, women entering pregnancy with minimal or no retinopathy are not considered to be at risk of aggravating retinopathy, the threat being more common in cases of severe retinopathy (Chew *et al.* 1995, Rosenn & Miodovnik 2000). Pregnancy itself has been found to be a major risk factor for the progression of retinopathy in some studies (Klein *et al.* 1990), as has also the duration of diabetes (Moloney & Drury 1982, Axer-Siegel *et al.* 1996), hyperglycaemia (Klein *et al.* 1990, Axer-Siegel *et al.* 1996) and rapid normalization of poor glycaemic control in early pregnancy (Phelps *et al.* 1986, Laatikainen *et al.* 1987, Rosenn *et al.* 1992, Chew *et al.* 1995, Lovestam-Adrian *et al.* 1997). Both pregnancy induced hypertension (PIH) and chronic hypertension (Rosenn *et al.* 1992, Axer-Siegel *et al.* 1996, Lovestam-Adrian *et al.* 1997) have also been found to be associated with progression of retinopathy during pregnancy. Circulating and local factors such as growth hormone, insulin-like growth factor 1 and other angiogenic factors may also contribute to its deterioration (Rosenn & Miodovnik 2000).

The introduction of laser photocoagulation was an essential improvement in the treatment of retinal changes during pregnancy. The early treatment of proliferative disease during pregnancy, or preferably before it, is recommended to prevent high-risk characteristics from developing (Davidorf & Chambers 1993, Best & Chakravarthy 1997).

Short-term observations related to pregnancy may not predict its overall long-term effects on diabetic retinopathy. A regression of retinal changes has been found to occur during the postpartum period (Rosenn *et al.* 1992). In a previous Finnish study, progression of retinopathy was found to occur less often in parous than in nulliparous women (Kaaja *et al.* 1996), being in accordance with Hemachandra *et al.* (1995) who did not find an increased risk of diabetic retinopathy or its progression in parous women. In the Eurodiab study, the prevalence of retinopathy was lower in women who had ≥ 2 pregnancies (34%) compared with women who had only one (45%) or no pregnancies (48%). In the same study, the rate of proliferative retinopathy was 7-8% in parous compared with 16% with nulliparous women. (Chaturvedi *et al.* 1995) These results suggest that pregnancy does not change the long-term prognosis of retinopathy.

2.3.2 Nephropathy

Diabetic nephropathy is a progressive disease of the glomerulus characterized by increased permeability to protein, glomerular scarring and finally, renal failure. It complicates 6-10% of diabetic pregnancies. (Kitzmiller *et al.* 1981, Reece *et al.* 1988) Microalbuminuria, defined as an albumin excretion of 30-300 mg/day, precedes clinical nephropathy (Bloomgarden 1999). Diabetic nephropathy is diagnosed, if in the absence of bacteriuria, persistent dipstick-positive proteinuria, an albumin-excretion rate greater than 300mg/day or a total protein excretion rate greater than 500 mg/day is found. The lifetime risk of developing nephropathy is 30-40% in Type 1 diabetes (Combs & Kitzmiller 1991), the peak incidence being after 15 years of duration (Bloomgarden 1999).

During pregnancy, the factors affecting the development of diabetic nephropathy include increased glomerular filtration rate, hypertension, increased protein intake and excretion, and glycaemic control. During normal pregnancy there is a 40-60% increase in glomerular filtration rate, which may accelerate the progression of nephropathy (Rosenn & Miodovnik 2000). In recent studies, pregnancy has not been associated with an increased risk of subsequent nephropathy nor does it accelerate the progression of a pre-existent nephropathy (Kaaja *et al.* 1996, Miodovnik *et al.* 1996). When nulliparous and parous women have been compared, no significant differences in the prevalence of nephropathy have been detected (Hemachandra *et al.* 1995, Kaaja *et al.* 1996). Chaturvedi *et al.* (1995) found no significant difference between nulliparous and parous women in the presence of microalbuminuria after adjusting for age and duration of diabetes, and the prevalence of macroalbuminuria was even less in parous women compared with nulliparous women (6% vs 10%, respectively), suggesting a protective effect of pregnancy. According to these studies, pregnancy does not appear to worsen the natural progression of nephropathy to end-stage renal disease.

2.3.3 Neuropathy

The peripheral, cranial and autonomic nerves may be affected in diabetes. In spite of the fact that peripheral neuropathy is quite common, it is only seldom met during pregnancy. It presents most often as bilateral distal paresthesias in the feet, but may also be expressed as a truncal neuropathy involving the intercostal nerves and as unilateral and painful, often imitating an intra-abdominal process. Cranial neuropathy usually manifests as a unilateral extraocular or facial nerve palsy in the absence of neurological findings, and is most often painless. (Hare 1994)

Autonomic neuropathy includes dysfunction of the nerves innervating the heart and blood vessels, bladder, bowel, stomach, and sweat glands (Reece & Coustan 1995). With respect to pregnancy, diabetic gastroparesis is the most important of the autonomic neuropathies, which - with the hyperemesis of pregnancy - often results in an exacerbation of nausea and vomiting. If diagnosed before pregnancy, it is considered as a

relative contraindication to pregnancy (Macleod *et al.* 1990). Pregnancy has not been found to be a risk factor for a deterioration of autonomic nervous function or development of autonomic neuropathy (Airaksinen & Salmela 1993). Chaturvendi *et al.* (1995) reported autonomic neuropathy to be less prevalent in parous than in nulliparous women, and Hemachandra *et al.* (1995) suggested that a short-term increase in the incidence of neuropathy may occur during pregnancy, but over the long-term, there is no such an association. Overall, it appears that pregnancy does not alter the natural course of diabetic autonomic neuropathy.

2.3.4 Coronary artery disease

Consistently poor glycaemic control is an independent risk factor for arteriosclerosis, especially in women with diabetes. In patients with Type 1 diabetes, arterial age equals chronologic age plus the number of years of diabetes. (Gordon *et al.* 1996a) The majority of diabetic women with coronary disease do not have the correct diagnosis before pregnancy. Therefore, electrocardiography and possibly an echocardiogram in patients with White class F/R is recommended in the evaluation of possible signs of cardiac ischemia (Gordon *et al.* 1996a). Problems during pregnancy are based on haemodynamic and cardiovascular changes, and on increased oxygen consumption. Hypoglycaemia may also activate a counter-regulatory response causing a release of catecholamines and thus tachycardia, arrhythmia and increased demands on the myocardium (Rosenn & Miodovnik 2000). Delivery and puerperium represent the period of greatest risk; these women are vulnerable to myocardial damage and pulmonary oedema in the immediate postpartum period, and it takes up to 12 weeks for cardiovascular haemodynamics to completely return to the prepregnancy state (Gordon *et al.* 1996a, Rosenn & Miodovnik 2000). Women in White class H are at great risk during gestation, and pregnancy is therefore not recommended.

Rosenn and Miodovnik (2000) reviewed 20 cases of diabetic mothers who suffered a myocardial infarction or ischemic cardiac event before, during or shortly after pregnancy between 1953-1998. Of 13 mothers whose events occurred during pregnancy or in the early puerperium, 7 mothers and 7 infants died. If myocardial infarction occurred before pregnancy, all the mothers and infants survived. All these deaths occurred before 1980, which may reflect an advance in the methods for diagnosis and treatment today.

2.3.5 Maternal mortality

Before the availability of insulin, maternal mortality occurred in 6 - 50% of diabetic mothers. Cousins (1987) reported 3 maternal deaths among 2614 diabetic pregnancies, the mortality rate being 0.1%, which was 10 times greater than the overall maternal mortality rate reported in the US between 1974 and 1978. Nowadays, maternal deaths in

diabetic pregnancy are rare. Most often they are associated with coronary artery disease and with diabetic autonomic neuropathy, mainly diabetic gastroparesis (Hare 1994).

2.4 Maternal complications during pregnancy

2.4.1 Hypoglycaemia

Severe hypoglycaemia is usually defined as an impairment of consciousness leading to the injection of glucagon by another person or to the intravenous administration of glucose by an emergency physician (Kimmerle *et al.* 1992). According to different studies, it complicates 34 - 41% of diabetic pregnancies, occurs most often during the first trimester and during sleep, and is pronounced in women with a history of hypoglycaemia before pregnancy (Kimmerle *et al.* 1992, Rosenn *et al.* 1995b, Hellmuth *et al.* 2000b). The main symptoms are palpitation, tremor and sweating as a sign of neuroglycopenia in the brain (Rosenn *et al.* 1995a). Counter-regulatory hormonal responses against hypoglycaemia, e.g. secretion of epinephrine, have been found to be diminished and delayed in Type 1 diabetic women, particularly during pregnancy (Rosenn *et al.* 1995a). Pregnancy combined with intensified insulin therapy may result in an additive effect, increasing the risk of hypoglycaemia, and hyperemesis during early pregnancy may also be a contributing factor (Rosenn *et al.* 1995b). Gestation itself may also predispose to hypoglycaemia, and diabetic patients with autonomic neuropathy have been found to be at particular risk for severe hypoglycaemia in some studies (Stephenson *et al.* 1996), but not in all (Airaksinen *et al.* 1990).

2.4.2 Ketoacidosis

Ketoacidosis is a condition characterized by insulin deficiency, hyperglycaemia and acidosis, and its clinical symptoms including malaise, drowsiness, weakness and hyperventilation, may be associated with Kussmaul respiration indicating metabolic acidosis. Because of the normal metabolic changes associated in pregnancy, diabetic women are at increased risk for ketoacidosis. (Chauhan & Perry 1995) Especially in women using an insulin pump, even a short failure in the insulin pump system combined with the increased risk of ketoacidosis due to pregnancy may lead to a dangerous situation. This has previously been an important factor increasing the rates of maternal morbidity and adverse foetal events, but its significance has diminished as a result of improved glycaemic control during pregnancy. Its incidence decreased significantly in Northern Finland between 1967 - 1987 from 13.6% to 1.0% (Anttila 1993). In their review, Kilvert *et al.* (1993) reported a 1.7% incidence of ketoacidosis during pregnancy and found its significance to PNM to be significantly decreased.

2.4.3 Hypertensive complications

The overall rate of hypertensive disorders during pregnancy is found to be four-fold in diabetic pregnancies (20.6% vs 5.0%) compared to that in the background population (Hanson & Persson 1998). According to different studies, pre-eclampsia is associated with Type 1 diabetic pregnancies in 13.7% (Garner *et al.* 1990), 20% (Sibai *et al.* 2000a) and 32.5% (Hsu *et al.* 1996) of cases, and PIH was found in 15.4% (Siddiqi *et al.* 1991) of the women. Distinguishing between pre-eclampsia and an exacerbation of the underlying disease is difficult in women with nephropathy. Occurrences of 41% (Reece *et al.* 1998) and 53% (Gordon *et al.* 1996b) for superimposed pre-eclampsia among women with diabetic nephropathy have been reported.

The incidence of pre-eclampsia increases significantly with the severity of diabetes (Garner *et al.* 1990, Sibai *et al.* 2000a). In several studies, its occurrence has been associated with unsatisfactory glycaemic control during early pregnancy (Hsu *et al.* 1996, Hanson & Persson 1998), but not in all studies (Garner *et al.* 1990). In a recent Finnish study, each 1% increment from the initial GHbA1c value corresponded to a 1.6-fold increase in the risk of pre-eclampsia but not with a risk of pregnancy-induced hypertension (Hiilesmaa *et al.* 2000). Age is not associated with an increased rate of pre-eclampsia (Hiilesmaa *et al.* 2000), nor does parity rate (Garner *et al.* 1990, Hanson & Persson 1998). Microalbuminuria or incipient nephropathy have been found to be the strongest predictors of pre-eclampsia in Type 1 diabetes (Combs *et al.* 1993, Ekblom *et al.* 2000). Nulliparity, poor glycaemic control in the first and second trimesters, and advanced White class are significantly associated with the presence of PIH, while improved glycaemic control throughout pregnancy may reduce its occurrence (Siddiqi *et al.* 1991). Satisfactory glycaemic control before pregnancy is suggested to be the best strategy for reducing the amount of all hypertensive complications in Type 1 pregnancies (Hsu *et al.* 1996, Hsu *et al.* 1998).

2.4.4 Preterm labour and delivery

Preterm delivery (< 37th GW) is common in diabetic pregnancies, the occurrence varying between 20-30% (Hanson *et al.* 1986, Molsted-Pedersen & Kuhl 1986, Greene *et al.* 1989b, Rosenn *et al.* 1993, Cnattingius *et al.* 1994, von Kries *et al.* 1997). These rates are 2-4 fold compared to the general obstetric population. Pre-eclampsia has been found to be the single most important cause of prematurity in diabetic women, but also advanced White class, previous premature delivery, increased duration of diabetes and carrying a male foetus have been associated with preterm delivery (Greene *et al.* 1989b, Sibai *et al.* 2000b). Preterm labor is also associated with sub-optimal glycaemic control throughout pregnancy, which may be contributed to by behavioural factors (Rosenn *et al.* 1993). Diabetic labour is often induced preterm in order to avoid an adverse foetal outcome such as intrauterine death. The rates of both spontaneous and indicated preterm delivery are increased among women with pregestational diabetes, being 16.1% and 21.9%,

respectively (Sibai *et al.* 2000b), while in a previous study, 54% of preterm deliveries were reported to be spontaneous (Rosenn *et al.* 1993). Beta-agonists have been used to inhibit preterm labour, but like corticosteroids given to induce foetal lung maturity, they may cause a rapid increase in blood glucose levels (Steel & Johnstone 1996).

2.5 Foetal risks

2.5.1 Spontaneous abortions

The miscarriage rate in diabetic pregnancies varies according to different studies from 7.7% to 24%, the rate being about 7% in the background population (Hanson *et al.* 1990, Nielsen & Nielsen 1993, Rosenn *et al.* 1994, The Diabetes Control and Complications Trial 1996, Casson *et al.* 1997). The risk for spontaneous abortion is mainly associated with poor periconceptual glycaemic control. In their review, Kitzmiller *et al.* (1996) reported the overall spontaneous abortion rate in diabetic women to be 14.3%, and 32.2% in a subset with substantially elevated glycohaemoglobin levels (> 6-9 standard deviation (SD) above the mean) at early prenatal visits. This is in accordance with the findings of Mills *et al.* (1988b), who found an increase of 3.1% in spontaneous abortion rates for each GHbA increase of 1 SD above the mean of the normal range. Type I diabetic women with initial GHbA1 concentrations in pregnancy above 12%, or median first-trimester preprandial glucose concentrations above 120 mg/dL, have an increased risk of miscarriage and malformations, this risk being comparable to non-diabetic women below these glycaemic thresholds (Rosenn *et al.* 1994).

2.5.2 Congenital anomalies

Congenital anomalies (CA) are the main cause of morbidity and mortality in infants born to Type 1 diabetic women, and their occurrence has remained unchanged during the last years. According to different definitions, they affect 2 - 9 % of diabetic pregnancies, the proportion of major anomalies being especially increased (Cnattingius *et al.* 1994, Casson *et al.* 1997, Hawthorne *et al.* 1997, von Kries *et al.* 1997, Suhonen *et al.* 2000), and they have also been reported to cause 30-40% of perinatal deaths in diabetic births (Schwartz & Teramo 2000). Increased anomaly rates are found also in Type 2 and GDM pregnancies (Schaefer *et al.* 1997, Schaefer-Graf *et al.* 2000). High CA rates are mainly associated with unsatisfactory periconceptual glycaemic control and might be prevented by the tight control of maternal blood glucose concentrations (Fuhrmann *et al.* 1983, Steel *et al.* 1990, Kitzmiller *et al.* 1991), although conflicting opinions have been presented (Mills *et al.* 1988a). An association between maternal obesity and increased CA rate in diabetic pregnancy has lately been reported (Moore *et al.* 2000).

By using developmental morphological dating for each organ system, it has been revealed that CAs must develop before the 7th week of gestation (Garner 1995). The most common types of anomalies involve the central nervous system (CNS), the cardiovascular, the gastrointestinal, the genitourinary and the skeletal systems (Reece & Homko 1994). Cardiac anomalies are the most common isolated malformations in diabetic pregnancy, the incidence being 3-4% (Reece & Hobbins 1986, Meyer-Wittkopf *et al.* 1996). In addition to septal defects and coarctation of the aorta, double outlet right ventricle, truncus arteriosus and transposition of the great vessels are common (Reece & Hobbins 1986, Ferencz *et al.* 1990, Reece & Homko 1994). Renal anomalies including, for instance, agenesis and ureteral duplication are also common, likewise are gastrointestinal anomalies, such as duodenal and anorectal atresia. The risk for neural tube anomalies is 10-fold in Type 1 diabetic pregnancy when compared with the non-diabetic population. The caudal regression syndrome complicates 0.5% of diabetic pregnancies but is not, however, pathognomonic of diabetes, with only 8-16% of affected infants being born to diabetic mothers. (Reece & Hobbins 1986, Garner 1995)

2.5.2.1 Teratogenic mechanisms

Hyperglycaemia. Hyperglycaemia during the first weeks of pregnancy with its metabolic derangements has been found to be teratogenic (Fuhrmann *et al.* 1983, Kitzmiller *et al.* 1991). Elevated GHbA levels at the time of conception or in the early pregnancy correlate directly with an increased frequency of congenital anomalies in several studies (Miller *et al.* 1981, Ylinen *et al.* 1984, Miodovnik *et al.* 1988, Greene *et al.* 1989a) but not in all (Mills *et al.* 1988a). Special cut-off levels measured by GHbA values, such as 8 SD above the non-diabetic mean, have been set to assess the increased risk of CA (Hanson *et al.* 1990), but in a recent Finnish study even slightly raised GHbA1c values during early pregnancy were associated with an increased risk for foetal anomalies (Suhonen *et al.* 2000).

Hypoglycaemia. In animal models, even 1-2 hours of hypoglycaemia during early pregnancy has been found to cause foetal malformations. The stage of neurulation and gastrulation, 8 and 9 days of gestation in the rat, were found to be critical. (Buchanan *et al.* 1986, Smoak & Sadler 1990) In humans, no such relation has been reported even in cases of multiple hypoglycaemic episodes (Mills *et al.* 1988a, Kitzmiller *et al.* 1991).

Yolk sac injury. Yolk sac is the primary target site for the adverse metabolic effects arising from hyperglycaemia in Type 1 diabetic pregnancy (Pinter *et al.* 1986, Reece & Hobbins 1986). Pinter *et al.* (1986) found that excess D-glucose during organogenesis has a primary deleterious effect on the yolk sac cellular structure and function resulting in embryopathy.

Free oxygen radicals. Eriksson and Borg (1993) reported that when a free oxygen radical scavenging enzyme, superoxidase dismutase, is added to a hyperglycaemic medium in which rat embryos were cultured, it was found to be protective against the teratogenic effects of, for example, hyperglycaemia. They hypothesized that the immature scavenging enzymes are overwhelmed in hyperglycaemia resulting in excess free radicals which cause teratogenesis. Increased free oxygen radical activity enhances lipid peroxidation leading to an imbalance in prostaglandin synthesis - this could be a link between excess free oxygen radical production and a deficiency in arachidonic acid and myoinositol reported by some study groups (Reece & Homko 2000).

Ketones and somatomedin inhibitors. Hyperketonemia has been suggested to be an etiologic factor in diabetes-associated malformations (Reece & Homko 2000). In animal studies, somatomedins have been shown to promote growth of the costal cartilage in vitro. Sadler *et al.* (1989) demonstrated, that the presence of the low-molecular-weight fraction of somatomedin inhibitors was associated with an increased incidence of malformations and impaired growth. They act in vitro synergistically with hyperglycaemia and elevated ketone concentrations, producing congenital defects and growth retardation. Their significance in humans has not been demonstrated.

Vasculopathys. Some studies have suggested maternal vasculopathy as being associated with congenital anomalies (Miller *et al.* 1981, Miodovnik *et al.* 1988) but no such correlation has been found in later studies (Damm & Molsted-Pedersen 1989).

2.5.3 Altered fetal growth

Macrosomia. Macrosomia is a problem in both gestational and Type 1 diabetic pregnancies. It is usually defined as a birth weight more than 4000g, and large for gestational age (LGA) as 2 SD above the mean weight for gestational age corrected for sex in an appropriate standard population (Schwartz & Teramo 2000). According to different studies, the rates of macrosomia or LGA have been 20-41% in Type 1 pregnancies (Jovanovic-Peterson *et al.* 1991, Hanson & Persson 1993, Nielsen & Nielsen 1993, Page *et al.* 1996, von Kries *et al.* 1997).

In 1954, Pedersen presented the theory of hyperinsulinism: maternal hyperglycaemia produces foetal hyperglycaemia and hyperinsulinism resulting in foetal pancreatic β -cell hyperplasia and, later in foetal macrosomia (Pedersen 1954). The significance of an improvement in glycaemic control is controversial. According to previous studies, the incidence of macrosomia may be reduced by tighter control of diabetes at conception and during the first trimester (Page *et al.* 1996, Gold *et al.* 1998), during the first and second trimester (Raychaudhuri & Maresh 2000), or during the second half of pregnancy (Koukkou *et al.* 1997). In addition to hyperglycaemia, macrosomia has also been associated with maternal obesity and weight gain during pregnancy, at least in GDM (Vohr *et al.* 1995), although conflicting findings have also been presented (Schwartz *et*

al. 1994). In the latter study, GHbA was found to be a weak predictor of birth weight and foetal hyperinsulinism. An only modest abnormality in glycaemic control in some mothers with LGA infants suggests that other factors than maternal hyperglycaemia must also be implicated in foetal growth acceleration (Persson & Hanson 1996). Increased placental glucose transport capacity in insulin-dependent diabetes mellitus may explain the occurrence of macrosomia despite well-controlled diabetes. Diabetes has been thought to cause an increase in basal membrane glucose transporter 1 (GLUT1) expression and persistent activity despite a lack of evidence for current or recent maternal hyperglycaemia (Gaither *et al.* 1999, Jansson *et al.* 1999).

Increased adiposity and organomegaly are considered to be the main causes of macrosomia. Morphometric studies of Type 1 pregnancy have indicated that the increased growth of foetal abdominal circumference is due to a deposition of fat in the abdominal and interscapular area. Babies born to diabetic mothers appear to also have a biphasic manner of growth: despite relatively overall normal size and weight, they may have smaller heads than their potential, as well as more fat (Koukkou *et al.* 1997). Foetal overweight is highly associated with pathology in diabetic vaginal deliveries, and contributes to an increase in operative deliveries, shoulder dystocia and perinatal morbidity (Moore 1997).

Growth delay. In 1985 Molsted-Pedersen and Pedersen reported early embryonic growth delay during the first 15 weeks in diabetic pregnancies. This was especially seen in malformed embryos, and has been speculated to be due to hyperglycaemia (Molsted-Pedersen & Pedersen 1985). Intrauterine growth retardation (IUGR) is mostly seen in women with an underlying vascular disease suggesting that a uteroplacental vasculopathy may restrict foetal growth in these patients. This risk is also increased in cases of CA and maternal hypertension. IUGR can be divided into intrinsic and extrinsic forms: CAs and chromosomal defects are present in the former, while nutrient limitation associated with maternal hypertension and advanced diabetic vasculopathy is associated with the latter form (Moore 1997). Small for gestational age (SGA), defined as 2 SD under the mean weight for gestational age corrected for sex in an appropriate standard population, was found in 7.0% of all infants of diabetic mothers (IDM) in a previous Finnish study, the rate being significantly higher in White classes F/R than in less severe diabetes (Anttila 1993).

2.5.4 Fetal asphyxia

Perinatal asphyxia, defined as an abnormal foetal hearth rate, low Apgar scores and cord blood acidosis is more common in diabetic than in non-diabetic pregnancies (Mimouni *et al.* 1988, Salvesen *et al.* 1993). Its presence has been associated with maternal antenatal hyperglycaemia (Widness *et al.* 1990), and hyperglycaemia preceding delivery, nephropathy appearing in pregnancy, and prematurity (Mimouni *et al.* 1988). Foetal hyperinsulinemia as a consequence of maternal hyperglycaemia may increase foetal

metabolic rate and oxygen requirements in many ways, especially in cases of pre-eclampsia and vascular disease, which can contribute to a reduction in placental blood flow and foetal oxygenation. Erythropoietin concentrations in foetal plasma and amniotic fluid are increased in diabetic pregnancies as a consequence of foetal hypoxia (Widness *et al.* 1981, Teramo *et al.* 1987). While amniotic fluid erythropoietin correlates with plasma concentrations, it can be used as an antepartum indicator of foetal hypoxemia (Teramo *et al.* 1987, Östlund *et al.* 2000).

Despite improved perinatal outcome in diabetic pregnancy, the rate of late intrauterine death is still high, asphyxia likely being its main cause (Schwartz & Teramo 2000). In a population-based study from USA, foetal death was eight times more common in diabetic pregnancies than in a non-diabetic control population (Connell *et al.* 1985). In a Swedish study, the rates of late foetal death were 1.3% among infants born to women with diabetes, and 0.4% in the non-diabetic controls (Cnattingius *et al.* 1994). Deficiency of iron in liver, heart and brain has also been found in IDMs dying during the early neonatal period, and may be an indication of chronic intrauterine hypoxia (Petry *et al.* 1992). Foetal acidemia, polycythemia and thrombocytopenia, possibly resulting in hyperviscosity and intravascular thromboses, might contribute to the increased incidence of late unexplained foetal deaths in diabetic pregnancies (Salvesen *et al.* 1992)

2.5.5 Fetal monitoring during pregnancy

A maternal assessment of foetal activity is the primary screening test in most surveillance programs (Landon & Gabbe 1993). In non-complicated diabetic pregnancy without severe microvascular complications, the beginning of intensive foetal testing may be safely delayed until 32 weeks of gestation. In cases of White classes R/F, foetal growth-retardation or maternal hypertension it is recommended that testing is be started at 26 weeks of gestation (Lagrew *et al.* 1993).

2.5.5.1 Cardiotocography

The non-stress cardiotocography (CTG) test (NST) is a widely used screening method to identify foetuses at risk for intrauterine death. Its use on a semi-weekly basis beyond 32 weeks of gestation provides an adequate level of foetal surveillance for the diabetic population (Golde *et al.* 1984, Landon *et al.* 1992). Diabetic women with poor metabolic control (Teramo *et al.* 1983), or with vascular disease (Landon *et al.* 1992), have significantly more often a suspicious or pathological foetal hearth rate recording than do women with good metabolic control or uncomplicated diabetes. Foetal heart rate variation has been found to be poor predictor of foetal acidemia (Salvesen *et al.* 1993), however, and standard foetal assessment parameters of computerized CTGs and biophysical testing may not be applicable to foetuses in diabetic pregnancies (Tincello *et*

al. 1998). The contraction CTG test is also used in predicting foetal distress but because of the high incidence of false-positive findings it is not useful as a sole method (Landon & Gabbe 1993).

2.5.5.2 Ultrasonography and fetal bioprofile

Ultrasound examination to backup semi-weekly NST has been used to assess the foetal biophysical profile (BPP). This includes foetal breathing movements, gross body movements, foetal tone and amniotic fluid volume. The predictive value of a normal BPP for a reassuring trace during labor was 95% in a study of 978 Type 1 women (Dicker *et al.* 1988), while in another study BPP was found to be of limited value in the prediction of foetal acidemia (Salvesen *et al.* 1993). It has been found to be reassuring in 90% of cases in which NST was found to be non-reactive (Landon *et al.* 1992). Foetuses of diabetic women have been found to have higher mean incidences of foetal breathing movements, hearth rates and breathing rates, however, but lower foetal movements and hearth rate acceleration counts than their non-diabetic controls (Devoe *et al.* 1994). The role of serial ultrasonography is important in assessing foetal growth, especially foetal growth retardation, and in evaluating amniotic fluid volume (Kjos *et al.* 1995).

2.5.5.3 Doppler examination

Diabetic patients with vasculopathy are a high-risk group for foetal growth retardation, which may be detected by early umbilical artery Doppler studies (Landon *et al.* 1989). According to most studies, the umbilical artery systole/diastole (S/D) ratio (Landon *et al.* 1989), uteroplacental and foetal pulsatility index (PI) values (Grunewald *et al.* 1996) and resistance index (RI) (Johnstone *et al.* 1992, Zimmermann *et al.* 1992) are independent of glycaemic control in a well-controlled diabetic population. Doppler flow velocimetry of the uterine artery is a poor predictor of diabetes-specific foetal morbidity (Zimmermann *et al.* 1994). The normal third trimester decline in uteroplacental and foetal placental PIs has been found to be absent in the diabetic group (Grunewald *et al.* 1996). Near term, the umbilical artery PI was also higher in diabetic than in non-diabetic pregnancies, indicating a higher placental vascular resistance in the former group. A high umbilical artery PI occurred in foetuses which later developed distress in labor. (Olofsson *et al.* 1987) However, Zimmerman *et al.* (1992) found a comparable decrease in umbilical RIs during pregnancy in both diabetic and non-diabetic pregnancies. Abnormal umbilical RI has been found to be a significant predictor of foetal compromise in diabetic pregnancy, but while this compromise may also occur in association with normal indices, it has been cautioned against relying solely on a normal Doppler waveform (Johnstone *et al.* 1992).

2.5.5.4 Amniotic fluid erythropoietin

Erythropoietin does not cross the placenta and its synthesis in the foetus is mostly stimulated by hypoxemia. Foetal plasma and amniotic fluid erythropoietin concentrations are frequently elevated in diabetic pregnancies, suggesting an increased incidence of chronic foetal hypoxia (Widness *et al.* 1981, Teramo *et al.* 1987). While amniotic fluid erythropoietin concentration in the absence of labor closely reflects foetal plasma erythropoietin levels, it might be used as an antepartum indicator of chronic foetal hypoxemia (Teramo *et al.* 1987). A relationship between the foetal growth and amniotic fluid erythropoietin levels has also lately been observed (Östlund *et al.* 2000).

2.6 Delivery

2.6.1 Timing of delivery

Apart from macrosomia, an increased risk of late foetal death during the final weeks of gestation has led to the practice of inducing diabetic deliveries preterm, resulting in a high Caesarean section rate and a high rate of preterm infants. Elective delivery has been adopted as a common practice in diabetic pregnancy (Landon *et al.* 1990), and in some reports it is recommended at the 38th GW if the lung profile is mature, if glycaemic control is poor or if there is a history of a prior stillbirth (Landon & Gabbe 1993). Also problems in prior deliveries including shoulder dystocia must be considered. According to another study, when glycaemic control has been optimal and there are no signs of foetal compromise or maternal pregnancy complications, such as pre-eclampsia, delivery can be delayed to near term (Neiger & Kendrick 1994). Today, improved foetal monitoring and better maternal glycaemic control might enable prolongation of pregnancy to near term, decreasing at the same time the neonatal morbidity caused by prematurity. In Northern Finland, the mean gestational age among diabetic women increased from 35.4 to 37.6 GW between 1967 and 1987 (Anttila 1993). Amniotic fluid insulin detection is used to identify normoinsulinaemic fetuses - these pregnancies could be allowed to continue to the onset of spontaneous labour (Fraser & Bruce 1999). The measurement of amniotic surfactant is not required with delivery after 38 weeks and is very rarely necessary at any gestational age (Steel & Johnstone 1996)

2.6.2 Mode of delivery

The Caesarean section rate in diabetic pregnancy is high; involving in addition increased rates of failed inductions, macrosomia and foetal distress (Cousins 1987). Caesarean section rates in diabetic women have been reported to be 45-50%, the corresponding

percentages being 9-12 in the background population (Hanson & Persson 1993, Cnattingius *et al.* 1994). In Northern Finland, the rate of Caesarean section among insulin-treated diabetes was 47.6% between the years 1981-87, and 62.5% of these were performed electively (Anttila 1993). Primary caesarean sections increase in a step-wise manner with the severity of diabetes: according to Cousins (1987), the primary caesarean section rate was 44.0% among White classes B-C and 56.7% in White classes D-F/R. Non-medical factors, such as a lower physician threshold for abdominal delivery have been found to play an important role in the decision for performing a caesarean delivery (Blackwell *et al.* 2000). The diagnosis of GDM itself has also been found to lower the threshold for surgical delivery (Naylor *et al.* 1996).

Kjos *et al.* (1993) performed a randomised study in which 200 women with uncomplicated insulin-treated diabetes of 38 GW with appropriate for gestational age (AGA) -estimated infants were randomised to expectant management or active induction of labour within 5 days. The expectant management was associated with an increased proportion of LGA infants (23 vs 10%) and shoulder dystocia (35 vs 0%), not with a reduction in caesarean section rates. The conclusion was that there is little benefit in delaying delivery after the 38th GW. Ultrasonographically estimated macrosomia ($\geq 90^{\text{th}}$ percentile or weight $> 4250\text{g}$) indicates a need for the induction of labor in diabetic women, reducing the rate of shoulder dystocia without a clinically significant increase in the caesarean section rate (Conway & Langer 1998). Elective caesarean section is recommended to prevent traumatic vaginal delivery if the estimated foetal weight is $\geq 4250\text{g}$ (Langer *et al.* 1991, Conway & Langer 1998). Diabetic woman with active retinal neovascularization may be at risk for vitreous haemorrhage during the second phase of vaginal delivery because of the Valsalva action, and therefore, treatment of neovascularization and/or caesarean section is recommended (Oguz 1999). If pregnancy is not complicated with macrosomia or untreated retinopathy, elective caesarean section is only recommended when the cervix is unlikely to be ripened with prostaglandins or if foetal macrosomia is suspected (Landon 2000). However, the patient's past history of macrosomia and shoulder dystocia, foetal adipose profile and clinical pelvimetry should all be considered.

2.7 Risks for newborn

2.7.1 Birth trauma

The increased risk of macrosomia in diabetic pregnancies has been found to predispose to birth traumas. In her study, Anttila (1993) found a significant correlation between birth injury and gestational related birth weight, the most common injuries being clavicular fracture, cephalhaematoma and brachial palsy. A different pattern of growth in diabetic pregnancy must be considered when the appropriate mode of delivery is chosen (Koukkou *et al.* 1997). Langer *et al.* (1991) reported that using 4250 g as the birth weight

limit for elective caesarean section could eliminate 80% of the cases of shoulder dystocia among diabetic women. Mimouni *et al.* (1992) compared the prevalence of birth traumas in 118 type 1 diabetic mothers and 354 control subjects. They did not find the rate of birth traumas to be significantly different in these two groups, but midforceps delivery was found to be a significant risk factor for brachial plexus injury.

2.7.2 Neonatal hypoglycaemia

Neonatal hypoglycaemia is defined by a serum glucose value less than 35 mg/dL (1.7 mmol/l) for full-term and less than 25 mg/dL (1.4 mmol/l) for premature infants (Reece & Homko 1994). The diagnosis should be based on two consecutive low values taken 30 minutes apart (Cordero & Landon 1993). Neonatal hypoglycaemia occurs when plasma insulin levels in the newborn remain high after cord clamping and transplacental source of glucose has been blocked (Reece & Homko 1994). Its incidence among IDMs is reported to range from 8% to 40% (Hanson & Persson 1993, Nordstrom *et al.* 1998). Macrosomic and SGA infants, infants with elevated cord blood C-peptide, and infants after perinatal distress are at risk of neonatal hypoglycaemia (Cordero & Landon 1993, Reece & Homko 1994). Poor maternal metabolic control during pregnancy, labor and delivery increase the risk of neonatal hypoglycaemia (Reece & Homko 1994), though an increase of maternal glucose value to 8 mmol/l in labour was not found to increase the risk of neonatal hypoglycaemia (Carron Brown *et al.* 1999). Defective counter-regulation by catecholamines may contribute to the development of neonatal hypoglycaemia (Schwartz & Teramo 2000), and IDMs have also been found to be unable to respond to hypoglycaemia by releasing adequate amounts of glucagon from the alpha cells of the pancreas to mobilize glycogen. Polycythemia may cause hypoglycaemia via an increased number of red blood cells directly absorbing glucose from the serum. (Mountain 1991) The incidence of neonatal hypoglycaemia has not significantly decreased despite improved maternal metabolic control. This is in accordance with the finding that early postnatal hypoglycaemia, mainly induced by foetal hyperinsulinaemia, has been found even in well-controlled pregnancies (Stenninger *et al.* 1997).

2.7.3 Respiratory distress

Robert *et al.* (1976) reported the risk of respiratory distress syndrome (RDS) as being 5.6 times higher in IDMs than in the general obstetric population, and that especially foetal hyperinsulinemia has often been associated with a delay in foetal pulmonary maturation (Warburton 1983). In later studies, foetal pulmonary maturation has also been found to be associated with maternal glycaemic control. Improvement of maternal metabolic control has been found to reduce the risk of pulmonary immaturities of the newborn to nearly the same level as that of the non-diabetic population (Piper & Langer 1993). In contrast,

Mimouni *et al.* (1987) found the risk of RDS to be increased in IDMs only in cases of prematurity and caesarean birth not preceded by labor (Mimouni *et al.* 1987). Foetal lung maturity has been found to be equal in IDMs and infants of non-diabetics, but the risk for neonatal wet lung is increased in IDMs (Kjos *et al.* 1990, Piazzo *et al.* 1999).

The occurrence of severe RDS decreased in a population-based Finnish study between 1967 to 1986 from 18.0% to 4.0% (Anttila 1993). Other studies have also shown the incidence of RDS in infants of diabetic women to have declined near to the level of the background population (Hanson & Persson 1993). The trend to deliver diabetic patients later as well as improvements in neonatal care have diminished incidence of RDS, while its occurrence is still highly associated with prematurity. The administration of antenatal steroids to improve foetal lung maturity has successfully been used with the adequate monitoring of maternal glycaemic control (Byrne *et al.* 1997).

2.7.4 Other morbidities

Polycythemia. Polycythemia is defined as a venous hematocrit exceeding 65%. Its incidence in IDMs varies from 2% (Hanson & Persson 1993) to 29% (Mimouni *et al.* 1986) and 40% (Salvesen *et al.* 1992), rates being five times those in a comparable control population. Foetal hyperglycaemia and hyperinsulinism result in relative chronic intrauterine hypoxemia, and thus to an increase in erythropoietin levels and in red cell production. Polycythemia is usually associated with a hyperviscosity of the blood affecting the velocity of blood flow and increasing the incidence of intravascular thromboses. The finding that foetuses with polycythemia are often acidemic and may therefore have an increased tendency for intravascular thromboses giving rise to the suggestion of a relation with unexplained intrauterine death (Salvesen *et al.* 1992).

Hyperbilirubinemia. Hyperbilirubinemia has been found more frequently after diabetic than non-diabetic pregnancy - it develops in approximately 16-25% of IDMs (Hanson & Persson 1993, Reece & Homko 1994) and needs treatment in 25-30% of cases (Mountain 1991). The pathogenesis is still uncertain but has been associated with intrauterine hypoxia with increased erythropoietin levels, macrosomia of the newborn (Mountain 1991) and high maternal GHbA values as a sign of poor maternal glycaemic control (Ylinen *et al.* 1981).

2.7.5 Mortality

During last five decades perinatal mortality in the largest tertiary level hospital in Finland fell from 28.5% to 2.4% (Schwartz & Teramo 2000). In Norway, Jervell *et al.* (1980) reported a decrease in perinatal mortality from 177.4 to 60.7 per 1000 births between 1967-68 and 1975-1976; for the total population the figures were 24.1 and 18.4/1000. In

a Finnish diabetic birth cohort study including White classes AB-R, the perinatal mortality rate decreased significantly, being 15.2% in 1967-1972 and 4.3% in 1981-1987. At the beginning of the study period, RDS and severe ketosis were the most common causes of perinatal mortality (PNM), while CA and asphyxia were the leading causes during the latter study period. (Anttila 1993) The basis for this decrease of PNM is in improved glycaemic control before and during pregnancy in addition to improvements in obstetric and neonatal care. Today, 30-40% of perinatal deaths in Type 1 diabetic pregnancies are reported to be caused by malformations, 20-30% by prematurity, and 20-30% by intrauterine asphyxia including late gestation foetal death (Schwartz & Teramo 2000). During the last decades, the improved detection of fatal CAs in early pregnancy, often leading to induced pregnancy termination, has been reported to have diminished the PNM rate in the common obstetric population (Saari-Kemppainen *et al.* 1990).

PNM rates in diabetic pregnancies have recently varied from 2.4 to 4.8% (Hanson & Persson 1993, Nielsen & Nielsen 1994, Casson *et al.* 1997, Hawthorne *et al.* 1997, von Kries *et al.* 1997, Schwartz & Teramo 2000), rates being 3 - 5 times that in the normal obstetric population. In a Swedish birth cohort study the rate of late foetal deaths was 1.3% and of infant mortality 0.9%, the corresponding figures being 0.4% and 0.5% in the background population, respectively (Cnattingius *et al.* 1994). In a British evaluation, both the stillbirth rate (25.0/1000 births) and infant mortality (19.9/1000 live births) were significantly higher than were national rates (5.0/1000 and 6.8/1000, respectively) (Casson *et al.* 1997). According to different studies, a high PNM rate has been associated with CAs (Connell *et al.* 1985), prematurity (Cnattingius *et al.* 1994), poor glycaemic control (Hanson & Persson 1993), a substandard use of prenatal care (von Kries *et al.* 1997) and vascular complications of diabetes (Kitzmiller *et al.* 1978, Lauszus *et al.* 1998). The mortality of non-malformed IDMs did not differ significantly from the national rate in a recent British study (Casson *et al.* 1997).

2.7.6 Long term prognosis

The transmission risk to the offspring by the age of 20 years has been found to be 1.3% if the mother has Type 1 diabetes, and 6.2% in the case of the diabetic father (Warram *et al.* 1984). Weiss *et al.* (2000) studied 75 offspring of Type 1 diabetic mothers at 5-15 years of age, and found 4 (5.3%) of them to have overt diabetes and 16 of 71 (22.5%) to have autoimmune antibodies - RR for Type 1 and Type 2 diabetes were 71.6 and 3.2, respectively. Buschard *et al.* (1989) studied 55 children at a mean age of 10.4 years, who had been *in utero* when Type 1 diabetes developed in their mothers. One child had diabetes, demonstrating that foetal β -cells remain unaffected during pregnancy by the mechanisms that cause diabetes in their mothers.

IDMs with neonatal hypoglycaemia (BG < 1.5mmol/L) displayed more difficulties in a validated screening test for minimal brain dysfunction and were more often hyperactive, impulsive and easily distracted at the age of 8 years. They had also a lower total development score than normoglycaemic children born to diabetic women.

Therefore, authors emphasized the importance of prevention and treatment of even asymptomatic hypoglycaemia to avoid disturbances in impaired neurodevelopment. (Stenninger *et al.* 1998) On the other hand, Rizzo *et al.* (1994) found no significant correlation between the measure of a child's intelligence scores and prevalent perinatal complications, such as the incidences of hypoglycaemia, adjusting background factors in 2- to 5-years-old IDMs. In an Austrian study, the body weight of the IDMs born to diabetic mothers with nephropathy were significantly lower even three years after delivery, their linguistic development was retarded, and their resistance to infections was found to be reduced (Biesenbach *et al.* 2000).

3 Aims of the present study

The population based diabetic birth cohort and register based national data of insulin-treated diabetic pregnancies were used as follows:

1. To investigate the realization of decentralized care of diabetic pregnancies and its effects on maternal glycaemic control and the peri- and neonatal outcome (I and IV)
2. To survey the effect of pregnancy on diabetic complications, and the significance and parity rate for the course of pregnancy (III)
3. To find factors predicting poor peri- and neonatal outcomes in diabetic pregnancy (II)
4. To evaluate the prevalence and types of congenital anomalies, and the causes of deaths until the age of one year in the offspring of Type 1 diabetic mothers (V)

4 Patients and methods

4.1 The study populations

Papers I-III. The study population comprises all 296 consecutive births from 210 Type 1 diabetic mothers managed in the catchment area of Oulu University Hospital between 1986 and 1995. Singleton births with a gestational age of 22 weeks or more or a birth-weight of ≥ 500 g were included in the study. The data on the women and their newborns were collected retrospectively from patient records. They were registered in every hospital according to a specific formula during pregnancy, delivery and the neonatal period and they contained information on the mother's medical background, and on the course of pregnancy and delivery as well as clinical information concerning the infants.

In 1986-1990, the care of diabetic pregnancies was centralized to the tertiary level Oulu University Hospital and was mainly performed on an in-patient basis. After 1991, management was decentralized to include the four secondary level hospitals in Kajaani, Kemi, Kokkola and Rovaniemi, and simultaneously, follow-up was changed to an out-patient basis. The causes leading to dispersion of the care were the long distances in this area, as well as a national tendency for decentralization. In order to evaluate the impact of the changes in treatment and follow-up, the study population was divided into two periods: 1986-1990 (period 1, n=135) and 1991-1995 (period 2, n=161).

Forty-six diabetic women went through their first two pregnancies during the study period. The characteristics of these first and second pregnancies were compared to evaluate the significance of recurrent pregnancy for the progression of the disease, and the occurrence of pre-eclampsia and satisfied glycaemic control in consecutive Type 1 diabetic pregnancies. To evaluate which women remained primiparous, the number of their consecutive pregnancies in 1996-1999 were checked from the delivery hospitals using the mother's unique identification number.

Unpublished data on 44 678 singleton, non-diabetic pregnancies during the years 1991-1995 from the same geographical area, obtained from the Finnish Medical Birth Register (MBR), were used for comparison in paper II.

The characteristics of the diabetic mothers are shown in table 1.

Papers IV-V. The data consists of information on 1460 mothers who according to the MBR had insulin treatment during pregnancy in 1991-1995. After excluding multiple pregnancies the final number of diabetic mothers was 1442. All rights for special reimbursements for the cost of the medication in certain chronic diseases, such as diabetes, are granted in Finland by the National Social Insurance Institution, which also maintains a register of the receivers of these benefits. The MBR data was combined with this data base to distinguish insulin-treated GDM from pre-existing diabetes; women who had the right for a special refund of the cost of diabetic medication before their pregnancy were classified as having Type 1 diabetes. The mother's unique identification number was used as the linkage key. On this basis, 954 women were found to have Type 1 diabetes and 488 insulin-treated GDM. The occurrence of CA and death of the offspring up to one year of age were derived combining the MBR data with the Register of Congenital Malformations (RCM) and the Cause of Death Register (CDR). Corresponding data on the control population were obtained from the 1993 MBR covering 62 546 singleton, non-diabetic deliveries (Paper IV) and the 1991-95 MBR and CDR (n=318 560) (Paper V).

Table 1. Characteristics of diabetic mothers managed in Northern Finland in 1986-95.

White class	n	n (%)	Age		Parity rate (range)	BMI kg/m ² (SD)	Onset of diabetes		Duration of diabetes			
			years	(SD)			years	(SD)	years	(SD)		
B	88	(30)	28,1	(4,7)	1,6	(0-12)	23,6	(4,0)	24,8	(4,5)	3,5	(2,2)
C	63	(21)	26,7	(4,7)	1,0	(0-4)	22,9	(3,5)	15,9	(3,7)	11,0	(4,0)
D	113	(38)	27,0	(4,7)	0,7	(0-3)	23,0	(2,6)	10,3	(5,4)	16,8	(5,4)
F	18	(6)	25,7	(2,8)	0,6	(0-5)	24,1	(2,7)	7,3	(3,9)	18,7	(4,6)
R	14	(5)	25,9	(4,6)	0,6	(0-2)	24,7	(2,7)	7,5	(4,6)	18,6	(5,1)
All	296		27,1	(4,6)	1,0	(0-12)	23,3	(3,3)	15,5	(8,1)	11,8	(7,3)

4.2 Health registers

4.2.1 The Finnish Medical Birth Register (MBR)

The MBR has been a nationwide, statutory register since 1987, and is complemented through linkage to national birth and death certificates (Gissler *et al.* 1995, Gissler *et al.* 1997). All pregnancies resulting in a live-born infant or a stillbirth at a gestational age of 22 weeks or more, or weighing more than 500 g, are included in the MBR. The MBR contains information on maternal background factors, follow-up, course and outcome of pregnancy and delivery, and neonatal care up to the age of seven days. Among the 69 items listed, maternal insulin-treated diabetes is noted. The validity of the MBR was assessed in 1991 and the data quality of the register is high for most of the variables (Gissler *et al.* 1995).

4.2.2 The Finnish Register of Congenital Malformations (RCM)

The Finnish RCM was established in 1963 and began regular monitoring in 1977. Its content and data collection were thoroughly renovated in the years 1985 and 1993. It contains information on all types of CAs identified mostly during the first year of life. The classification was based on ICD-9 (9th version of the International Classification of Diagnoses) during the study period. Certain minor conditions such as dislocation of the hip and persistent ductus arteriosus, are not included to the register. The reports for the RCM are mainly obtained from delivery units, neonatal, paediatric and pathology departments, death certificates and cytogenetic laboratories, but information is also received from other national medical registries, such as the MBR, the CDR, Hospital Discharge Register and the Abortion Register (<http://www.stakes.fi>).

4.2.3 The Cause of Death Register (CDR)

The CDR operates under the jurisdiction of the Statistics Finland and contains data on all deaths occurring in Finland. The causes of deaths were classified in the register according to ICD-9 during the study period.

4.3 The main principles in the care of diabetic pregnancies

In Finland there has been free health care for all pregnant women in maternity welfare clinics (MWC) in every commune since year 1941, and these clinics are practically 100% attended. Hospitals are classified according to medical indications. There are 5 tertiary level hospitals in Finland which also serve as central hospitals for their own area, each of them having about one million inhabitants and 2–4 secondary central hospitals in their administrative regions. Home deliveries and deliveries in private hospitals are exceptional.

Recommendations concerning standardization of the care of diabetic pregnancies, as well as detection and diagnosis of gestational diabetes, were given in Finland in 1993 (Teramo *et al.* 1993). According to these recommendations, diabetic patients are seen at the out-patient clinics of their delivery hospitals as soon as pregnancy has been verified in MWCs. The severity of diabetes is then classified according to White (White 1978) and metabolic control is optimised. The care team consists of a diabetologist, an obstetrician and a special nurse. Ophthalmologic examination is performed by an ophthalmologist during the first trimester and later in pregnancy according to clinical findings. Diabetic patients receive insulin and equipment required for monitoring glycaemic control for free of charge. Most of the women use intensive insulin therapy with 3–4 injections of short-acting and 1–2 injections of intermediate-acting human insulin daily by means of insulin pens.

In the present study, pregnant diabetic patients attended the antenatal clinic at least every fourth week up to the 28th week of pregnancy, and thereafter at 1-2 week intervals up to the 36th GW. During the last weeks of pregnancy the visits were intensified to mostly twice weekly, or the mothers were hospitalised until delivery. Ultrasonographic scanning was offered to every one in the delivery hospital to assess gestational age and to check for congenital malformations at 16-18 weeks of pregnancy. Foetal well being was checked at every visit by ultrasound scanning, and cardiotocography was performed after the 32nd GW.

A paediatrician examined all newborns immediately after delivery and at least once more before discharge from hospital. The infants were admitted to a neonatal unit for observation and treatment only as a result of medical indications.

Gestational diabetes is diagnosed by a two-hour OGTT, using a 75 g dose of glucose. It is recommended to be performed between weeks 26 and 28 of gestation among women with risk factors such as BMI ≥ 25 kg/m², a previous macrosomic (> 4 500g) infant, or age ≥ 40 years. In cases of prior gestational diabetes or glucosuria in the current pregnancy, the OGTT is performed earlier. The recommended cut-off levels in capillar blood are 4.8 mmol/l for fasting, 10.0 mmol/l after 1 h and 8.7 mmol/l after 2 h (Teramo *et al.* 1993). The use of insulin is recommended when fasting plasma glucose concentrations are repeatedly > 5.5 mmol/l and/or 2-hour postprandial plasma glucose is > 7.8 mmol/l despite standard dietary management. Follow-up is thereafter similar to that in Type 1 diabetes (Teramo *et al.* 1993).

4.4 Definitions

4.4.1 Diabetic complications

Retinopathy was classified into four types. In grade zero the patients showed no retinal changes. In grade I there was background diabetic retinopathy with microaneurysms, and in grade II (pre-proliferative retinopathy) the criteria included hard exudates, haemorrhages and infarcts. Grade III was classified as proliferative retinopathy with neovascularisation and fibrous tissue. Aggravation of retinopathy was defined as any progression of pre-existent retinal changes during pregnancy.

If the patient had a positive dip test result as regards albumin, the degree of albuminuria was measured by means of a 24-hour urine collection before the 24th gestational week. Nephropathy was diagnosed if urinary albumin excretion exceeded 0.3 g/24 h.

Arterial hypertension was diagnosed if blood pressure was >140 mmHg systolic and 90 mmHg diastolic, or if antihypertensive medication was used at the time of the first antenatal visit. Mild pre-eclampsia was diagnosed if blood pressure after the 24th week of pregnancy was repeatedly >140/90 mmHg, combined with proteinuria of more than 0.3 g daily, and moderate or severe pre-eclampsia was diagnosed with proteinuria > 1 g/ 24 h. Superimposed pre-eclampsia was diagnosed in cases of pre-existing elevated blood pressure and/or proteinuria, when there was an increase in blood pressure of more than 30/15 mmHg or at least a 100% increase in proteinuria.

Symptomatic severe hypoglycaemia was defined as episodes during pregnancy requiring active assistance from another person.

4.4.2 Glycaemic control

The women monitored themselves according to a seven-point blood glucose profile 2-3 days weekly at home and reported the values to the specialist nurse once a week in general. Fasting blood glucose concentrations were maintained between 3.0 and 4.8 mmol/l as far as possible, and all values were maintained under 6.8 mmol/l. All patients used reflectance meters at home for glucose monitoring.

The concentration of glycated haemoglobin (GHbA1 or GHbA1c), assayed at least once a month, was used as an index of glycaemic control. The reference intervals for GHbA were < 8.0% in 1986-1992 and 4.0-6.0% after 1992. Glycaemic control was considered optimal when GhbA1 values at the first antenatal visit, at the 20th and 28th week of pregnancy, and before delivery, were within reference ranges. In the case of poor glycaemic control there was no GHbA value within those ranges during pregnancy.

The register study included no data on maternal glycaemic control during pregnancy.

4.4.3 Neonatal monitoring

Apgar scores were given according to the generally accepted principles at 1, 5 and 15 minutes.

Small (SGA) and large for gestational age (LGA) infants were defined as those with a birth-weight at 2 or more SDs below and above the normal means for gestational age (AGA) and sex, respectively, according to Finnish standards (Pihkala *et al.* 1989). Premature delivery was defined as delivery at less than 37 completed weeks (259 days). In case of perinatal morbidity, the infant was treated or observed at a neonatal unit. Samples for blood glucose determination of the newborn were taken during the first 2-4 hours of age and glucose was monitored thereafter at least during the first 48 hours after birth. A blood glucose concentration of or less than 1.7 mmol/L (30 mg/100 ml) more than twice or one low value in association with the administration of intravenous glucose was classified as hypoglycaemia. A diagnosis of RDS was made on the basis of any need for respiratory support, on clinical assessment and on radiological findings.

Malformations were classified according to the RCM and the diagnosis was based on structural abnormalities. Major malformations were considered to be fatal or potentially life threatening ones, or those requiring considerable surgical treatment. The remaining malformations were classified as minor. Anomaly of single organ, or anomalies limited to certain organ or organ group were defined as isolated, and as a multiple anomaly if several organs were involved.

The PNM rate covered stillborns and early neonatal deaths from the 22nd gestational week to the age of 7 days. Late neonatal deaths (8-28 days) and postneonatal deaths up to the age of 3 months (paper II) or 1 year (paper V) were also analysed. In cases of perinatal death, autopsies were performed.

4.4.4 Statistical methods

Statistical analysis was performed with SPSS[®] (Papers I-III) and SAS[®] programs (Papers IV-V). Comparisons of distributions between groups were made by using the Chi square test and differences between means by using Student's t-test when the variables followed a normal distribution, and in cases in which the distribution of values was not normal, the Wilcoxon two-sample test. Relative risks (RR) and corresponding 95% confidence intervals (CI) were calculated in paper II for some factors associated with adverse pregnancy outcome and known at the beginning of pregnancy, and odds ratios (OR) and 95% CIs for LGA infants were calculated by using a logistic regression model, adjusting maternal BMI and GHbA values at different stages of pregnancy. Considering the first and the second pregnancy of 46 parous women as a matched pair in paper III, the Mantel-Haenszel risk ratio and its approximate 95% CI were calculated for pregnancy complications and status of glycaemic control.

5 Results

5.1 Incidence of diabetic pregnancies (Papers I and IV)

Insulin-treated diabetes complicated 4.5/1000 births in Finland in 1991-1995, and its incidence increased during the study period from 3.9/1000 to 5.0/1000. This increase was seen in both Type 1 diabetes and in insulin-treated GDM. The prevalence of Type 1 diabetes among pregnant women was 2.9/1000 in the whole country and 3.3/1000 in Northern Finland.

5.2 Changes in the care of diabetic mothers (Papers I and IV)

Paper I. Until 1990, the care of all pregnant diabetic women in Northern Finland was centralized to the tertiary level university hospital and was carried out mostly on an in-patient basis. In 1991-95, 48% (n=77) of all diabetic pregnancies, and 56% of women belonging to White classes F/R, were treated in central hospitals (range 8-26 in each). As a consequence of the change in the care policy, the number of out-patient visits increased (0.6 vs 8.2, $p < 0.005$) between two periods, and the number of hospital days decreased significantly (35.5 vs 15.7, $p < 0.005$). The first antenatal contact at the delivery hospital was earlier in the second study period (10.6 vs. 9.3 GW, respectively, $p 0.006$), but the follow-up on the ward before delivery began at nearly the same time in both periods (36.7 vs 37.1 GW, respectively, $p 0.202$).

Paper IV. The total number of insulin-treated diabetic deliveries in tertiary centres in the entire country decreased between 1991/92 and 1994/95 from 59% to 47% (95% CI 39–58%), as did the proportion of Type 1 diabetic deliveries from 62% (n=220) to 52% (n=205) (95% CI 38–72 %). The number of early antenatal visits (≤ 7 GW) in women with Type 1 diabetes increased significantly during the study period (47 vs 54%, $p < 0.05$) as did the number of out-patient visits (from 7.8 to 11.5, $p < 0.001$).

5.3 Glycaemic control (Papers I and III)

Seventy-three percent of women entered pregnancy with unsatisfied glycaemic control in the both study periods in Northern Finland. After the first antenatal visit, metabolic control improved rapidly, and was significantly better during the second and the third trimester in the latter period (Table 1). There was a non-significant increase in the number of hypoglycaemic episodes between the two periods, 22% in period 1 and 29% in period 2.

Women with short duration and less severe diabetes (White B) more often had satisfactory glycaemic control in early pregnancy and during the whole pregnancy than did women with complicated diabetes. Symptomatic hypoglycaemia was met significantly more often in White classes F/R than in White class B/C (Table 2). Women entered their second pregnancy more often with satisfactory glycaemic control than their first one (29.5% vs. 22.2%), and they were also able to maintain it at a satisfactory level more often during the whole pregnancy (15.8 vs 23.1%).

Table 1. The proportions of patients with satisfactory glycaemic control in the different stages of pregnancy stratified into two periods. N (%)

Satisfactory glycaemic control	Period 1 (n=135)	Period 2 (n=161)
First antenatal visit	36 (27)	44 (27)
H20 *	79 (59)	116 (73)
H28 *	79 (60)	111 (73)
H36	78 (65)	96 (72)
During the entire pregnancy	16 (13)	32 (25)

* $P < 0.05$

Table 2. Glycaemic control during pregnancy stratified according to the severity of diabetes. N (%)

Glycaemic control	White B/C (n=151)	White F/R (n=32)
Satisfactory periconception*	54 (38)	3 (10)
Always optimal GHb*	33 (27)	1 (4)
Always poor GHb	16 (13)	3 (12)
Hypoglycaemic episodes*	33 (22)	15 (47)

* P < 0.05

5.4 Diabetic complications (Paper III)

Retinopathy complicated 134 (45.3%) diabetic pregnancies. Of these, 66% were cases of background retinopathy, 16% pre-proliferative and 15% proliferative form. Two women had diabetic cataracta. The incidence of retinopathy increased with the duration of diabetes and was found in all cases after 25 years. Retinopathy was aggravated in 25 cases during pregnancy - pre-proliferative and proliferative changes progressed most often (Table 3). Thirteen of these women needed laser-treatment during or shortly after the pregnancy. The first retinal changes developed during pregnancy in three cases (in White classes C, D and F, one in each), and all these changes occurred during the first pregnancy. Spontaneous improvement during pregnancy was found in one case. Although retinopathy was aggravated more often during the first pregnancy, the occurrence of retinopathy or its severe form was not increased at the beginning of the second pregnancy.

Clinical nephropathy was observed in 23 (7.8%) cases, 16 of these women were primiparous. Unlike retinopathy, its proportion did not increase after 20 years of diabetes, and after 25 years it was found in 20% of women.

Eighteen (6.1%) women in the entire study group had arterial hypertension, and 12 of these belonged to White classes F/R. Twelve (67%) of these women were primiparous. The incidence of arterial hypertension also increased up to 20 years duration of diabetes after which it reached a plateau.

Table 3. The aggravation of retinopathy during pregnancy according to prior retinal changes. Data is missing in 8 cases.

Grade of retinopathy	N	Aggravation	Proportion (%)
No retinopathy	158	3	1.9
Background retinopathy	88	7	8.0
Pre-proliferative retinopathy	22	7	31.8
Proliferative retinopathy	20	8	40.0
Total	288	25	8.7

5.5 Obstetrical findings (Papers I, II, IV)

5.5.1 Pre-eclampsia

Paper II. Of the mothers, 16.9% (n=50) had pre-eclampsia during pregnancy, which in 14 cases (28.0%) was classified as superimposed. In the entire study population, pre-eclampsia was found in 25.6% (32/125) of the first, 10.9% (11/101) of the second and 10.0% (7/70) of consecutive pregnancies. Its occurrence rose with the severity of diabetes (Table 4).

Table 4. The incidence of pre-eclampsia according to White classes.

	Pre-eclampsia			All women	Incidence (%)
	Mild	Moderate/ severe	Total		
White class:					
B	2	3	5	88	5.7
C	2	5	7	63	11.1
D	5	18	23	113	20.4
F	0	7	7	18	38.9
R	1	7	8	14	57.1
Periods:					
1 (1986-90)	8	13	21	135	15.6
2 (1991-95)	2	27	29	161	18.0

5.5.2 Duration of pregnancy

Papers I and II. The mean duration of gestation was 38.1 weeks (SD 2.5), and there was no significant difference between the two study periods. Fifty-six deliveries (18.9%) were preterm - five of which occurred before the 28th GW and five between the 29th and 32nd GW. Seventeen (30.4%) of these labours began spontaneously, four (7.1%) were induced because of intrauterine death and elective caesarean section was performed in 21 (37.5%) cases due to pre-eclampsia or threatened asphyxia. The reason for preterm elective delivery can be classified as relative in 14 cases (25.0%).

Paper IV. In the entire country, 29.6% of Type 1 diabetic deliveries were preterm, the proportion being six times higher than in the control population ($p < 0.001$). Of all diabetic births, 30.2% were preterm in tertiary and 16.2% in secondary hospitals.

5.5.3 Mode of delivery

Paper II. The caesarean section rate was 52% (n=153), 38% (n=113) were uncomplicated vaginal deliveries, 8% (n=25) were delivered by vacuum extraction and 1% (n=3) were assisted breech deliveries. One delivery was complicated by rupture of the uterus and hysterectomy was performed, while the data pertaining to the mode of delivery was missing in one case (1%).

The rate of labour induction was 35.8% (n=105), 34.5% (n=101) were elective sections and 29.7% (n=87) of deliveries began spontaneously. The proportion of caesarean sections was 69.6% in preterm deliveries, the rate being 47.5% in deliveries after the 37th GW (p 0.001). The incidence of caesarean section rose with the increased severity of diabetes (Table 5), and was similar among both primi- and multiparous women. Of the primiparous women, 16.0% (n=20) were delivered with vacuum extraction, the corresponding rate being 2.9% (n=5) in multiparous mothers (p < 0.001).

Table 5. Caesarean section frequency according to White classes. Data are n.

White class	Total number	Caesarean sections	Proportion (%)
B	88	32	36.4
C	63	26	41.3
D	113	68	60.2
F	18	14	77.8
R	14	13	92.9

Paper IV. The percentages of caesarean sections for the entire country were 63.5 in Type 1 diabetic pregnancies and 34.6 in women with insulin-treated GDM, both being significantly (p < 0.001) higher than in the background population (14.4%).

5.6 Birth outcome (Papers II, IV and V)

5.6.1 Birth weight

Paper II. The mean birth weight was 3597g (SD 861) and range 494 - 5285g. It increased during the study period (3497g in period 1 and 3682g in period 2, p > 0.05), and was higher in the secondary level than in the tertiary level hospitals (3818g and 3557g, respectively, p > 0.05). The proportion of LGA infants did not change during the study period, when a non-significant decrease in the rate of SGA infants was found. All SGA-infants were delivered in the tertiary level hospital during the study period (Table 6). Constantly poor glycaemic control during pregnancy was associated with macrosomia, but an improvement of maternal glycaemic control up to the 28th GW had a favourable

effect on the LGA rate. The control of maternal BMI had no significant influence on the incidence of LGA-infants.

Table 6. Gestational age-related birth weights in diabetic pregnancies in the two study periods, as well as in the different hospital levels during the second study period.

	Period 1 (n=135)		Period 2 (n=161)		p- value	Period 2				p- value
						Tertiary level (n=84)		Secondary level (n=77)		
	n	%	n	%		n	%	n	%	
LGA	28	(20.9)	31	(19.3)	0.75	14	(16.7)	17	(22.1)	0.39
SGA	12	(9.0)	5	(3.1)	0.04	5	(6.0)	0	(0.0)	0.02

LGA = large for gestational age, SGA = small for gestational age

Paper IV. The proportion of LGA infants in the entire country in Type 1 diabetic pregnancies was 34.7%, the rate being 3.2% in the background population ($p < 0.001$). The total rate of LGA infants among insulin-treated GDM women was 25.8%, the rate decreasing during the study period from 33.1% to 21.5% ($p < 0.05$). The proportions of SGA infants were similar in Type 1, GDM and in the non-diabetic population, the total rate showing a tendency to decrease during the study period.

5.6.2 Apgar scores

Paper II and IV. In the entire country, 11.8% of Type 1 IDMs received an Apgar score less than 7 at one minute, the rate being significantly higher than in the control population (3.9%, $p < 0.001$). In Northern Finland, the corresponding rate was 11.4% (33 infants). At five minutes, 10 (3.5%) infants received an Apgar score less than 7, the rate of low scores being equal in White classes B-D and F-R (3.5% and 3.4%, respectively).

5.6.3 Perinatal morbidity

Paper II and IV. In Northern Finland, 141 (48.8%) of all newborns were observed or treated in the paediatric unit, and 38 (13.1%) of them needed observation for more than 10 days. These rates did not differ significantly between the two study periods (50.8% vs 46.9%, and 11.5% vs. 13.8%, respectively). In the entire country, 45.6% of IDMs in the Type 1 group and 20.1% in the insulin-treated GDM group were observed in the neonatal unit.

Neonatal hypoglycaemia was diagnosed in 16.3% of all IDMs in Northern Finland. Its occurrence increased significantly between the two study periods, being 6.7% in period 1 and 23.6% in period 2. It was found more often among preterms (28.0%), LGA-infants (24.1%) and in IDMs in White classes F/R (26.7%). Of mothers of hypoglycaemic infants, 63.6% had a GHbA-value within the reference range at the last antenatal visit prior to delivery.

RDS was observed in 17 cases (5.9%) during the study period. It was as common during both study periods, and it was found most often among preterm (28.0%) and SGA infants (40.0%).

5.6.4 Birth trauma

Paper II. Twenty newborns (6.8%) had a birth injury, of which 16 were clavicular fractures. The other injuries were brachial palsy, cranial fracture and intra-abdominal and adrenal haemorrhage, one case of each. Seventeen of these newborns were delivered by vaginal route, including six vacuum extractions and one assisted breech delivery, and three infants were delivered by caesarean section. Thirteen (65%) deliveries were induced, and 16 (80%) of all injuries were found among infants being AGA.

5.6.5 Anomalies

Paper II. Sixteen (540/10000) infants had congenital anomalies; 11 were classified as major and 5 as minor malformations (Table 7). All mothers with a malformed infant showed poor glycaemic control at the first antenatal visit. Four of these belonged to White class B, four to class C, seven to class D and one to class R. Nine of these mothers were primiparous.

Table 7. Congenital anomalies in IDMs in Northern Finland in 1986-95.

	Anomaly
1.	VSD ¹ , anomalies of thoracic vertebrae, syndrome NUD suspecta
2.	Malformation of brain, heart and spleen, corda univentr. cum transpositio
3.	Subaortic VSD ¹ , ASD ² suspecta
4.	Syndactylia digiti 2-3 extremitas inferioris l.a.
5.	ASD ²
6.	Extranumerous thumb l.dx
7.	Anomalies of thoracic vertebrae, reflux vesico-urethralis l.a.
8.	Microtia l.dx
9.	VSD ¹ , riding aorta, pulmonal stenosis
10.	VSD ¹ , ASD ² , PDA ³ , CoA ⁴
11.	Tetralogia Fallot, multiple VSD ¹ , riding aorta
12.	Pes equinovarus l.sin
13.	Trilobular heart, duodenal atresia, situs inversus viscerum
14.	Hypoplastic left heart syndrome
15.	Caudal regression syndrome
16.	Transposition of great arteries, VSD ¹ , stenosis arteriae pulmonalis

¹ ventricular septum defect, ² atrial septum defect, ³ patent ductus arteriosus, ⁴ coarctation of aorta

Paper V. A significant CA was diagnosed in 60 IDMs, the prevalence at birth being 629/10000 in the entire country. Of all cases, 41 (68%) were isolated and 13 (22%) multiple (≥ 2) anomalies, and a specific syndrome was diagnosed in six cases (10%). After excluding syndromes, the total number of registered anomalies was 73. Cardiac malformations were most common, and anomalies in the genitourinary tract and the musculoskeletal organs were next in frequency. Most cardiac and genitourinary anomalies were isolated, while the musculoskeletal and gastrointestinal anomalies were mostly part of multiple anomalies (Figure 1). Sixty-three percent of the malformed infants were boys, the proportion being 49% in the non-malformed group ($p < 0.05$).

The diabetic mothers of malformed infants were significantly younger than the mothers of non-malformed infants (28.1 vs. 30.3 yr, $p < 0.001$) but a comparison revealed no significant difference in the proportion of primiparous mothers or mothers who smoked during the first trimester of pregnancy. The first antenatal visit occurred more often at the 8th gestational week or later among the mothers of malformed than non-malformed infants (54% vs. 45%, p non-significant).

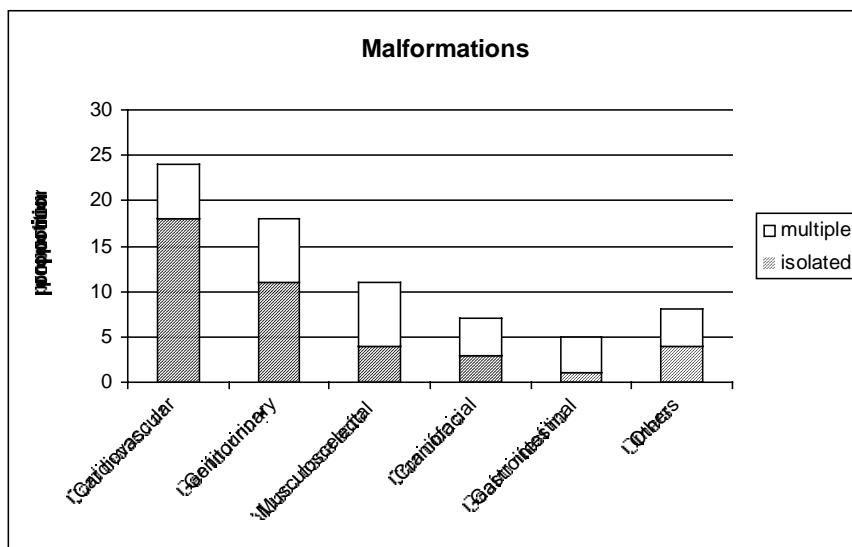


Fig 1. The distribution of CAs and proportions of isolated anomalies according to the organ systems involved in Finland in 1991-1995.

5.6.6 Mortality

Paper II. Nine (30.4/1000 births) perinatal deaths occurred during the entire study period: 7 of these were intrauterine and 2 were neonatal deaths. CA was the cause of death in three and prematurity in two cases, and severe growth retardation with asphyxia in one case. Three intrauterine deaths remained unexplained. The corrected PNM rate was 20.0/1000, and after excluding births at less than 28 complete gestational weeks, the PNM rate was 17.1/1000. Three infants died at an age less than three months: two of these due to multiple anomalies and one due to a chronic lung disease as a result of severe RDS.

All but one mother of perinatally died newborns had unsatisfactory glycaemic control at the first antenatal visit. The final GHbA-value before delivery was within the reference range in 5 mothers, including all unexplained intrauterine deaths. Of the mothers with a perinatal loss, 5 belonged to White class B, 2 to class D and 2 to class F. Five were primiparous.

Papers IV and V. In the national statistics, PNM was 13.6/1000 (n=13) in the Type 1 diabetic group and 18.4/1000 (n=9) in the insulin-treated GDM group, both of these rates being significantly higher than in the non-diabetic population. Of perinatal deaths in Type 1 pregnancies, nine were intrauterine and four early neonatal deaths. The mean

gestational age of those nine stillborn fetuses was 33.1 weeks (range 28-38). Both CA and prematurity with its associated consequences caused 23% of perinatal deaths, the rest being intrauterine, mostly unexplained deaths.

One infant died in the late neonatal and five in the postneonatal period. Mortality was especially increased in the postneonatal period compared with the non-diabetic population (5.3/1000 vs 1.4/1000, OR 3.8, 95% CI 1.6-9.2). Respiratory distress was the most common cause of death among live borns, the mean gestational age being 27.2 weeks (range 25-29). The odds for intrauterine death was 2.4 (95% CI 1.2 - 4.7) and for infant death 2.6 (95% CI 1.4-4.8) in the diabetic group when compared with the non-diabetic population.

Table 8. Mortality rates in Type 1 diabetic and non-diabetic pregnancies in Finland in 1991-1995. OR = odds ratio, CI = confidence interval, PNM = perinatal mortality.

Mortality			Type 1 diabetic		Non-diabetic		OR	95% CI
			N=954		N=318 560			
			n	(/1000)	n	(/1000)		
PNM			13	(13.6)	1976	(6.2)	2.2	1.3 - 3.8
Deaths	within	8-364	6	(6.4)	610	(1.9)	3.3	1.5 - 7.3
	days							
Total			19	(19.9)	2586	(8.1)	2.4	1.6 - 3.9

6 Discussion

6.1 Subjects and data quality

The data from the present study are all population-based and are therefore well representative of their background populations. Although information obtained from clinical studies is often more detailed, it is mostly hospital specific and the number of cases is usually relatively low. Therefore, the register based MBR data provided the possibility to observe national trends in a large, unselected population, as well as enabling quality assurance of the methods used. When the data was combined with other health registers it was possible to analyse rare complications such as CAs and perinatal and infant deaths, and it also enabled an increase in validity and to complete data lacking from the primary source of information. The validity of the MBR is high for the most of the variables (Gissler *et al.* 1995), and when its data includes approximately 90% of all Type 1 diabetic pregnant women treated in Finland (Oksa 1990), the results of this unselected sample can be considered reliable. While the results of both studies mostly conformed to each other, clinical information was used to some degree to supplement and explain register data.

The clinical data includes information on all Type 1 diabetic pregnancies treated in Northern Finland during a ten-year period. It was evaluated from the entire catchment area and from its five hospitals, and a hospital-based bias was therefore avoided. Despite the retrospective character of the study, all data was recorded in delivery hospitals during pregnancy, delivery and the neonatal period according to a standard protocol and can therefore be considered reliable.

6.2 The incidence of diabetes in pregnancy

According to this study, insulin-treated diabetes complicated 4.5/1000 births, majority of the cases being Type 1 diabetes. While the coverage of the study is about 90%, the real

incidence of insulin-treated diabetes may be somewhat higher, perhaps 5.0/1000. These rates are comparable with previous studies in which the incidence of Type 1 diabetes varies from 1.8 (Engelgau *et al.* 1995) to 4.0/1000 (von Kries *et al.* 1997), the total rate of pre-existing diabetes being 2.1/1000 (Connell *et al.* 1985). The incidence of diabetes showed a tendency to increase during the study period, which may reflect a real increase previously reported (Bingley & Gale 1989), but may be partly due to the effect of the new data collection system of the MBR introduced in 1990. The uniform regimen to diagnose and treat diabetes during pregnancy, introduced in 1993, may also have increased especially the rate of GDM (Teramo *et al.* 1993). As the onset of diabetes occurs at an ever younger age in Finland (Tuomilehto *et al.* 1995, Karvonen *et al.* 1999), and the incidence rate of Type 1 diabetes in children less than 15 years is one of the highest in Europe (Green *et al.* 1992, Karvonen *et al.* 2000), diabetes will complicate more and more pregnancies in the near future. This also means, that there will be more diabetic women of a childbearing age, who will have had diabetes long enough to develop vascular complications. This will require still more capacity from maternal health care.

6.3 Changes in care

A mainly out-patient based self-monitoring of blood glucose levels contributed in this study to the obvious improvement in glycaemic control during pregnancy. This result supports the findings of Hanson *et al.* (1984), who found the same GHbA levels in diabetic women by self-monitoring of blood glucose at home as by hospital care during the last trimester of pregnancy. The out-patient based management has also been found to efficiently decrease maternal morbidity without increasing infant morbidity and mortality (Bourgeois & Duffer 1990). Not only is the self-monitoring of glycaemic control motivating for the diabetic woman, it also encourages the woman to assume more responsibility for her own care. This experience may contribute to subsequent satisfied glycaemic control, which has been found to be more common in parous women (Chaturvedi *et al.* 1995). In addition, out-patient care is cost-saving - it resulted in a significant decrease in the amount of hospital days, and fewer working days were then lost. The decreased number of hospital days also contributes to the quality of the women's daily life.

The superiority of centralized care of diabetic pregnancies is often emphasized, mostly as it enables to improve and maintain the clinical experience of personnel and at the same time, improves neonatal outcome (Pedersen 1967, Olofsson *et al.* 1984, Traub *et al.* 1987, Hadden & Traub 1998). It has been recommended that twenty to thirty diabetic pregnancies be treated annually to maintain sufficient clinical experience (Hadden & Traub 1998). In Finland, not even all tertiary level hospitals treat that number of diabetic pregnancies per year, and only two of the 16 secondary level hospitals treat more than 10 Type 1 diabetic pregnancies annually, not including women with insulin-treated GDM. The geographical structure of Finland, however, necessitates the decentralization of care to the smaller hospitals. Shared care has been successfully performed in Sweden, where

40 hospitals care for pregnant diabetic women (Cnattingius *et al.* 1994). The situation is different e.g. in Denmark, where shorter geographical distances, as well as the tradition of Pedersen, have facilitated a nearly complete centralization of diabetic care (Nielsen & Nielsen 1993). The precondition for successful, decentralized, out-patient based care is active health care system, uniform guidelines and sufficient, continuous education of personnel. In Finland, the population is homogenous and relatively well-educated, which make this kind of care policy possible. Nevertheless, while - according to our data - 7 central hospitals in Finland treat four or less diabetic pregnancies annually, the centralization of care to some extent should be discussed. The first step is, however, to centralize the care of these pregnancies in each hospital to a permanent care team. In some cases in which the pregnant diabetic woman has a long-standing and well-acting relation with her internist, it might be of benefit to continue with this monitoring. Although continuity in a doctor-patient-relation is mostly an advantage in diabetic care, in this case special familiarity of the care of diabetic pregnancy is, however, prerequisite.

In the present study, no increase in the rate of adverse peri- and neonatal events was found despite changes in the care policy. Increased rates of PNM, preterm deliveries and caesarean sections in tertiary level compared to secondary level hospitals reflect a successful selection of patients to the appropriate hospital level. This is supported by the finding that at the end of the study period, no newborn needed to be transferred to another hospital. These findings are in agreement with those in the report of Connel *et al.* (1985), postulating that good prenatal care contributes more to a decrease in PNM than the level of the delivery hospital. However, while neonatal morbidity and mortality are significantly increased in cases of insulin-treated GDM pregnancies, hospitals taking care of them should also be equipped with adequate neonatal facilities.

6.4 Glycaemic control

Though metabolic control in pregnancy improved significantly during the study period, more than 70% of women still entered their pregnancy with poor glycaemic control. Rapid correction after the first antenatal visit reflects that satisfactory glycaemic control is relatively easy to achieve through counselling - the improvement, however, comes too late to decrease the risk of CA and other adverse perinatal outcomes. Practically all women used multiple daily insulin injections, which has been found to improve maternal glycaemic control and perinatal outcome compared with twice daily injections (Nachum *et al.* 1999). Glycaemic control in diabetes has improved during the last decades due also to the development of monitoring equipment and to new, rapid-acting insulins. The prevalence of Type 1 diabetes is especially high in Finland, and increased experience with diabetic care and diabetic pregnancies helps to achieve a better outcome of pregnancy.

In this study, parous women booked earlier to antenatal care and also more often had satisfactory glycaemic control, which they were able to maintain throughout pregnancy. This is in contrast to previous studies, where parous women (Janz *et al.* 1995, Holing *et al.* 1998), or even women with prior adverse outcome of pregnancy (Casele & Laifer

1998) were not more likely to plan their next pregnancy. It is probable, that the significance of past pregnancy experience is important in diabetes. This period of intensive care may also be the reason why parous women have been found to maintain better glycaemic control later in their lives (Chaturvedi *et al.* 1995). A good, continuous doctor-patient-relation is essential in increasing the rate of planned pregnancies (Janz *et al.* 1995, Holing *et al.* 1998), which is supported by the finding that women who have visited an obstetrician to discuss about diabetes and pregnancy have planned their pregnancies more often (Holing *et al.* 1998). Adequate advice as to target glucose or GHbA-levels may help to achieve optimal control of glycaemia before entering pregnancy (Casele & Laifer 1998). When the care of an adolescent girl shifts from the paediatric unit to the internal medicine unit, a concomitant visit to an obstetrician might be of benefit. After delivery, it would also be useful to discuss the prior pregnancy and its problems, and to assess their possible recurrence and prevention. At the same time, proper contraception could be chosen.

A high GHbA level in early pregnancy was the most important risk factor not only for CA, but also for perinatal death and prolonged hospitalisation of the newborn. In contrast, when glycaemic control was maintained at an optimal level throughout the entire pregnancy, there were neither CAs nor perinatal deaths, and the rate of operative deliveries decreased. Although a single GHbA value cannot be used as an absolute predictor of foetal outcome, its predictive significance should be considered when planning antepartum surveillance in diabetic pregnancies. Poor glycaemic control in early pregnancy has also been associated with an increased incidence of pre-eclampsia (Hsu *et al.* 1996, Hanson & Persson 1998, Hsu *et al.* 1998, Hiilesmaa *et al.* 2000) and LGA-rate (Page *et al.* 1996, Raychaudhuri & Maresh 2000). In this study, correction of glycaemic control immediately after the first antenatal visit did not decrease the rate of LGA infants. This is in harmony with the finding, according to which foetal hyperinsulinemia in response to maternal hyperglycaemia during the first weeks of pregnancy stimulates foetal β -cell function leading to foetal overweight (Page *et al.* 1996). However, foetal growth is not prescribed by glycaemic control alone – placental glucose transport capacity in diabetic pregnancy is also increased, contributing to the occurrence of macrosomia even in well-controlled diabetes (Gaither *et al.* 1999, Jansson *et al.* 1999).

6.5 Diabetic complications

The proportion of retinopathy began to increase steadily after a 5 years history of diabetes and was found in all cases after a duration of 25 years. The prevalence of retinopathy was similar to a previous Finnish study (Anttila 1993), and the occurrence was comparable with the common diabetic population (The EURODIAB IDDM Complications Study 1994). As has been reported in some previous studies, advanced retinal changes were most often aggravated when the appearance of the first retinal changes, or the worsening of a mild retinopathy, were exceptional (Chew *et al.* 1995, Rosenn & Miodovnik 2000). Retinopathy worsened most often during the first pregnancy, which has not been described previously. Despite that, the occurrences of

retinopathy or its severe forms were not increased in the beginning of the second pregnancy, reflecting the reversibility of these changes in most cases. The rapid correction of poor glycaemic control in early pregnancy, which was more common in the first pregnancy, may contribute to the deterioration of retinopathy (Phelps *et al.* 1986). Also the introduction of intensive insulin treatment is associated with transient retinal changes (The Diabetes Control and Complications Trial Research Group 1993). The adequate follow-up and treatment of retina during and after the first pregnancy may have limited the deterioration of these changes in consecutive pregnancies. Therefore, it would be favourable to include an ophthalmological examination in the pre-pregnancy counselling to define retinal status before pregnancy and to perform treatment to the retina when needed.

The incidence of nephropathy continued to decrease when compared with a previous study in the same geographical area (Anttila 1993). This may at least partly be a result of advanced monitoring of glucose metabolism, while avoidance of diabetic vascular complications has mostly been associated with good glycaemic control (Orchard *et al.* 1990). In this study, previous metabolic control was not evaluated. It was interesting that - unlike retinopathy - the occurrence of nephropathy did not increase after an 20 year history of diabetes. Diabetic hypertension also behaved similarly. These findings might be explained by the genetic factors predisposing to diabetic nephropathy (Fagerudd *et al.* 1999).

Glycaemic control was most often unsatisfactory during pregnancy in women with severe retinopathy or nephropathy. Their goal of blood glucose values may not be as strict as in the others because of the increased risk for hypoglycaemic episodes (Stephenson *et al.* 1996). Problems in maintaining satisfactory glycaemic control may still increase the risk of pregnancy complications and adverse neonatal outcome in White classes F/R, further leading to a limited number of pregnancies - women with nephropathy or proliferative retinopathy were more likely to remain primiparous than other diabetic women. Because of the increased obstetrical and perinatal risks in White classes F/R, these women need special support and surveillance during pregnancy.

According to this study, pregnancy was not found to worsen the vascular complications of diabetes, at least over the short term. This is supported by the finding that the proportion of diabetic complications in this cohort was similar to that in the common diabetic population (The EURODIAB IDDM Complications Study 1994). The aggravation of retinopathy in the primiparous was often reversible, and some changes between pregnancies might be more likely to be related to the natural course of diabetes rather than to pregnancy. These findings are in accordance with a recent Finnish study, in which pregnancy was not associated with a worsening of diabetic complications (Kaaja *et al.* 1996), and the EURODIAB IDDM study, in which pregnancy was speculated to even be a limiting factor on the progression of diabetic complications (Chaturvedi *et al.* 1995). According to our study, it appears that complicated diabetes is often a limiting factor for consecutive pregnancies, and mostly women with less severe diabetes have more than one pregnancy. It is also likely that childless diabetic women represent a special subgroup, possibly advised against pregnancy, and should not be used as a control group when the effect of pregnancy on diabetic complications is assessed.

6.6 Timing and mode of delivery

In the national data, the rate of preterm deliveries in Type 1 diabetic pregnancies was six-fold compared to that of the background population. The data was insufficient with respect to the reason for preterm delivery, but while only 25% of preterm deliveries were spontaneous in the clinical data, it is likely that the rate of iatrogenic prematurity is also high at the national level. In diabetic pregnancy, preterm delivery may be unavoidable in some cases due to the increased risk of pre-eclampsia (Greene *et al.* 1989b, Sibai *et al.* 2000a) or foetal asphyxia (Mimouni *et al.* 1988, Salvesen *et al.* 1993). While neonatal morbidity is mostly related to low gestational age (Hanson *et al.* 1986, Hanson & Persson 1993), the reason for iatrogenic preterm delivery should always be carefully considered. Antepartum surveillance should be individually tailored with regards glycaemic control from early pregnancy, foetal growth and maternal complications. Reliable methods are needed to identify foetuses at true risk of intrauterine asphyxia to avoid unnecessary preterm deliveries.

A high rate of caesarean sections is partly associated with a high rate of premature deliveries, in which the rate was especially high. The probability of caesarean delivery increased with the severity of diabetes, but in contrast to a previous study (Blackwell *et al.* 2000), was similar between primi- and multiparous women. This reflects that caesarean delivery in the first pregnancy easily predisposes to sequential operative deliveries increasing their total proportion. The rate of operative delivery remained high despite advanced methods of antenatal surveillance, or an increased use of prostaglandin induction of labour. Even a significant decrease in the rate of macrosomia in GDM group had no effect on the section rate. It may be that a diagnosis of diabetes predisposes to operative delivery (Jarrett 1997) as has been shown in previous studies (Landon *et al.* 1990, Blackwell *et al.* 2000). However, after excluding macrosomia or untreated retinopathy as commonly accepted indications, elective caesarean section is recommended only when the cervix is unlikely to be ripened with prostaglandins (Landon & Gabbe 1993).

6.7 Birth outcome

Despite the fact that infants were admitted to a neonatal unit only as a result of medical indications, nearly half of all newborns required paediatric observation and treatment. The hospital managing diabetic deliveries should therefore be equipped with an adequate neonatal unit. The occurrence of RDS continued to decrease when compared with a previous study from the same catchment area (Anttila 1993). Apart from improved glycaemic control during pregnancy and advanced neonatal care, this may be due to the more common use of surfactant. The incidence of neonatal hypoglycaemia in period 1 was comparable to a previous Finnish study (Anttila 1993), but the rate increased significantly during the second study period. The occurrence was highest in the central hospitals (31.2%), and may be partly due to their practice of beginning preventive intravenous glucose infusion after a single low glucose value. The increase was, however,

also seen in the tertiary level hospital, and may therefore be partly explained by the more intensive follow-up of glucose values of the newborn. Neonatal hypoglycaemia has been associated with maternal hyperglycaemia in late pregnancy (Ylinen *et al.* 1981) or during delivery, although a modest relaxation of maternal glucose control during delivery does not increase the rate of neonatal hypoglycaemia (Carron Brown *et al.* 1999). In the present study, no significant difference was found in the final GHbA values before delivery between the mothers of hypo- and euglycaemic infants. However, our data was insufficient as to glycaemic control during delivery. Our finding that neonatal hypoglycaemia was more often seen in cases of macrosomia than after poor glycaemic control, was different from other findings reported earlier (Ylinen *et al.* 1981) and might also be a consequence of increased placental glucose transport capacity.

Pedersen & Moelsted-Pedersen (1965) presented four groups with a poor prognosis for the infant in diabetic pregnancy. These prognostically bad signs of pregnancy were clinical pyelonephritis, pre-comatose or severe acidosis, pre-eclampsia and negligence of care. In the present study poor glycaemic control during the first weeks of pregnancy was found to be the most important factor predicting adverse neonatal outcome such as increased CA rate, neonatal morbidity and mortality in diabetic pregnancy. Severe diabetes, primiparity and smoking were more common in women with adverse neonatal outcome. These factors, verified at the first antenatal visit, were indicators of the subgroup needing special support and feto-maternal surveillance during the entire pregnancy.

6.8 Congenital malformations

Despite some conflicting reports, the CA rate remains high in diabetic births (Damm & Molsted-Pedersen 1989). The decreased prevalence in the CA rate in the present study compared with a previous evaluation from the same catchment area is due to standardized description, not to any actual decrease (Anttila 1993). As in most previous studies, the occurrence of CA was associated with unsatisfactory periconceptual glycaemic control (Fuhrmann *et al.* 1983, Ylinen *et al.* 1984, Hanson *et al.* 1990, Steel *et al.* 1990, Kitzmiller *et al.* 1991). There is no certain cut-off level for a "safe" glycaemic level to inhibit the occurrence of CA: a fairly broad range of "acceptable" glycaemic control has been reported (Greene *et al.* 1989a), while in a recent Finnish study even modestly elevated GHbA levels were associated with an increased occurrence of CA (Suhonen *et al.* 2000). Although the date of the first antenatal contact, and therefore also any possible correction of glycaemic control, was shifted to occur earlier towards the end of the study period, it is still too late to prevent the development of CAs.

The prevalences of CAs were in the midrange of previously reported CA range and therefore comparable with other studies. However, a very wide variation in CA prevalence has been presented, which may mostly be contributed to their definitions. In this study, the definition of CAs is based on the criteria of the RCM and Eurocat (<http://www.ihe.be/eurocat/eurocat.htm>), and therefore these rates are comparable with national and standardized international rates. The low prevalences of CAs may be found

in highly specialized centres, in which pre-pregnancy care has been successful and well-organized (Fuhrmann *et al.* 1983, Damm & Molsted-Pedersen 1989). Careful pre- and postnatal diagnoses in diabetic pregnancies may result in a bias in relation to the non-diabetic group. In most clinical studies, the prevalence of CAs is based on a paediatric examination before the discharge from hospital. Although this method is accurate, the time perspective is often missed - e.g. genito-urinary tract anomalies and part of congenital heart diseases are often diagnosed after the first week of life. This was seen also in this study, where the CA prevalence in the register study was somehow greater than in the clinical one.

Although CNS anomalies are known to be common, they were seldom met in this study. According to unpublished Finnish data from 1991-95, selective pregnancy terminations due to CNS anomaly among diabetic mothers explain this low prevalence. The policy of pregnancy terminations affect the birth rate of CA, and was also seen as a diminished proportion of CA as the cause of perinatal death. Despite well-organized ultrasound screening, most CAs remained prenatally undetected according to the RCM data. One reason may be the high prevalence of cardiovascular anomalies, in which the sensitivity of ultrasound detection is especially low, partly being due to insufficient visualisation during the most common screening weeks (16-18 GW) (Saari-Kemppainen *et al.* 1994). A four-chamber view of the heart will detect 60% of serious abnormalities, while an accurate evaluation of the great artery connections detects up to 90% of serious cardiac malformations (Allan 2000). As the risk of CA is significantly increased in diabetic births, and most of these are difficult to define, ultrasound examination should be performed for this risk group at least once during pregnancy in a centre where the detailed foetal structure can be evaluated by an experienced observer. The measurement of foetal nuchal translucency thickness at the 10th-14th GW might also be useful for the screening of major defects of the heart and great arteries (Hyett *et al.* 1999).

An excess of CAs among boys was a surprising finding. That dominance even persisted after excluding genital malformations, which are typically easier to diagnose in male infants. A less prominent sex-bias has also been observed in the total population (Ritvanen & Sirkkiä 1996). Boys are treated more often in neonatal units (Gissler *et al.* 1999) too, which may lead to an excess of examinations and hence to an increased rate of CA diagnoses. In a recent animal study, the sex ratio for live, malformed fetuses in diabetic mice litters was reported to be significantly skewed toward male fetuses (Machado *et al.* 2001). This might be due to an increased sensitivity of male fetuses to disturbances in the early postconceptual period, due, for instance, to maternal hyperglycaemia. This finding needs to be studied more closely.

6.9 Mortality

PNM has decreased from 4.3% in the 1980's (Anttila 1993) to 3.0% in the same area in 1986-1995. In the entire country, PNM among diabetic mothers was two-fold compared to the background population, which is close to the WHO's St Vincent target (WHO Study group 1990). In other countries, PNM rates have varied from 2.8 to 4.8% (Hanson

& Persson 1993, Nielsen & Nielsen 1994, Casson *et al.* 1997, Hawthorne *et al.* 1997, von Kries *et al.* 1997), rates being 4 to 5 times than that in the common obstetric population. The lowest PNM rate in diabetic pregnancies, 10.4/1000, was found in a Norwegian register study between 1994-97 (Hawthorne *et al.* 2000). In contrast, the PNM rate was unexpectedly high in the insulin-treated GDM group in the present study, the risk being comparable to that for Type 1 diabetes. Overall mortality rates in the present study are low, especially when the 22nd GW is taken as the lower limit for PNM. In addition to advanced antenatal surveillance and neonatal care, it also reflects a successful trend in the care of diabetic pregnancies.

The majority of all perinatal deaths occurred during the foetal period, and often remained unexplained. Although intrauterine death is a well-known hazard in diabetic pregnancy (Lang & Kunzel 1989, Cnattingius *et al.* 1994), its final cause is still unresolved - being mainly associated with chronic hypoxia and poor maternal glycaemic control (Hanson & Persson 1993, Reece & Homko 1994, Schwartz & Teramo 2000). This well-known threat has led to the common practice of inducing diabetic labour preterm, which, on the other hand, increases the rates of operative delivery and neonatal morbidity. The occurrence of foetal deaths in this study began to rise in the early third trimester, however, and preterm delivery is therefore not a solution to this problem. New, reliable methods are needed to identify the foetuses at risk of intrauterine death. Amniotic erythropoietin has been a promising indicator of intrauterine asphyxia (Teramo *et al.* 1987, Östlund *et al.* 2000), but as an invasive method it has not become established in routine practice.

In addition to severe diabetes with vascular complications, poor glycaemic control in early weeks of pregnancy was also found to be a predicting factor for poor neonatal outcome, including perinatal death. In those subjects in whom glycaemic control was optimal during the entire pregnancy, no perinatal death was observed in this group. In the clinical study group, the final GHbA value was within the assay's reference range in both intrauterine deaths near term (37th and 39th GW). In contrast, only one mother with perinatal death entered pregnancy with satisfactory glycaemic control. These findings emphasize the significance of the factors occurring during early pregnancy on the perinatal outcome. Poor glycaemic control in early pregnancy might therefore be an important indicator of the need for intensified foetal surveillance during the final weeks of pregnancy, but the method by which this might threaten foetal well-being during this late stage of pregnancy is not known. In previous studies, poor glycaemic control in early pregnancy has been associated with at least an increase in the pre-eclampsia rate (Hanson & Persson 1998, Hsu *et al.* 1998, Hiilesmaa *et al.* 2000). Unsatisfactory glycaemic control may also reflect other life style factors which might predispose to adverse foetal outcome.

According to the present study, the significance of CA as the cause of perinatal death is decreasing, which may be due to selective pregnancy termination. On the other hand, due to advancements in neonatal care, compromised infants may survive longer, and their deaths are therefore not included in the PNM rate. In contrast to the low PNM rate, the proportion of postneonatal deaths was significantly higher in IDMs when compared to the background population. Of these deaths, most were due to typical diabetic complications - CA, severe prematurity and birth trauma - and without these the rate

would be comparable with that of the non-diabetic population. In addition to PNM, it would also be important to evaluate infant survival after the early neonatal period to obtain a true picture of the outcome of diabetic pregnancy.

7 Summary and conclusions

In 1991-95, insulin-treated diabetes complicated 4.5/1000 births in Finland, and the incidence of Type 1 diabetes among pregnant diabetic women was 2.9-3.3/1000. The incidence of diabetes showed a slight tendency to increase during the study period, which most probably reflects an increase in the incidence of diabetes in Finland. The care of diabetic pregnancies is shared amongst tertiary and secondary hospitals and is usually performed as team care with an internist, an obstetrician and a specialist nurse. The purpose of this study was to evaluate the treatment, course and outcome of these pregnancies in Finland using a register-based as well as clinical cohorts of diabetic women.

The following conclusions can be made from the results obtained in the present study:

1. The decentralized, mainly out-patient care of diabetic pregnancies was not associated with a significant increase in adverse events. In order for care to be successful, patients must be appropriately selected with regards different hospital levels and the personnel involved must be motivated and well educated. As the number of treated pregnancies in most hospitals is low, centralization in some degree, considering geographical differences, might be of benefit to maintain sufficient clinical experience.
2. Glycaemic control improved during the study period and was significantly better during the second and third trimester in 1991-95 when compared with that during 1986-90. Seventy-three percent of women entered pregnancy with unsatisfactory glycaemic control during the both study periods, however, which was apparent as a persistently high CA rate despite an otherwise improved perinatal outcome.
3. Retinopathy became aggravated more often during pregnancy in primiparous women, but its occurrence or occurrence of its severe forms were not increased until the beginning of the second pregnancy, reflecting the reversibility of retinal changes. While the prevalences of retino- and nephropathy did not differ in this cohort of parous women from the corresponding rates of the diabetic population in general,

pregnancy does not seem to worsen the prognosis of maternal diabetes - at least over the short term.

4. Unsatisfactory glycaemic control in early pregnancy was the most important factor predicting poor peri- and neonatal event in diabetic pregnancy. The risk was also increased in cases of severe diabetes, primiparity and smoking. These factors at the first antenatal visit are indicators of a subgroup with a particular need for counselling and intensive feto-maternal monitoring during pregnancy.
5. Although the prevalence of congenital anomalies has not decreased, their significance as the cause of perinatal death is diminishing. This may be partly due to an improved detection of fatal CAs in the antenatal period, which may sometimes result in selective pregnancy terminations. The occurrence of CAs was especially increased among boys. Although the PNM rate was low compared with other studies, postneonatal mortality in IDMs was high, the causes of deaths being related to diabetes. Therefore, a combined mortality rate, including induced abortions, stillborns and infant deaths, would give a more realistic idea of outcome in diabetic pregnancies.

8 References

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